

Genetic Testing in the 21st Century: Are we ready?

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Key Points

- **Genes are the blueprint of health and disease.**
- **Genetic testing is expanding rapidly throughout the developed world and giving rise to new opportunities for the advancement of human health.**
- **We now know that the causes of many common diseases such as cancer and cardiovascular disease include a genetic component – in fact most of us will develop a genetic disorder at some stage in our lives.**
- **Genetic tests can be used**
 - **to diagnose diseases**
 - **to predict the risk of an individual developing a particular disorder or disease**
 - **to provide personalised diagnosis so that treatment options can be tailored and accurate advice given**
 - **to test for susceptibility to drugs and determine the risk of side effects.**
- **The community can access information through the internet about healthcare developments worldwide, and is coming to see genetic testing as an important element of mainstream healthcare that should be accessible to those who will benefit.**
- **The translation of genetic information from research to clinical practice has, however, been erratic. Currently the provision of genetic testing in Australia is uncoordinated, inequitable and inefficient.**
- **Australia must not be left behind. We need a National Genetics Framework that is efficient, equitable, and adaptable to contend with rapid evolution in this field.**
- **The National Genetics Framework must encompass a process for timely evaluation of genetic tests and a coordinated, quality assured, nationwide program for providing genetic tests for all Australians.**
- **The National Genetics Framework must include guidelines for ethical decision making, planning for workforce requirements, an appropriate funding mechanism for genetic tests, and provision for specialist counselling where required.**
- **The RCPA is committed to working through the issues inherent in establishing the National Genetics Framework and seeks to further the discussion with all stakeholders so that this initiative can be progressed.**

Introduction

We have embarked on an era of extraordinary and exciting opportunities in genetic medicine. It is essential that Australia is not left behind as the world of genetics surges forward.

As human knowledge has expanded medical and technological advances have occurred across the spectrum of health care, and we have benefited in terms of longevity and quality of life. Genetics stands apart as being the one area that will enable the management of disease to be tailored to the individual – from ultra-personalised analysis and diagnosis, to customised treatments and prognostic advice, to specifically honed prevention strategies.

Genetics, therefore, creates a new wave of prospects that will further enhance our lives in myriad ways. People will be more motivated to engage in preventative activities that correlate directly to their personal risks. Patients will benefit from receiving the right treatment from the outset, thus avoiding delays and not being exposed to treatments that will not work for them. There will be cost savings to the community as we dispense with a one-size-fits-all approach, reducing morbidity and mortality and targeting the resources available for investigations and treatments to where they are most likely to be effective.

The RCPA has put forward this discussion paper because it is imperative that planning is instigated *now* for the future of genetic services in Australia, so that our health system can keep pace with the rest of the developed world.

Setting the scene

The last twenty years has seen enormous growth in our understanding of the genetic basis of human disease. The Human Genome Project, completed in April 2003, was a triumph in international research terms, mapping the 25,000 or so genes in the human genome ahead of schedule. This project has paved the way for determining the functions of nearly half of those genes to date, and work continues on deciphering the remainder and linking genes to known disorders and diseases. The potential opportunities thus created are extraordinary.

Many people are familiar with the notion of genetics in the context of prenatal testing. The ability to determine whether a baby will be born with one of a number of inherited genetic conditions has existed for some years. So what's new? What is so extraordinary about the genetic testing that is available today?

The significance of genetic testing is no longer limited to rare inherited disorders of a single gene or chromosome – genetics now encompasses much more than that. The majority of genetic mutations occur after birth and there is a growing tide of information about the genetic variants that accumulate during life and contribute to conditions such as cardiovascular diseases and different types of cancer. In fact it is now clear that the cause of many common diseases includes a genetic component, and we have a much better understanding of the interaction between genes and other factors in the environment.

By way of explanation, a genetic variant present at conception will be copied into every cell in the developing body, including cells in the gonads (ovaries or testes). Such a variant can be transmitted to the next generation and, if the variant causes a disorder, the disorder will be termed 'familial'. Examples of familial disorders caused by such a variant are cystic fibrosis and haemophilia. Other in-born genetic variants may increase susceptibility to disease during life e.g. BRCA1 and BRCA2 gene mutations, which are known to increase the risk of breast cancer.

In addition to in-born genetic variants, every cell in a person's body will acquire genetic errors over time. Some errors may be initiated by factors in the environment – like smoking – whereas others appear to be random. The accumulation of these errors can eventually contribute to the development of diseases but, as they are not present in the reproductive cells of the gonads to be passed on to the next generation, these genetic errors and the associated diseases are not familial.

Cancer is essentially a non-familial genetic disease. It is due to the gradual development of genetic errors with age, and is usually not related to inherited genetic errors. Given the burden of cancer in the community, it is thus clear that the significance of genetics has moved well beyond prenatal testing.

Medical genetic testing has a key role to play in the identification of both familial and non-familial genetic variants – from prenatal testing to determine the likelihood that a familial variant will be passed on; to testing for a gene that is predictive of an increased risk of developing a specific disease; to examining how certain genes are being expressed in a patient's tumour in order to guide the subsequent management. A genetic test may be the only way in which a diagnosis can be made for certain, or it may remove the need to do other expensive or invasive tests. Genetic testing has already become integral to microbiology, with detection of microbial genes enabling more rapid diagnosis and targeted approaches to the management of infectious diseases. Pharmacogenetics is a rapidly expanding area, creating opportunities that enable us to determine who will most benefit from a given drug, and also which individuals will react adversely to a particular drug.

Box 1: Familial heart disease

Approximately 1 in 200 people carry a gene causing increased risk of familial heart disease such as cardiac arrhythmias, cardiac failure, or coronary artery disease, all of which can lead to sudden death. Conventional testing can identify some of those at-risk, but if the underlying genetic cause has been identified in a family, genetic testing can give a more accurate indication of the risk for each family member. Programs of genetic testing and counselling are more effective in reducing the burden of familial cardiac disease than other methods, and similar models have reduced the burden of familial breast and bowel cancers in some States and Territories, but there is little or no funding for genetic testing in familial heart disease in Australia.

The implications of these genetic advances are already being felt. With many common diseases now recognised as including a genetic component, it is considered that 71% of children admitted to paediatric hospitals have a genetic

disorder¹, and 60% of adults will develop a genetic disorder by the age of 60². When one reflects on this in the context of a community that is better educated and more interested in health issues than ever before, it sets the stage for expectations that genetics will become an important element of mainstream healthcare and accessible to those who will benefit.

What are the challenges?

The translation of genetic information from research to clinical practice has been erratic. Advances in genetic medicine are typically episodic and unpredictable, and whilst some tests can shift rapidly from a research environment to a clinical activity, it can take time for the clinical utility of a new development to be fully appreciated. Knowledge of the contribution of genetics to disease varies widely within the community and also amongst healthcare professionals. In addition, there are shortages of the skilled personnel and equipment required to perform genetic tests and provide genetic counselling.

As with other aspects of health care, the provision of genetic testing across Australia will always present challenges. We have a dispersed population and a division between State and Federal government responsibilities for different elements of health care funding. Governments throughout the world are facing the challenges of balancing scarce resources with demand for access to drugs, tests, therapies, and the ripple effects of single changes in healthcare systems. What sets genetics apart in the context of the broader health system is the escalating demand for hundreds (and potentially, thousands) of genetic tests.

The RCPA is concerned that the advances in genetics have not been matched by the development of an integrated system of genetic testing in Australia. Responses have been reactive rather than adaptive. Funding of genetic services across Australia has been provided primarily by State governments and has evolved variably without any national coordination. Even within states there is generally no mechanism determining the genetic tests that will be provided; rather individual laboratories decide which tests they will perform based on local demand, funding, and expertise. This has resulted in marked variations in the availability of individual genetic tests within and between the states, as well as considerable differences in the resources allocated to employing and training the requisite staff.

The RCPA, with funding from the Quality Use of Pathology Program of the Federal Department of Health and Ageing, is currently undertaking a comprehensive survey of the genetic tests done in Australia, and once complete this information will be made available to clinical services to assist with referral of specimens to appropriate laboratories. Based on the information presently available, there is clearly wide disparity between states in regard to the availability of genetic tests. A number of genetic tests are done in the larger states, particularly NSW, Victoria and

¹ McCandless et al, *Am J Hum Genet* 2004; 74:121-7.

² Cited in *Our inheritance, our future. Realising the potential of genetics in the NHS*.
<http://www.dh.gov.uk/assetRoot/04/01/92/39/04019239.pdf>

Queensland, whereas no testing is done in the Northern Territory and very few tests are available in Tasmania and the ACT. Even more alarming is the fact that some of the tests deemed to be of 'unequivocal clinical value' by the UK Genetic Testing Network (used as a proxy as there is no comparable Australian body), are available in only one state, and a few are not available at all in Australia.

Genetic testing is already fundamental in some cancers where an accurate diagnosis cannot be determined through traditional methods, yet access to the requisite tests is limited to state-based centres of excellence with limited funds. Where requests for genetic testing cannot be met, the diagnosis and optimum treatment remains uncertain.

Variability in access is felt most keenly by those with relatively uncommon genetic disorders. Most laboratories do not offer these tests so there may be significant delays and costs involved in sourcing them. The injustice is clear when one considers that Australians with rare non-genetic diseases can be diagnosed using tests that are widely available, and so do not incur the penalty for rarity that is borne by families with a genetic disorder.

What is required and how can we achieve it?

Australians should undoubtedly have access to appropriate genetic testing regardless of the state in which they live. Delivery of genetic testing should be designed to accommodate the changes that continue to occur in this rapidly evolving field – changes in knowledge, methodology and patient demand. And it must reflect the interconnecting roles played by genetic pathologists, clinicians, counsellors, and other providers and consumers of genetic services.

Australia needs a **National Genetics Framework** that is effective, efficient and equitable. The RCPA considers that the following two elements are pivotal to creating an appropriate framework for this purpose:

1. A process for expedited assessment and review of genetic tests.

and

2. A nationwide program to deliver medical genetic testing.

Both these elements must be developed, and they must be integrated so that the national testing program can be readily adapted to accommodate newly assessed tests, and the assessment of tests can be undertaken in a way that is responsive to the framework devised for national service delivery.

1. Expedited assessment of genetic tests

The present system of assessing genetic tests is, like the service delivery, variable and poorly coordinated. The basis on which state funded genetic services evaluate tests with a view to deciding whether or not to provide them is not transparent but appears to focus primarily on safety and efficacy and is likely to draw on evidence from other laboratories in Australia and from international experience. It is worth

noting also that there is anecdotal evidence of laboratories using different methods to test the same gene with significant differences in test interpretation.

In contrast, there is a highly structured procedure in place for the inclusion of any new test (genetic or otherwise) on the Medicare Benefits Schedule (MBS), summarised as follows:

- An application is made to the Medical Services Advisory Committee (MSAC) for assessment of the safety, effectiveness and cost-effectiveness of a 'new' test. (Each test is deemed new regardless of whether it is performed routinely in state-based laboratories).
- MSAC considers the application and appoints an expert subcommittee to investigate and report back to MSAC. This investigation process requires an extensive review of the available literature and other sources of evidence. Previous analyses undertaken elsewhere do not alter the level of analysis conducted by MSAC.
- MSAC considers the report from the subcommittee and makes a recommendation to the Minister for Health and Ageing regarding whether the item should be publicly funded, and if so suggests an indicative fee.
- The Minister decides whether or not to accept the recommendation and, if so, arranges for placement of the item on the MBS.

Following this MSAC process has resulted in one gene test being added to the MBS approximately every two years in the last decade. It is not feasible to continue introducing tests at this pace given the rapid expansion of genetic testing that is required to bring Australia into line with the testing currently provided in comparable countries such as the United Kingdom (UK) and United States (USA). Moreover, submitting a separate application for each genetic test could require thousands of submissions (in view of the potential number of genes for which tests may be developed) and this would bring the MSAC scheme to a standstill.

The need for prompt assessment that is integrated with other healthcare funding evaluations is exemplified by the following experience with a cancer treatment and the associated genetic tests:

Box 2: Delay in approving a genetic test for leukaemia treatment

*The drug imatinib targets a specific genetic abnormality known to cause chronic myeloid leukaemia. It was listed on the Pharmaceutical Benefits Scheme (PBS) in 2004, with benefits restricted to patients who had evidence of this genetic abnormality in their tumour cells. A surrogate marker of the abnormality can be used, but a specific DNA-based assay provides a more sensitive and precise measure of tumour load³, and costs less. It took **four years**, however, for this assay to be evaluated by MSAC and listed on the MBS, and acceptance of results on peripheral blood (as opposed to bone marrow) has only occurred recently.*

³ Branford S, Hughes TP, Rudzki Z. Monitoring chronic myeloid leukaemia therapy by real-time quantitative PCR in blood is a reliable alternative to bone marrow cytogenetics. Br J Haematol. 1999 Dec;107(3):587-99.

One temporary option for dealing with this could be to enable MSAC to receive applications for "classes" of tests, so that submissions can be made for similar groups of diseases or similar testing methodologies, thus enabling some progress while more permanent solutions are being considered for evaluation of genetic tests.

Another challenging aspect of the MSAC evaluation process in regard to genetic tests is the evidence required to demonstrate cost effectiveness. Most genetic tests do not fit neatly into a simple cost effectiveness analysis, and using such a model does not take into account the significant familial, social and other benefits of genetic tests. For example, a woman whose brother is diagnosed with colon cancer and found to carry an inherited error in the MSH2 gene could be tested to determine whether she also carries this genetic error and is thus at increased risk of colon cancer; her gene test result would give guidance as to the need for regular colonoscopies. Relying on family history alone she could be given annual colonoscopies even though she may not be at increased risk. In other words it would be more cost effective (not to mention less invasive) for this patient to determine her risk before submitting for annual colonoscopies, yet this evidence would not necessarily be captured in an MSAC evaluation of a test for the MSH2 gene.

Box 3: Lack of coordination between Pharmaceutical Benefit Scheme and Medical Benefit Scheme

Gefitinib is a drug that is selectively active against some lung cancers. Gefitinib was listed on the PBS in late 2004, with the benefit being restricted to patients whose lung cancer cells have a particular class of genetic abnormality. There is, however, no Medicare rebate for the cost of the test required to attain that PBS benefit. The test is currently provided by only two laboratories in Australia at a charge of approximately \$1,000. 10-20% of those tested are shown to have the abnormality and will thus benefit from gefitinib; the remaining 80-90% pay for a result that provides them with no benefit. Moreover, the PBS restriction is now out of date in that a second class of genetic abnormality has been identified that renders tumours susceptible to gefitinib, but this is not included in the PBS restriction. Hence patients may pay for the test, be shown to have a susceptible tumour, yet still be denied access to the medication.

The introduction of genetic testing has already led to the development of models for evaluating genetic tests in the USA and the UK. The Genetic Testing Network in the UK evaluates genetic tests proposed for the National Health Service using the following criteria:

- the seriousness of the condition;
- the prevalence of the condition;
- the purpose of the test in relation to diagnosis, treatment, prognosis and management, pre-symptomatic testing, and risk assessment;
- the complexity of the test;
- the population in which the test is to be used;
- the performance of the test, including clinical sensitivity, specificity and predictive value;
- the clinical utility of the test;
- ethical, legal and social considerations, and
- the cost of the test.

An alternative model is the ACCE framework which considers **Analytic validity**, **Clinical validity**, **Clinical usefulness** and any **Ethical**, social, or legal implications. Australia could build on an overseas model such as one of these rather than creating a new evaluation tool from inception.

Regardless of the model determined for evaluating genetic tests, it may be necessary to put restrictions in place for some tests when they are included on the MBS. These could include restricted indications for testing, limitations on the frequency of testing for an individual patient, or restricting test requests to particular clinician groups. Genetic tests for familial variants can introduce additional clinical, psychological, ethical, and even legal and financial issues⁴. To address these issues, a restriction requiring specialist counselling in association with the relevant test could be included where appropriate.

2. National genetic testing program

A national program defining which genetic tests should be available and where they should be performed will contribute to quality assurance, equity of access and cost-effective resource allocation.

As the number of genes that can be tested continues to grow, the number of Australians who could benefit from genetic tests will also increase. Without a national program for the delivery of genetic testing, patients will be at the mercy of ad hoc decisions by individual laboratories as to which tests they can or will perform. A national program will enable planning to ensure that genetic tests for relatively common disorders are provided in each state or region, and the program can also be designed to limit the unnecessary duplication of genetic testing.

At present genetic testing is provided in four ways in Australia:

- Through a laboratory accredited to provide the genetic tests listed on the MBS (currently only six gene tests) and thus eligible for a Medicare rebate;
- By state run public laboratories – usually free of charge to public patients resident in that state whereas those from interstate and patients seen in private clinics may be charged;
- Through some research laboratories – either as part of their research activities or on a fee-for-service basis; and
- By a few small, private laboratories on a fee-for-service basis.

Where no Medicare rebate is available for a genetic test – as in the majority of cases – there is no imperative for a laboratory offering it to be accredited under the NATA⁵/RCPA accreditation scheme. Thus there is no certainty that this laboratory will have effective quality control in place or be participating in external quality assurance. In practice many such laboratories will be accredited because they offer rebatable genetic tests as well, but a planned approach to the provision of genetic testing will engender more confidence in regard to quality assurance, and will enable

⁴ This aspect of genetic testing for heritable mutations has been addressed by the National Pathology Accreditation Advisory Council (NPAAC)⁴ in *Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis (2006)*. A supplementary NPAAC guideline, *Classification of Human Genetic Testing*, was published in 2007.

⁵ National Association of Testing Authorities

appropriate regulation of the testing environment as a safeguard for the community. This is particularly an issue with tests for rare disorders, where quality may be enhanced by concentrating testing to one or a few centres of excellence.

A national program could also be used to facilitate data collection and interpretation. Datasets can be created to be comprehensive and consistent from the outset, and this will in turn assist with future planning of genetic testing services by identifying such information as where there is growth, waiting times, and where use of one test has been overtaken by another.

A single standing committee should be established to advise both the Federal and State Governments on the development and implementation of a national genetic testing program, and to act as an ongoing source of genetic testing expertise to assist with future planning requirements. This will ensure a coordinated approach to testing and optimal allocation of resources over time. The committee could also facilitate the process established for consistent evaluation of genetic tests proposed for inclusion in the national program as outlined above.

Other issues that must be examined

Several other elements must be encompassed in the National Genetics Framework.

A. Ethical guidelines

It is imperative that the National Genetics Framework include guidelines and processes for ethical decision making.

Ethical issues associated with genetics are not new, and perceptions will continue to vary between different professional, ethnic, and social groups. Excellent work has been done and continues to be progressed in this regard by the NH&MRC⁶ through its Human Genetics Advisory Committee. The ongoing ethical debate surrounding prenatal testing has, however, tended to predominate and divert the focus from much broader issues of ethics in genetic testing.

Testing the genes expressed in a tumour to guide the most appropriate treatment for a patient is unlikely to provoke ethical dilemmas. Nor is a pharmacogenetic test that can determine a patient's risk of serious side effects if given a particular drug. In contrast, testing for a gene that predisposes someone to a specific disease could have wide ranging implications and raise ethical issues as a consequence.

Ethical issues may arise, moreover, in determining who will have access to these and other genetic tests. The resources required to perform the tests will be limited even with the rollout of a planned national program, and there must be a robust process for deciding how these resources can be allocated equitably. Matters of consent and confidentiality are already recognised by regulatory authorities as significant issues in genetic testing, and hence incorporated in NATA/RCPA accreditation requirements. Other issues that may provoke ethical concerns include patenting of genetic tests, ownership and use of genetic information (including when

⁶ National Health and Medical Research Council

it can be released to relatives, an issue currently being addressed by the NH&MRC) and the provision of counselling services.

B. Clinician and Community Education

Referring clinicians must be educated about the appropriate utilisation and interpretation of genetic tests. There is evidence that the genetic tests currently available nationally through Medicare are not being used consistently across Australia, and this appears to reflect different knowledge levels of referring practitioners.

At the same time there needs to be information available for the community as to the role, opportunities and limitations of genetic testing. The community is increasingly well educated about health matters generally, and more likely to seek information from sources other than their healthcare providers. It is important that patients have access to information that is accurate and appropriate, and this cannot be assured with the internet sources they are relegated to using currently.

C. Workforce Planning

The RCPA has been warning for years that there is an urgent need to augment the pathologist workforce, and nowhere is this truer than in genetics. There are fewer than a dozen genetic pathologists in the whole of Australia and currently only four training positions are available.

There are, of course, flow on effects from these workforce constraints.

- A work environment survey undertaken by the RCPA in 2007 indicated that genetic pathologists work on average more than 50 hours per week, well in excess of safe levels proposed by organisations such as the AMA.
- Trainees in other pathology disciplines should acquire experience in molecular genetics but lack of rotation opportunities through genetic laboratories mean that many of these trainees cannot gain this exposure.
- On a larger scale, pathologists report alarm at the relative decline in Australian expertise in genetics that is evident when they attend international education events. The rest of the world is resourcing the training of individuals in this highly skilled area while Australia appears to be standing still, with limited career paths resulting in expertise moving offshore or into other fields.

Through the National Genetics Framework training positions must be created, including in the private sector where feasible, to increase the number of genetic pathologists and scientists trained and qualified in molecular genetics so that Australia is able to cope with an explosion in demand for all forms of genetic testing. Shorter scholarships could also be considered to encourage people to move into genetics from related areas. In conjunction with new training positions, the Framework must enable a larger number of laboratories to strive for excellence *now* so that they can attract and retain senior people qualified in genetics to stem the decline in expertise and foster growth.

D. Funding Mechanism

As part of the National Genetics Framework an appropriate funding mechanism is needed. The resources required to perform different genetic tests vary significantly in

terms of physical requirements (eg reagents, equipment etc) and the time taken by skilled laboratory personnel to perform the analysis and issue a report. In light of this, and given the rapidity with which this field is evolving, it would be simpler and more adaptable to define the workloads associated with genetic tests in terms of the procedures involved rather than determining a total amount for each test.

A system of procedure-based codes could provide a transparent basis for costing individual genetic tests through aggregation of the relevant components. The reimbursement associated with the procedural codes could be altered over time to reflect changing work practices, including high-volume batching and the use of robotics. The definitions of the codes, and the codes associated with a specific test, would also change over time, and although it is likely that these changes will occur more slowly, it is essential that any system of procedure-based codes is reviewed regularly.

E. Access to Counselling

The National Genetics Framework should include a provision for counselling to be available for anyone who is referred for or seeks a genetic test. Individuals need to understand why a genetic test is or isn't appropriate, and what the result will mean for them. An explanation may be needed as to why a particular treatment will or will not be prescribed based on a pharmacogenetics test result or the analysis of a tumour. There may be implications for patients' treatment options, lifestyle choices, decisions such as child bearing and obtaining life insurance, and consequences also for their genetic relatives.

There are genetic testing companies now touting for business on the internet, with offers ranging from paternity testing to diagnosis of certain diseases to detailed heredity analysis. Many of the claims are dubious and there is no certainty as to the quality of the laboratories where the tests are performed so the validity of the results could be questionable. Most concerning of all is that Australians engaging with these companies will receive test results without the benefit of counselling to ensure that they fully understand the significance of those results.

Conclusion

The genetic revolution is creating myriad opportunities for the advancement of human health. It is a revolution that will be driven by patients as they learn what is possible throughout the world and then seek to identify what is available locally.

If Australia is to maintain a world class health system it is imperative that a National Genetics Framework is established for the evaluation of genetic tests and provision of tests in a program that is efficient, equitable and can accommodate change. There will inevitably be social, ethical and financial complexities to address as this process is undertaken, but these will not diminish of their own accord, so delays to await their resolution cannot be justified.

The RCPA is committed to working through the issues and welcomes comments from other interested parties to further the debate on the delivery of medical genetic testing in Australia.