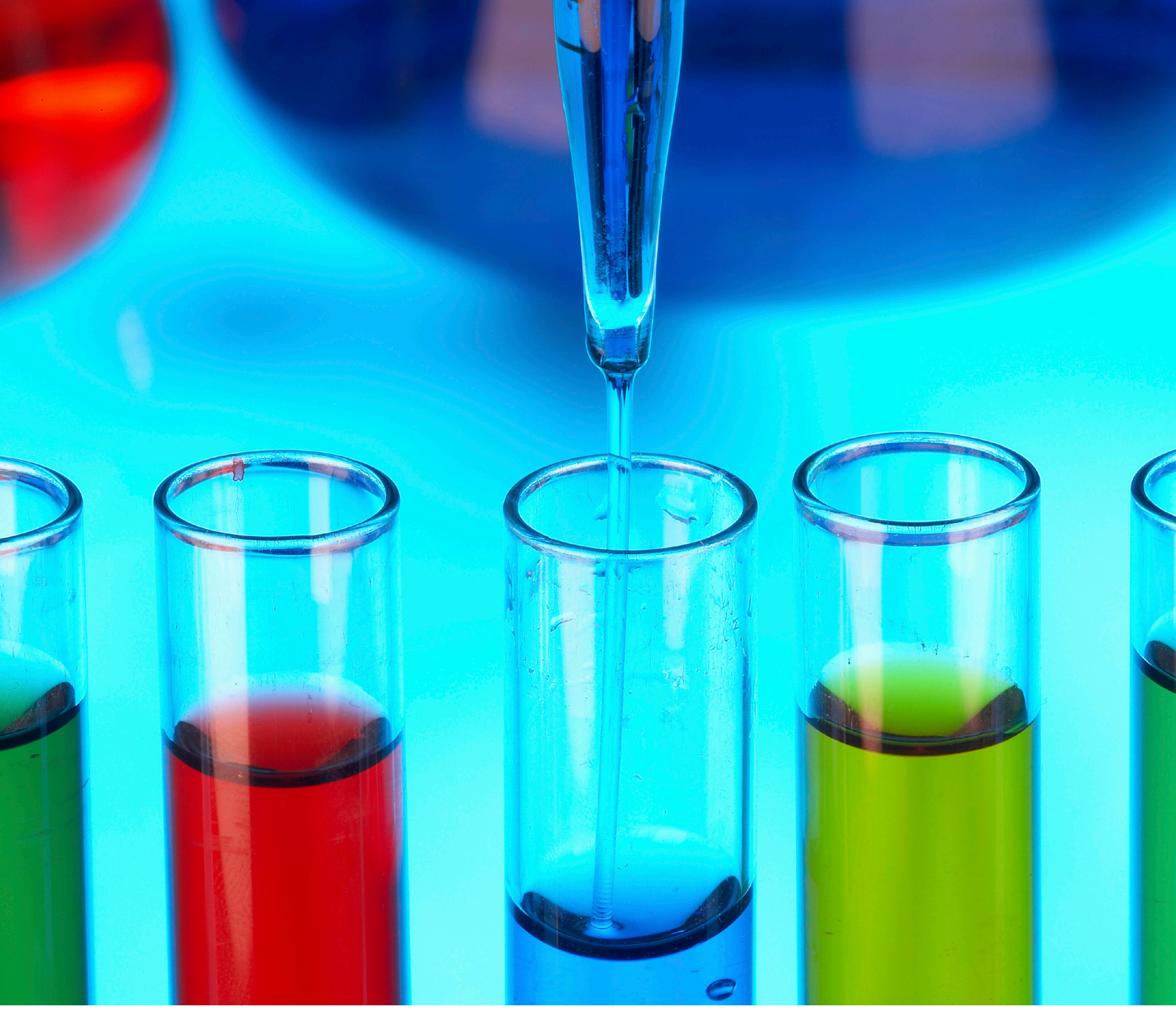

WORKING TO BUILD A HEALTHY AUSTRALIA

Australian Government
National Health and Medical Research Council
NHMRC

Medical Genetic Testing

Information for health professionals

April 2010

Electronic documents

ISBN Online: 1864964685

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NHMRC Publication reference: E99

Contents

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Acknowledgements

NHMRC would like to acknowledge the contribution of the following

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Human Genetics Advisory Committee (HGAC)

Australian Health Ethics Committee (AHEC)

Aboriginal and Torres Strait Islander Health and Research Advisory Committee (ATSIHRAC)

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Introduction

This Information Paper replaces a previous NHMRC publication, *Ethical Aspects of Human Genetic Testing: an Information Paper (2000)*, which required updating to reflect recent advances in genetics and genetic testing. The previous paper dealt principally with operational issues related to genetic testing practice, such as obtaining consent, counselling, privacy and confidentiality. As part of its scheduled review, the NHMRC decided to broaden the scope to include relevant clinical issues as well as ethical, legal and social issues.

The paper also includes some discussion on genetic testing in the context of research. It should be noted that the *National Statement on Ethical Conduct in Human Research (2007)* (*National Statement*) is the core guidance document for researchers and Human Research Ethics Committees (HRECs) in Australia.

Scope

This Information Paper deals with a specific aspect of medical testing performed in the course of clinical care - the testing of human nucleic acids i.e. DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), for inherited or non-inherited (somatic) genetic variants. The term 'genetic testing' will be used throughout the paper to refer to testing of nucleic acids. It is acknowledged that the term can also have a broader interpretation, including cytogenetic testing, molecular cytogenetic testing, and biochemical testing. Developments in proteomics, metabolomics, transcriptomics and other 'omics' will also have important implications on our understanding of genetic disease. However, these forms of genetic testing lie outside of the scope of this Information Paper, except where otherwise indicated.

The Information Paper deals predominantly with germline (inherited) genetic disorders although there are a number of references to somatic cell (acquired) genetic testing. Abnormalities in DNA or RNA profiles (transcriptomes) in somatic cells are increasingly being reported in association with different cancers. Although the laboratory aspects of testing for germline and somatic cell defects are similar, the ethical, legal and social issues are different because of the familial nature of germline defects. Somatic cell genetic testing is included as it is a growing area with potential ethical, legal and social issues. For example, the results of a somatic cell DNA test on a tumour sample could exclude an individual from having access to potentially life-saving chemotherapy. New developments in genomics that utilise somatic cell testing based on a tumour's transcriptome signature may be used for clinical decision making, although the evidence for clinical utility may not be complete, highlighting ethical dilemmas on the provision of information before formal evaluation is concluded.

The paper identifies key issues that should be considered in relation to genetic testing, and identifies relevant resources, guidelines, standards, and requirements that are pertinent for the delivery of genetic testing in Australia. This paper does not seek to provide a comprehensive statement regarding all of the issues associated with genetic testing, and does not dictate standards for the provision of such testing.

Context

Medical genetic testing occurs in the context of our current understanding about variations in the genetic code, which can cause or increase susceptibility to disease, and current ability to detect these variations. Overlying this contextual 'landscape' are four inter-related elements that dictate the delivery of such testing:

- the genetic testing resources available for medical testing
- the regulatory and legal frameworks for such testing
- the ethical framework within which such testing should be done
- the rapidity of change in all elements of medical genetic testing.

Audience and objectives

The purpose of this Information Paper is to provide a source of information for use by health professionals involved in genetic testing. This Paper seeks to support the health professional in:

- assisting patients when considering genetic testing
- ordering the appropriate genetic test
- interpreting its result in the context of clinical decision making
- providing follow-up care and support to the patient and family.

This Information Paper may also be useful to people providing training and accreditation to these health professionals, and for those developing policies pertaining to medical genetic testing.

In addition to addressing technical issues of test utilisation and performance, the Information Paper highlights the ethical, legal and social issues resulting from genetic testing, including:

- direct to consumer testing, personalised medicine and other emerging technologies
- genetic testing for purposes other than the direct health care of the individual such as; relationship testing, insurance, workplace or sport applications, and research.

How to use the text boxes in this document

Additional information has been included in text boxes throughout the document. The purpose of the text boxes is to provide further explanation, examples, commentary and resources to supplement the core text. The information has been categorised and colour coded as follows:

Commentary

Information in this category is presented in a blue box and serves to either provide the reader with an expanded explanation of the core text to further illustrate a point or to offer comments, interpretation or clarification of the core text.

Examples

Information in this category is presented in a **green** box and provides case examples in order to illustrate how the information in the core text might apply in a real life scenario. The examples can assist the reader to conceptualise the information in a clinical context.

Resources

Information in this category is presented in a **red** box and provides the reader with references and websites for further reading should they wish to pursue an issue in more detail.

It is intended that the text boxes complement and enhance the core text to provide the reader with additional information and context but that the core text be read and understood as stand alone text.

Through the NHMRC's *e*Genetics webpages (**www.nhmrc.gov.au**), this Information Paper will be available to members of the public and broader professional community to be used for education or as a source of information on specific topics in genetic testing. The paper will be updated periodically to address new developments in genetic testing.

Summary: Key points for good practice

The sequencing of the human genome was completed in 2003 and identified approximately 20,000 different genes. Of these, only a proportion have been associated with disease and a small proportion of those are currently tested in clinical practice. However, with rapidly evolving knowledge and technologies, testing volume is increasing, results are available more quickly, and costs of DNA sequencing are falling. The regulatory framework within which medical genetic testing is provided in Australia is also changing.

In some respects, genetic testing is simply another medical test and issues of consent, quality, utility etc. are no different from the issues encountered in other forms of medical testing. But the novelty of genetic testing, and the potential to identify genetic variants which carry implications for the risk of disease in the future for both the patient and the patient's genetic relatives, mean that genetic testing can pose ethical questions for individuals, families and society that are quite distinct from those associated with other forms of medical testing. Genetic information can assist individuals and families in identifying both risks and relevant interventions to prevent or reduce the morbidity of heritable disease.

This Information Paper outlines a process of considering, ordering and interpreting genetic tests that takes into account both the technical and associated ethical, legal and social issues. The process focuses on the health professional providing the patient and family with appropriate care and advice at all stages.

Assisting patient decision-making

Genetic information can be complex, and this needs to be acknowledged in approaches to assisting patients (and families) in decision-making about genetic testing. As well as following general principles for providing medical information to patients, specific genetic issues should also be considered. The health professional who sees the patient should be **appropriately qualified** (e.g. as a medical practitioner or genetic counsellor), knowledgeable about the specific area, able to communicate effectively, aware of the consequences of genetic test results for individuals and families, and able to deal with emotional responses to stressful information. The degree of counselling required depends on the level of uncertainty regarding the clinical implications of the test result, the potential implications for the patient, and the further implications for the patient's family. For example, it may be appropriate for a health professional to provide information about a genetic test being requested to identify the underlying cause of an affected patient's condition (diagnostic genetic test). Use of the same genetic test to determine the genetic status of an unaffected genetic relative, and thereby determine the risk of that genetic relative becoming affected in the future (predictive genetic test), carries very different implications and professional genetic counselling may be required before the test is performed. The role of the health professional is to assist individuals, couples and families to make decisions that are genuinely their own and appropriate to their personal situation, and to access relevant expertise in implementing that decision.

If a patient chooses to proceed with genetic testing, consent, whether written or implied, is required. Written consent may be required for predictive, prenatal, pre-implantation and population screening genetic tests. It may also be advisable to obtain written consent when testing affected patients if the test may give an uncertain result, or a certain result with uncertain implications. Additional considerations apply in seeking consent for genetic testing in children, people with reduced capacity to provide informed consent and people from culturally and linguistically diverse backgrounds.

Information provided to the patient as part of the consent process may cover the probabilistic

nature of the result, how it will be communicated, that it will be confidential, procedures and costs involved in testing, and information about the disease for which the patient is being tested. The ethical issues specific to the test being considered may also be discussed and information and contact details of relevant support groups provided.

Key points for good practice in assisting patient decision-making are to:

- provide information following the general principles outlined in Section 4.1
- provide information about the nature of the specific test
- ensure that genetic counselling is provided for decision-making about tests likely to provide uncertain outcomes and/or to have significant implications for the patient and their family (see Section 4.1.1)
- if aspects of the doctor–patient relationship are likely to influence decision-making, offer referral to another appropriate health professional to assist in the provision of information, genetic counselling, or decision-making (see Section 4.2.2)
- if a genetic test is requested by a patient and the test may be inappropriate or the process compromised, consider consulting other health professionals (see Section 4.2.2)
- discuss any request for predictive genetic testing of a child with experienced health professionals and proceed only when the result is likely to be of direct medical benefit during childhood (see Section 4.3.3)
- for patients with reduced capacity to provide informed consent, involve a family member, friend, legal guardian or professional advocate as appropriate and ensure that the information presented is understood and correctly interpreted (see Section 4.3.4)
- for patients from culturally and linguistically diverse backgrounds, involve family members, friends, independent advocates and/or interpreters as appropriate (see Section 4.3.6)
- outline the ethical, legal and social issues raised by the specific genetic test being considered (see Section 4.5).

Ordering genetic tests

The jurisdiction-based approach to funding genetic tests has led to inconsistent practices regarding who can order genetic tests. In some jurisdictions, certain genetic tests can only be ordered by specialist clinical geneticists employed in the public sector. However, genetic testing to confirm diagnosis of some diseases may be managed by a general practitioner (GP) and there is inevitable involvement of the GP in the long-term care of a patient (and family) following genetic testing. Irrespective of who has ordered a test, it is essential that the health professionals involved in the patient's continuing care are aware of what a genetic test can and cannot offer and of the clinical interpretation of the test result.

Testing can be complex in situations in which different mutations can cause the same genetic disease in different families, and diseases can be caused by multiple mutational mechanisms. The result of this complexity is that laboratories may screen multiple genes for mutations, or test a small number of known common mutations, rather than offering a single genetic test for each disease. Selection of the most useful genetic test involves consideration of the genes to be screened and the mutations being sought, the suitability, availability and cost of the test, and the ethical and regulatory issues that may arise. The selected test should then be assessed for suitability to the specific circumstances, analytical validity, clinical validity and clinical utility. Section 5.3 defines and discusses in greater detail the terms analytic validity, clinical validity and clinical utility.

Key points for good practice in ordering genetic tests are to:

- obtain detailed family history information, perhaps in the form of a family tree
- order genetic testing only if permitted to do so within your jurisdiction (see Section 5.1)
- determine the best genetic test to answer the clinical question following the considerations outlined in Section 5.2
- assess the test in terms of its ability to correctly identify mutation(s) in the gene being tested, the relevance of this result for the condition under consideration, and the potential impact that the test result may have on clinical management (see Section 5.3)
- order tests through a diagnostic laboratory that is accredited to the NATA/RCPA ISO 15189 standard taking into consideration the location of the laboratory, turnaround time of results and cost (see Section 5.4)
- consider carefully the implications of ordering a genetic test from an overseas laboratory where accreditation standards may be difficult to assess
- provide patients with information concerning storage of genetic test results and samples, including where and for how long they will be stored and how and by whom they can be accessed (see Section 5.5).

Providing the results

Genetic test results are analysed by laboratory professionals who present a test report to the requesting health professional to facilitate understanding and subsequent clinical decision-making. The health professional then interprets the analytical result in the light of the clinical context and provides the information to the patient. At each of these stages, it is essential that care is taken to identify all information relevant to decision-making.

As with the provision of any significant medical information, the patient should be encouraged to have a partner, family member or friend accompany them for support when receiving the test results. Information should be provided to them with consideration to facilitating understanding of complex information and sensitivity to the potential for distress. The health professional should also be prepared to facilitate a process of family communication.

Key points for good practice in providing results of genetic tests:

- be aware of up-to-date resources to assist in the interpretation of genetic test results (see Appendix G: Bibliography and resources)
- in reporting the analysis of test results, include all information necessary to support clinical decision-making following recommendations developed by the Royal College of Pathologists of Australasia (see Section 6.1)
- in interpreting test results, draw a distinction between the genetic variant identified (genotype) and the clinical outcome (phenotype) that this may cause (see Section 6.2)
- in deciding the extent to which test results are shared with other health professionals involved in the patient's care, consider the patient's desire for confidentiality, organisational policies regarding record-keeping, and the utility of the result for other health professionals (see Section 6.3); a balance between confidentiality and clinical care may at times be needed to avoid suboptimal clinical care if genetic test results are not made available
- in providing results to the patient and family, take time to ensure that the patient understands and can utilise the information being presented (see Sections 4.1 and 6.4.1)

- in situations where the test results have implications for family members, provide written information or agree to be contacted by family (see Section 6.4.2)
- in situations where the patient disputes the results of a genetic test, try to identify the reasons for the dispute and resources that may address the problem; referral to another health professional may be considered (see Section 6.4.3).

Recent developments and emerging technologies

Genetic testing is changing rapidly in relation to the knowledge base (such as epigenetics), emerging technologies (such as microarrays), utilisation in non-medical settings (such as relationship testing, insurance, workplace or sport applications and research), and access to testing (including direct to consumer testing and personalised medicine). Further information on these developments and technologies can be found in Parts C and D.

Part A: Background to genetic testing

1 Introduction to genetics and genetic testing

1.1 DNA basics

All cells in the human body (except mature red blood cells) have a nucleus that contains tightly coiled threadlike structures known as chromosomes. Humans normally have 23 pairs of chromosomes, one of each pair inherited from the mother and the other from the father. Each chromosome is composed of DNA, which itself is made up of a sequence of the chemical bases: adenine (A), cytosine (C), guanine (G) and thymine (T). Along the length of each chromosome are segments of DNA that are called genes. All of the DNA in the cell makes up the human genome and the study of this is called 'genomics'.

Resources

There are numerous resources on the internet for health professionals wanting general information about genetic testing:

www.nhmrc.gov.au/your_health/egenetics/practitioners/gems.htm

www.phgfoundation.org/

www.geneticseducation.nhs.uk/

www.nchpeg.org/

www.marchofdimes.com/gyponline/index.bm2

Each gene has its own unique position on one of the chromosomes and a unique sequence of the A, C, G and T bases which, when arranged in triplets to code for amino acids, represent the genetic code. DNA is used as a template to produce RNA, which in turn may contain the information used by the cell to make a specific protein or participate in the regulation of gene expression. Proteins carry out various functions in the body: some are the basic components of tissues (structural proteins); some carry out chemical reactions (enzymes); some act as messengers (hormones); and some regulate gene expression (transcription factors). Therefore cells are the basic building blocks of the body and proteins the basic building blocks of the cell. Genes provide the instructions for the production of proteins by the cell.

The DNA in the genome consists of three billion nucleotides. A human cell contains two copies of the genome i.e. six billion nucleotides (three billion from each parent). The nucleotides making up genes (and therefore coding proteins) account for about 5% of the genome. The genes, together with variations in the DNA close to genes that can affect how they work, form the 'coding DNA' and this constitutes the genetic code. The remaining 95% is sometimes referred to as 'non-coding (nc) DNA' because it does not directly code for proteins. The ncDNA is involved in regulating genes, controlling the physical structure of chromosomes, and other ill-defined tasks. Variations in the genetic code are a major cause of differences in human appearance, capabilities and predisposition to develop disease. On average, there are about 10 million differences between the genomes of two unrelated people. Genetic relatives inherit the same variations that may involve single base changes in their DNA (called SNPs—single nucleotide polymorphisms) or more complex copy number variations in the genetic code.

The genome in a single cell is copied every time a cell splits into two. Every cell in the body

contains a copy of the genetic code which was present at the moment of conception. But the process of repeatedly copying the genetic code introduces errors. The accumulation of these genetic errors over time contributes to the ageing process including diseases related to ageing.

Commentary

In July 2009 the House of Lords Science and Technology Committee Subcommittee published a report on Genomic Medicine. The report is the result of an inquiry assessing genome technologies and their impact on clinical practice following the completion of the Human Genome Project. Many issues discussed in the Report are pertinent to the discussions in this document, and reference to this document appears at numerous points throughout this Information Paper.

Link to the House of Lords Science and Technology Committee Subcommittee report Genomic Medicine (2009): **www.publications.parliament.uk/pa/ld200809/ldselect/ldsctech/107/10702.htm**

The great bulk of the genetic code is contained in the chromosomes and held in the nucleus of the cell. However, there is also a short strand of DNA in each mitochondrion. Mitochondrial DNA codes for some of the proteins that are necessary for mitochondrial function. In contrast to nuclear genes, mitochondrial genes are almost exclusively inherited from an individual's mother as spermatozoa contribute very few mitochondria to a fertilised egg. The accumulation of genetic errors in mitochondrial DNA over time gradually compromises mitochondrial function, and is one of the principle causes of the decline in organ function associated with ageing.

1.1.1 Non-coding RNA

There are a number of RNA species making up nc RNA. These include rRNA, tRNA, siRNA, miRNA and others (r – ribosomal; t – transfer; si – small interfering; mi – micro). Most of our understanding of the genome is about the genetic code, with less being known about the remaining ncRNA. However, there is increasing evidence about the clinical importance of miRNA species both in development and disease causation. For example, mutations in miRNA have been found to be associated with a number of human diseases including Alzheimer disease and various cancers (Erson and Petty 2008).

1.2 How genetic diseases occur

Commentary

The term genetic diseases can be used interchangeably with terms such as genetic disorder and genetic condition. For the purpose of this document the term 'genetic disease' will generally be used.

Genetic diseases are caused by sequence variations in the DNA. These changes may be present from the moment of conception, and so be present in the DNA of every cell of the body. This would include cells in the gonads (testes or ova) and such variations could then be passed on to children. Variations that are present in the gonads are referred to as germline variants. Other variations in the genetic code occur with the passage of time, and will be restricted to the specific cell and cells derived from it. If these variations are limited to cells that are not in gonads, then the variations will not be passed onto children. Such variants are referred to as somatic variants.

Sequence variations in DNA can differ in their effect:

- some cause disease (disease-causing variants, or mutations)
- some have less certain effects on health (susceptibility-creating, protective or disease-modifying variants)
- some underlie individual differences such as hair colour or height (polymorphisms)
- others have no effect on the individual (harmless variants).

It is important to note that some variants cannot be classified into any of the above.

Commentary

In this document, the term mutation is used when referring to a disease-causing variant. A polymorphism may affect susceptibility, it may modify the effect of a disease-causing variant or it may have no effect. In this document, the term polymorphism is used to refer to variants that have no phenotypic (clinical) effects.

Most variations in DNA are present in large numbers throughout the genome, without known effect on gene function, and are not associated with disease. Individually, they can be used for diagnosis of diseases where the gene mutation responsible for the disease is near the variation in the DNA (linkage analysis) and in combination can be used to uniquely identify an individual (DNA 'fingerprinting' or 'profiling').

All medical diseases have some genetic component. However, absolute predictions about future health or disease, based solely on a person's genetic information, are inexact as the causation of most disease is multifactorial, with varying contributions from gene mutations, complex interactions between inherited mutated genes, spontaneous gene mutations occurring during life, environment, lifestyle and chance.

Commentary

Genetic factors have a role to play in the development of any disease. Even adverse events such as accidents can have a contributing genetic component. For example, genetic factors can predispose a person to risk-taking behaviour resulting in adverse consequences such as substance abuse, accidents, and perhaps violence.

A genetic variant can cause or increase the risk of disease in a range of ways:

- Inherited mutations in a single gene or multiple genes can be sufficient to cause the disease, though in many cases the environment or other modifying genes can influence severity.
- Some inherited mutations contribute to disease through interactions with the environment.

Examples

An example is an unusual form of diabetes called maturity onset diabetes of the young (MODY). This type of diabetes is caused by a mutation in a single gene e.g. glucokinase, and is inherited as a mendelian trait. Despite the underlying single gene mutation causing MODY, diet alone may suffice to correct it suggesting both gene and environmental influences are strong and perhaps interacting.

- Other inherited genetic variations do not cause disease but can have subtle effects on a person's risk of disease, or on the response to an external threat such as infection or trauma; for example, germline genetic variants contributing to the risk of cancer.
- The accumulation of variations with age progressively degrades the genetic code. Some of these variations are mutations, and each cell develops its own set of mutations. The average genetic sequence assessed over thousands of cells in a person remains the same throughout life (and so testing for a heritable mutation need not be repeated at a later age), but each cell develops a unique repertoire of mutations that ultimately dictates the behaviour of that cell.
- A single cell can accumulate mutations that cause deregulation of cell division (i.e. cancer). These mutations are copied in all the cells of a cancer, and so genetic analysis of cells from a cancer will demonstrate both heritable mutations that would be evident in testing the patient's normal cells, plus the mutations that lead to the development of cancer from the original malignant cell. The latter are somatic variants and are not heritable.
- Some genetic variants can alter response to treatment (see Section 1.4.1).

In terms of disease causation, the focus of this Information Paper is on changes that occur in the DNA sequence. However, it is also known that the expression of a gene can be altered despite the sequence remaining normal. This is caused by epigenetic changes brought about by physical or chemical alterations to the DNA (see Section 8.5 for more discussion on epigenetics).

An individual's ethnic background can be a clue to risks for genetic disorders. For example, thalassaemia is found in parts of the world where malaria was or is endemic, making origin from the Mediterranean, Southern China, Middle East, South East Asia, and parts of the Pacific a risk factor. Similarly, Tay Sachs disease is found in people of Ashkenazi Jewish background. Ethnicity is not routinely collected in medical records; country of birth information is collected which is less useful in subsequent generations. Linking ethnicity with genetic information has the potential to stigmatise or discriminate. However, if not linked DNA tests may not produce a useful result if the particular mutation sought is not found in an ethnic population. For example, the HFE (haemochromatosis) DNA test for an individual of Asian origin will never be positive unless at least two genetic relatives were Anglo-Saxon Caucasian, being the population having the type of autosomal recessive genetic haemochromatosis detected by the HFE DNA test.

Examples

A genetic variant can be both a risk and a benefit. A person who carries one mutated copy of the gene which produces ß-globin is relatively resistant to the adverse effects of malaria compared to a person with two normal copies of the gene. But a person with two mutated copies of the gene can develop a serious and potentially fatal blood disorder, ß-thalassaemia. The balance between risk and benefit is a major factor in determining the frequency of the mutant gene in a population.

1.3 Types of genetic diseases

Genetic diseases are usually classified as Mendelian or multifactorial diseases. The classification that follows is not definitive as there are complexities. Factors contributing to variable penetrance may be genetic and/or environmental.

1.3.1 Mendelian (single gene or monogenic) diseases

Around 2,300 comparatively rare familial diseases are now known to be primarily due to an inherited mutation in a single gene i.e. Mendelian or monogenic diseases. The genes responsible for a further 1,600 or so Mendelian diseases remain to be identified. Some Mendelian diseases can be caused by a mutation in any one of a number of genes involved in pathogenesis.

Resources

The principal international repository of information about Mendelian diseases is called OMIM (Online Mendelian Inheritance in Man) and provides a valuable resource that is regularly updated at **www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM&itool=toolbar**

The inheritance of the mutated gene can be inferred from the pattern of the disease appearance (phenotype) in the family. This may be best demonstrated by drawing a family tree. Examples of Mendelian diseases include cystic fibrosis (autosomal recessive), haemophilia (X linked), familial adenomatous polyposis (autosomal dominant) and Leber's optic atrophy (mitochondrial DNA mutation).

A Mendelian disease may affect only one person in the family. This could be due to:

- autosomal recessive or X-linked inheritance (with unaffected carriers of the mutation in the family)
- non-penetrance (with some carriers of the mutation not being affected, often for unknown reasons)
- the affected person having a new dominant mutation that occurred in the egg or sperm from which they developed
- non-paternity.

Commentary

Research strategies for identifying the gene responsible for a Mendelian disease have improved over the last 30 years. These methods typically focus on identifying the location of the putative gene on a specific chromosome, and then testing genes in that region for mutations. This strategy is called 'positional cloning'.

1.3.2 Multifactorial (complex) diseases involving gene—environment interactions

In multifactorial genetic diseases, the disease is due to the combined effects of mutations in multiple genes plus the effects of environmental factors. There is no single gene or environmental factor that can be said to be the sole cause of the disease. Different clusters of mutations in different genes may cause the same disease. Each mutation may be inherited independently of the others, and a family tree will not necessarily demonstrate the familial predisposition.

Finding the underlying genes and mutations responsible for a multifactorial disease can be very difficult. The techniques to find these genes are still evolving and currently involve case-control (association) studies, a method which is not as robust or efficient as positional cloning.

Resources

There is no single repository of information about the genetic contributions to multifactorial disease. At present, the dominant research method is to analyse large groups of patients with and without the disease in question for the presence and absence of specific genetic variants across the entire genome (Genome-Wide Association Studies or GWAS). One of the catalogues for such studies can be viewed at **www.genome.gov/gwastudies/**

Many common diseases such as diabetes, dementia and obesity are multifactorial genetic diseases. Large-scale association studies involving thousands of subjects and thousands of DNA markers (SNPs) are identifying some of the genes involved in these diseases.

Commentary

There are over 30 genes associated with the development of type 2 diabetes. The risk of a person developing this form of diabetes is partly explained by the inheritance of genetic variants from each parent. Most of these variants are relatively weak in causing diabetes, with a relative risk of developing diabetes being only 1.1. This means that the risk of a person with this variant developing diabetes in the next year is only 10% greater than the comparable risk for someone lacking this variant. In other words, the majority of people with one of the variants will not develop diabetes. Lifestyle factors such as diet and exercise are also factors in causing diabetes. For an individual person, it is usually impossible to predict accurately whether that person will develop diabetes. Analysis of genetic and lifestyle factors provide some predictive power, but there is always the influence of chance.

Commentary

While a distinction is often made between Mendelian and multifactorial diseases, the complex nature of genetic inheritance means a disease can be both Mendelian and multifactorial. For example, mutations in the BRCA1 gene are associated with the development of breast and ovarian cancer and exhibit an autosomal dominant pattern of inheritance. The mutation places the person at greatly increased risk of developing cancer, but some women with such a mutation will never develop breast cancer. This mutation and the associated predisposition demonstrate a Mendelian pattern of inheritance. However, there are other non-Mendelian factors which may influence whether a woman will develop breast or ovarian cancer by a certain age, including lifestyle and pregnancy history. The inheritance of other genetic variants can modify the cancer risk. In other words, the cancer predisposition is inherited in a Mendelian fashion, but the development of cancer in this context is still a multifactorial process.

1.3.3 Non- heritable somatic cell diseases

Not all genetic diseases are caused by heritable mutations. Somatic mutations i.e. mutations limited to non-gonadal tissues, can cause non-heritable or 'somatic' genetic diseases. These are diseases which develop in somatic cells, usually during adulthood, and are not a result of genetic mutations present from conception. Therefore, there is no preceding family history of the disease. Children are not at risk of inheriting this disorder from their parents.

Most cancers are due to somatic mutations which cause aberrant cell division or loss of normal programmed cell death. The gradual accumulation of mutations with age is inevitable and must eventually result in a person developing cancer. However, if one of these cancer-related mutations is present at conception i.e. it is inherited, the mutation will be copied into every cell of the developing person who will be much more likely to develop cancer at a young age. The inheritance of a cancer-related mutation results in a familial predisposition to develop cancer. Other age-related disease such as dementia can also be attributed to the gradual accumulation of genetic errors with age, and the presence of such a mutation at conception can be evident as a familial predisposition to develop dementia.

Commentary

If the genetic code of a fertilised egg was flawless at conception, the process of copying and maintaining the genetic code would still result in the accumulation of genetic errors with age. There may be differences between individuals in the rate at which these somatic mutations accumulate, the differences being due to genetic variations in DNA repair proteins or in the environmental exposure to DNA toxins. The accumulation of mutations with age is relentless and inevitably results in disorders of ageing such as organ failure and cancer. The risk of cancer by the age of 75 years is approximately 33% (Cancer Australia). The presence of a germline mutation results in every cell in that person having this mutation, and so places that person at an increased risk of developing the disease which can occur at an earlier age than sporadic forms of the same cancer.

1.4 What is a genetic test and what information can it reveal?

Genetic tests provide DNA sequence information that can be used to identify mutations or other genetic variants. A classification of genetic tests could be based on the methodology used, the gene tested, or the purpose for which the test is performed. In practice, the most useful classification is based on the purpose of the test or the context in which the test is performed.

Commentary

A challenge bringing modern genetics (and genomics) practice to the bedside or the health professional's consulting room is the complex terminology used. This is illustrated by the term 'predictive' genetic test. Alternative descriptions used (some of which have subtle differences in interpretation) include: presymptomatic genetic test; susceptibility/pre-dispositional genetic test; and in terms of family testing or DNA screening the term 'cascade' testing can appear. Throughout this Information Paper the term 'predictive' genetic test is used because it best illustrates what the genetic test is attempting to do. It is acknowledged that 'presymptomatic' genetic test is a better descriptor but 'predictive' has a clearer meaning to health professionals and the public with less experience in genetic testing. All terms above refer to genetic testing of individuals or family members who have no signs or symptoms of a clinical disorder. However, finding a mutation in the appropriate gene increases their long term risk of getting this disorder. 'Predictive' is used by some when the variation is almost certain to lead to disease e.g. familial adenomatous polyposis; 'Presymptomatic' is used by some when the variation might or might not lead to disease e.g. breast cancer testing using BRCA1 or BRCA2; 'Susceptibility/pre-dispositional' is used by some when the genetic test provides some absolute or relative risk over a lifetime that a genetic disease will develop e.g. type 2 diabetes which is associated with over 30 genes all of which have very small effects individually and so the final risk calculated might be quite low. Alternatively, some use this term instead of 'presymptomatic'. Testing or screening asymptomatic family members for a DNA mutation associated with a genetic disease is also predictive genetic testing, but in the context of tracking the disease through a family it is also called 'cascade screening'.

1.4.1 Types of genetic tests

- *Somatic cell genetic testing* involves testing tissue (usually cancer) for non-heritable mutations. This may be for diagnostic purposes, or to assist in selecting treatment for a known cancer.
- *Diagnostic testing for heritable mutations* involves testing an affected person to identify the underlying mutation(s) responsible for the disease. This typically involves testing one or more genes for a heritable mutation.
- *Predictive testing for heritable mutations* involves testing an unaffected person for a germline mutation identified in genetic relatives. The risk of disease will vary according to the gene, the mutation and the family history.

- *Carrier testing for heritable mutations* involves testing for the presence of a mutation that does not place the person at increased risk of developing the disease, but does increase the risk of having an affected child developing the disease.
- *Pharmacogenetic testing for a genetic variant* that alters the way a drug is metabolised. These variants can involve somatic cells or germline changes. Even if these variants are heritable (i.e. germline changes), the tests are usually of relevance to genetic relatives only if they are being treated with the same type of medication.

Examples

There are some situations in which it may be beneficial to test genetic relatives for heritable pharmacogenetic variants. For example, malignant hyperthermia (MH) is a rare complication of anaesthesia. MH susceptibility is inherited in an autosomal dominant trait. MH is genetically heterogeneous with variants in several different genes influencing susceptibility within individual families. Other pharmacogenetic testing is best performed on an individual case-by-case basis. For example, abacavir is a drug used to treat HIV and AIDS. Hypersensitivity reaction to abacavir is strongly associated with the presence of the HLA-B*5701 allele. HLA-B*5701 screening is recommended for individuals with HIV and AIDS to reduce the risk of a hypersensitive reaction (Mallal et al 2008). There would be no benefit in screening family members if they are not taking abacavir.

The type of genetic testing and the associated ethical concerns are principally determined by the clinical context in which the test is done rather than by technical aspects such as the gene being tested or the method used by the laboratory.

Examples

The same laboratory method and target gene can be used in different contexts for different clinical purposes. For example, mutation analysis of the BRCA2 gene may be used to identify somatic (non-heritable) mutations in the tumour tissue of a patient with breast cancer (somatic genetic testing). Analysis of the same gene (and by the same method) of the BRCA2 gene in normal tissue (usually blood) of a patient with familial breast cancer may demonstrate that the patient has a familial predisposition to develop this type of cancer (diagnostic testing). Analysis of the BRCA2 gene in an unaffected female genetic relative may identify a woman who is at greatly increased risk of developing cancer in the future (predictive testing). Analysis of the same gene in an unaffected male genetic relative may identify a man who is not at greatly increased risk of developing breast cancer, but whose daughters could be at greatly increased risk of developing breast cancer (carrier testing). Somatic testing and diagnostic testing may also identify affected women whose cancers are specifically susceptible to certain chemotherapeutic agents such as PARP inhibitors (pharmacogenetic testing). Note that each of these situations potentially raises different clinical and ethical considerations, even though the target gene and method used by the laboratory are the same.

1.4.2 Genetic information

A genetic test necessarily reveals genetic information. If this test identifies germline genetic variants, the genetic information is of potential relevance for the patient's family. If the test reveals somatic genetic variants, the genetic information is of no direct relevance to the patient's genetic relatives. A single DNA sample contains copies of all of the heritable genetic variants in an individual. The sample can be used to identify an individual and be stored and re-tested over time leading to a progressive accumulation of information.

Genetic information can also be inferred from other sources. The patient's family history, or assessments such as clinical examination, medical imaging, or non-genetic tests, may allow the health professional to draw inferences about the underlying genetic status of a patient and of the patient's genetic relatives or ethnic group.

In other words, genetic information may be revealed by:

- studying entire chromosomes, RNA, proteins, substances in blood or tissues, and medical imaging techniques
- clinical examination leading to diagnosis of a genetic disease
- studying a person's family tree, which allows genetic inferences to be made about a person on the basis of clinical findings or tests from other genetic relatives.

Genetic information can relate to a disease that is:

- *clinically apparent* - a genetic test is performed to confirm a diagnosis in someone who has features of a particular disease; or
- *latent* - a genetic test is done on an unaffected person to determine the likelihood that he or she will develop the disease in the future.

Information from genetic testing can be very precise (e.g. that a mutation is or is not present), but this does not necessarily provide a precise estimate of the risk or severity of disease.
An individual's genes are only one of the factors that determine his or her future health (albeit a substantial factor in many cases). Genetic susceptibility does not always imply genetic inevitability:

- While the presence of a mutation can help to confirm a diagnosis, it does not necessarily mean that there is a causal relationship between the mutation and the patient's disease—a mutation does not necessarily cause disease, and a disease may be due to a mutation in one of a number of genes.

Examples

For example, a woman in her early 20's has a family history of Huntington disease (HD). She decides to have genetic testing to determine if she has inherited a mutation in the HD gene as she is worried she is beginning to show symptoms of the disease. She has been suffering from depression for the last year. If she does have a mutation in the HD gene there may be a causal relationship between the mutation and her depression. However her depression could be unrelated to the DNA mutation and due to some other reason.

- The presence of a mutation can also indicate that a person is at increased risk of a disease, but in reality only a proportion of those with a particular disease-related mutation or other variant will develop the disease. Key information, including other risk factors such as the environment or other genes, will often be lacking. Such tests do not usually predict when symptoms of the disease will develop and may be unable to predict which features of the disease will occur or how severe the disease will be. In reality the person may develop none, any one, or any combination of symptoms over a lifetime and at any age.

Examples

Context determines the clinical significance of a genetic test.

The BRCA2 gene is long (approximately 13,000 nucleotides) and complex. Polymorphisms (benign variations) in this gene are common in the general unaffected population. Analysis of the gene in a woman with familial breast or ovarian cancer and a strong family history may reveal a heritable (i.e. germline) pathogenic variant (mutation) that could account for the patient's personal and family history of cancer. However, breast cancer is a common disease and some carriers of a BRCA2 mutation will develop breast cancer by chance alone and not because of the familial mutation. Similarly, some genetic relatives will develop breast cancer despite not carrying the family's BRCA2 mutation. Defining the relationship between a genetic variant and disease may be even more difficult if the pathogenicity of a BRCA2 variant is unclear. Approximately 15% of women with familial breast cancer who have BRCA2 testing will have a variant identified that could be pathogenic or could be a rare benign variant. It may be difficult or impossible for the laboratory to determine the clinical relevance of such a variant.

- It can be difficult to distinguish a benign variation in DNA sequence (polymorphism) from a mutation. The DNA of two unrelated people will differ at millions of polymorphisms, and genetic relatives will have many polymorphisms in common. The presence of a rare variant in a gene in affected genetic relatives does not necessarily mean that it is the causative mutation; it may simply be a polymorphism that they have both inherited. It may be straightforward for the laboratory to provide an analytical result (a certain DNA variant is present) but difficult for the laboratory to provide an interpretation (it could be a mutation or be a polymorphism), and therefore the test may have no clinical utility (the health professional cannot use the result for decision-making).

Examples

The relationship between gene and disease is not simple.

The majority of young adults with a phaeochromocytoma have a non-familial disease i.e. the diagnosis represents the gradual accumulation of somatic mutations in a cell of the adrenal medulla. The diagnosis of sporadic phaeochromocytoma does not usually carry medical implications for the genetic relatives of the patient. However, an underlying heritable mutation in any one of a number of genes can be identified in up to 25% of young adults with a phaeochromocytoma. Phaeochromocytoma may be the presenting diagnosis in a person with an inherited (germline) mutation in any one of the following genes: VHL, RET, NF1, SDHB, SDHC, or SDHD. The subsequent clinical consequences for the patient and genetic relatives vary markedly according to which gene is involved. A patient with a heritable VHL mutation is at high risk of developing renal cancer and haemangioblastomas of the central nervous system. A patient with a heritable RET mutation is at high risk of developing medullary thyroid cancer and hyperparathyroidism. Mutations in NF1 cause neurofibromatosis type 1. Heritable mutations in SDHB, SDHC, or SDHD cause hereditary paragangliomas and can increase the risk of renal cancer. These medical implications apply both to the index patient (who presented with phaeochromocytoma) and to genetic relatives who have inherited the causative mutation.

The main outcome of future developments in genetics will be to provide more accurate and comprehensive information than is available now, although that information will still be probabilistic (increasing the accuracy of predictions of disease risk) rather than deterministic (indicating whether the patient will or will not develop the disease).

Limitations of genetic tests

- Current methods do not detect all mutations that might occur in the gene.
- Genetic testing may not produce a clinically useful result if a variant of unknown clinical significance is identified.
- Genetic tests provide probabilistic, not deterministic, information and so do not necessarily determine clinical outcome.

Examples

Results of genetic tests can often consist of risk assessments and this type of genetic information is probabilistic (certain degree of likelihood) and not deterministic (without doubt). For example, a 28 year old women presents for counselling and testing because of a BRCA1 mutation which is in her family. Detection of a germline mutation will indicate that she is at an increased risk of developing breast and ovarian cancer. However the absence of a mutation does not mean she will definitively not develop these cancers. It may turn out that she carries a mutation in the TP53 gene instead or that environmental factors may contribute to her risk of developing these cancers.

- There may be a number of different genes that can cause the disease; some of these genes may not have been identified as yet.
- A mutation in one gene can cause different diseases.

Examples

A man has a mutation in the cystic fibrosis transmembrane regulator (CFTR) gene. He has been clinically diagnosed with cystic fibrosis (CF) and displays symptoms such as recurrent infections of the respiratory tract and deficiency of pancreatic enzyme secretion. As well as having CF the man is infertile. This has also been caused by the same mutation in the CFTR gene resulting in genital tract abnormalities (congenital bilateral absence of the vas deferens). Some infertile males with the same abnormality in the vas deferens do not have clinical features of cystic fibrosis. This is explained by finding mutations with mild effects in the CFTR gene and so only sufficient to cause infertility.

- Genetic tests, like any medical test, are subject to laboratory error.

1.5 Changing nature of genetic testing

Increased diversity of tests—Approximately 20,000 human genes have been identified, but only a few are currently tested in clinical practice. The OMIM catalogue includes information on a growing number of genes (currently over 12,000), as well as the Mendelian diseases for which the genetic basis is known and those for which the gene has yet to be identified. The most comprehensive listing of laboratories providing genetic tests (**www.GeneTests.org**) documents a trebling of the number of gene tests being offered in the last decade. There are 1,787 genetic tests available, of these approximately 400 types of tests were provided in Australia in 2006 (RCPA 2008). Approximately 1% of these types of test were funded by Medicare; the remainder were funded by the patients themselves or through State and Territory governments.

Increased volume of testing—There is limited information about the changing volume of genetic testing in Australia. In 2007, the volume of Medicare-funded medical testing (of all types) was 7% higher than during 2006. However, the volume of Medicare-funded genetic testing increased by 90% during this period. In other words, genetic testing is expanding at a much faster rate than other forms of medical testing (RCPA 2008).

Evolving technologies and approaches—The technologies used for testing are evolving rapidly. For instance, it is likely that conventional cytogenetic analysis, which uses light microscopy to examine for abnormalities of chromosomal number or structure, will be replaced by micro-array analysis, which is much more sensitive. Furthermore, the cost of DNA sequencing has fallen, and the speed has increased by orders of magnitude in the last few years (ten Bosch & Grody 2008).

Commentary

Most analyses of human chromosomes for medical purposes are funded by Medicare. The Medicare regulations restricted funding to tests for determining a patient's karyotype (number and structure of chromosomes) by cytogenetic means. However, in late 2008 the regulation was amended such that funding is provided for determination of a patient's karyotype by any means. A karyotype can be determined by micro-array studies, thereby moving this analysis from the cytogenetic laboratory to a molecular genetics laboratory.

For a general introduction to micro-arrays, see Jaluria et al 2007
www.microbialcellfactories.com/content/6/1/4

It is increasingly recognised that a single disease can be caused by a mutation in any one of a number of genes. By testing for mutations in all of these genes, diagnostic tests for these diseases are improving.

In the past, the identification of a germline mutation primarily assisted in confirming a diagnosis and counselling genetic relatives. But the presence of a specific mutation is increasingly the basis for selecting therapy, giving the test both a diagnostic and a pharmacogenetic/prognostic role.

Rapid changes in testing for somatic mutations—It is likely that the pattern of somatic changes in a cancer can be used to identify which cancers have a familial basis, without any family history being available. This has already been reported in relation to BRCA1 breast cancers (Hedenfalk et al 2001), and would introduce family-wide ethical issues into somatic testing. In addition, the methodologies for somatic testing are changing rapidly, with the introduction of micro-array analyses that have yet to be addressed in terms of standards and quality assurance.

Examples

The pattern of somatic mutations identified in a cancer can be used to predict prognosis or select the most appropriate therapy. The pattern can also be quite specific for the tissue of origin. In patients with disseminated adenocarcinoma from an unknown primary, micro-array analysis of tumour tissue can identify a particular pattern of mutations that identifies the tissue of origin. For an example, see Tothill et al 2005 **http://cancerres.aacrjournals.org/cgi/content/abstract/65/10/4031**

Increases in carrier testing—This testing is likely to increase as the cost of multi-gene carrier screening falls.

Rapid changes in pharmacogenetic testing—Absorption, kinetics, metabolism, effectiveness, and risk of side effects of a medication are different for each person, with much of this variation determined by genetic factors. The identification of the relevant genetic variants for each drug has the potential to dramatically alter the choice, dosage, and duration of drug therapy for an individual patient. Multiple genes are involved and effective pharmacogenetic testing will probably require multi-gene assays (and computer algorithms) to determine optimal doses and risks of adverse reactions.

The risk of medico-legal consequences if these tests are not done before initiating therapy has been raised, although this is not currently an issue in Australia as the Therapeutic Goods Administration (TGA) has not required such information on drug labels. The US Food and Drug Administration (FDA) now include pharmacogenetic information on 10% of labels of approved drugs, with a requirement for genetic testing prior to prescribing in some cases but not all (see Appendix E).

Commentary

The success of pharmacogenetic testing is reliant upon the availability of quality genetic tests that accurately determine drug response and drug effectiveness and algorithms that allow genotype based information to be translated into prescribing recommendations. Assessing the likely benefit of pharmacogenetic testing undoubtedly rests upon the clinical utility of the test. This is a rapidly changing area of medical testing, and numerous resources are available: **www.pharmgkb.org/index.jsp**

1.6 Overview of the genetic testing process

The process of genetic testing incorporates:

- pre-test procedures such as information gathering, discussion of options and patient education
- decisions by the health professional and patient about the clinical question being asked
- selection of the genetic test
- characteristics of the test (or test performance)
- sample requirements
- analysis of the sample by the laboratory professional
- interpretation of the result by the laboratory professional
- reporting and distribution of reports to relevant health professionals
- interpretation of the result by the health professional, and subsequent decision-making by the health professional and patient
- follow-up and support of the patient
- follow-up of genetic relatives (if appropriate).

Most genetic testing occurs within a clinical service, although there are some genetic tests offered directly by laboratory professionals to the consumer (see Section 7.1). Some genetic tests are also offered as part of a research protocol (see Section 7.7).

The genetic testing process is described in more detail in Part B.

2 Ethical, legal and social issues

Developments in genetics pose ethical questions for individuals and families, as well as for society. Genetic information raises novel ethical issues because it is both personal and shared with family members. It may also be shared with other members of an ethnic or cultural group. Genetic information can also be predictive of future disease development.

Resources

The ethical, legal, and social issues associated with genetic testing (often referred to as ELSI), have been a prominent feature of genetic debates in recent years. There are extensive resources devoted to these issues including:

Essentially Yours: The Protection of Human Genetic Information in Australia
www.austlii.edu.au/au/other/alrc/publications/reports/96/index.htm

www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml

www.library.nhs.uk/GENETICCONDITIONS/ViewResource.aspx?resID=59911

Ethical, legal and social issues are also a focus of discussion for the Human Genetics Commission in the UK (**www.hgc.gov.uk**) and the Human Genetics Advisory Committee in Australia (**www.nhmrc.gov.au/about/committees/hgac/index.htm**). Further details regarding the Australian Health Ethics Committee can be found at **www.nhmrc.gov.au/health_ethics/index.htm**

Ethical considerations in genetic testing relate to the type of information that the test provides rather than the test methodology. The ethical principles are the same, whether the diagnosis of a heritable predisposition is made by DNA analysis, other laboratory investigation, clinical examination, or ascertainment of family history. These ethical considerations are increasingly relevant with the dramatic growth in capacity to make diagnoses (or to predict the likelihood of developing the disease) through genetic testing.

2.1 Ethical issues

The ethical consequences of any form of medical testing also apply to genetic testing. For example, if a genetic test is being done to assist in the diagnosis of an affected patient, there is the same need for patient understanding, consent (implied or explicit), and respect for confidentiality as in any diagnostic test.

However, two characteristics of genetic testing can raise distinct ethical issues.

- As discussed in Section 1.4.2, the test result may provide only an indication of potential risk of disease; the test result on its own gives the person being tested no tangible context. The medical and ethical significance of genetic testing is dependent on the context in which the testing is being considered.

Examples

The predictive power of a genetic test can be striking. For example, an apparently healthy baby boy with an identified mutation in the DMD gene will develop progressive muscular dystrophy (Duchenne muscular dystrophy) by five years of age and has a lifespan of approximately two decades. But it is important to note that this predictive power is not a feature of all genetic tests. For example, a healthy young woman in the general Australian population has a lifetime risk of developing breast cancer of approximately 10%. If a young woman is shown to carry a germline BRCA2 mutation, her risk of developing breast cancer is approximately 50%; the risk is increased, but there remains a 50% chance of her never developing breast cancer. There are many genetic variants associated with a small increase in the risk of disease; the majority of people carrying such a variant will never develop the disorder in question.

- The test result may carry potentially significant implications for other family members who may not have been involved in the test process. This raises issues of:

Autonomy: the individual decides whether the test should be done.

A person should have the freedom to choose whether to proceed with a genetic test. It is inappropriate for a person to be pressured into having (or rejecting) a genetic test. This principle of autonomy is challenged in situations in which family members may, albeit with good intentions, seek to make a decision on behalf of an individual. Autonomy is also the principal consideration underlying the general reluctance to do genetic tests during childhood to identify a predisposition to develop adult-onset disease (Borry et al 2009). In such a situation, there is no medical requirement for the disease predisposition to be identified during childhood, and the child does not have the maturity or legal status to take responsibility for the decision to have the genetic test.

Confidentiality: the health professional protects the privacy of the individual.

A person should have control over the release of personal genetic information to other people. Genetic information may carry current and future consequences for both the individual and family. Confidentiality is a well recognised principle when applied to medical information, but health professionals must recognise that confidentiality regarding genetic information extends to include family members. Genetic information should not be provided to other health professionals, family members, or third parties without the express permission of the patient.

Beneficence: what may be a beneficial result for the patient may be harmful for a genetic relative.

A medical intervention, whether it be a diagnostic test or treatment, is selected on the basis that it would be of benefit to the patient. Beneficence in genetic testing may not be as clear-cut. For example, a person with a severe familial dementia is unlikely to directly benefit from the genetic test which identifies the germline mutation responsible. However, this information may be of considerable benefit for family members who wish to know their own genetic status and make significant personal decisions. In this example, the investigation is being performed principally for the benefit of people other than the patient. This is not necessarily inappropriate or unwelcomed by the patient, but it is important that the beneficiaries of an investigation are considered and identified.

Justice: ensuring appropriate access to genetic testing and the results of genetic tests.

In Australian society, there is an expectation that people who need a standard medical investigation can access that investigation. This principle of 'equity of access' is one aspect of justice in relation to medical genetic testing. Another consideration is the extent to which a person has a right to access the result of the medical genetic tests performed on a genetic relative (see Section 2.2.1 for more discussion).

It is important to note that not all genetic tests require special ethical consideration. For example, a genetic test to detect somatic variants in tumour tissue does not carry medical consequences for family members, and does not require special ethical consideration.

Commentary

The distinction between genetic tests that require special consideration versus genetic tests that require only the same consideration as other medical investigations is a key consideration for Australian regulatory authorities. Australian medical laboratories are accredited against standards developed by NPAAC. NPAAC classifies genetic tests according to the ethical and technical complexity, and requires pre-test genetic counselling for the more challenging investigations (see **www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-nad.htm and Section 2.1**).

2.1.1 The uniquely personal and identifying nature of genetic information

Genetic information is intrinsically personal as each of us has a unique DNA sequence that is a major contributor to our individuality. By birth, even the sequences of identical twins have differences. Information about the genetic sequence, and the inferences that can be drawn from it, can have a great impact on an individual in terms of perceptions of health and body image, and perceptions of worth as an individual, family member and member of society.

Commentary

Identical twins are usually considered to be genetically identical. However there can be differences between the genetic sequences of identical twins. When comparing individual cells between identical twins, there will be an accumulation of different genetic errors that occurred during cell division. But the DNA sequence, averaged over many cells (as would be found in a small blood sample), will be the same as at conception. Nonetheless, the cell-by-cell differences will play a role in the later development of diseases such as cancer, and twins are likely to have different medical histories. Identical twins can also demonstrate significant differences in gene activity, even if the average gene sequences are identical. Epigenetic modifications such as DNA methylation (see Section 8.5) can alter gene activity and can differ between twins.

The ability to perform tests to reveal the DNA sequence can create the need to make decisions, sometimes of great significance, for example:

- deciding whether to find out if symptoms of a family illness are likely to appear at a future time
- choosing between reproductive options and techniques, such as pre-implantation diagnosis, prenatal diagnosis, or not having biological children.

2.1.2 The shared nature of genetic information

Genetic information about one person may also reveal information about genetic relatives, in past, present and future generations. For example, an inherited genetic variant identified in a person has, by definition, the potential to be passed on to that person's children, has usually been inherited from the person's parents, and may also be present in other genetic relatives (e.g. siblings, cousins).

If a heritable mutation is identified, the tested person may be asked to communicate relevant information about this finding to genetic relatives. Generally, individuals are prepared to do this. However, this can raise unexpected ethical dilemmas as it requires an individual to balance the loss of personal privacy involved in disclosing the genetic information derived from a test, against the benefit to genetic relatives from the knowledge that they might have inherited a genetic predisposition to a significant health problem. Genetic information can have an impact on how family members relate to each other; it can strengthen some relationships and weaken others, and can potentially change existing social and legal obligations within families.

The follow-up of test results with patients and family members is discussed in Section 6.4.

2.2 Potential implications of test results on patients and families

The type of genetic information revealed through testing varies widely, depending on the probability that someone with the mutation will develop the disease, whether the disease is serious or life threatening if it does develop, and whether it is preventable or treatable. For example, genetic information may:

- be considered by the health professional or the patient as being straightforward
- imply an increased risk but no certainty of developing a disease
- have serious implications for present and future generations
- relate to a disease that is presently incurable but has serious manifestations that can be ameliorated
- have financial and life insurance implications
- have the potential to cause or alleviate significant psychological harm.

Genetic testing can have profound implications for individuals and their families. The possible implications, including the fact that testing may provide information of significance to other family members, should be discussed before testing, if appropriate (see Chapter 4).

2.2.1 Genetic relatives

Inadvertent release of information

Health professionals often discuss diseases in the context of the family's experience of the disease. The family health history may be updated at the time a family member is consulted and, when explaining the disease to that person, the history or the clinical features of another genetic relative may be used to illustrate a point (eg how the disease is inherited, and who might be at risk). Health professionals can readily make the incorrect assumption that there has been a free flow of information about a genetic disease within the family. However, this can result in inadvertent breaches of privacy/confidentiality and care should be taken. Sometimes the transfer of information will have been postponed pending an appropriate opportunity or there may be communication difficulties within the family.

Commentary

If a clinical service has had contact with more than one member of a family, the record of the family's experience of the disease that is held by the service may be more comprehensive than is known by any one member of the family. It is essential that this pooled information is used to guide risk assessment and genetic testing in the family, but the specifics as to which person had what disease may need to be withheld from family members.

The specific legislation and regulations pertaining to privacy in health care vary according to jurisdiction (State or Territory) and whether the healthcare professional is operating in the public or private sector. Information regarding national and state privacy legislation can be found at **www.privacy.gov.au/law**. Health professionals should also seek advice from local authorities.

Disclosure of genetic information to genetic relatives without consent

In Australia, privacy protection in health care comes from common law duties of confidentiality, complemented by statutory requirements regulating the collection, storage and use of information. The *Privacy Act 1988 (Cwlth)* (the Privacy Act) contains privacy principles that cover the public and private sector, and similar principles are found within the various State and Territory legislations. This prohibits health professionals from disclosing personal information without an individual's consent.

There is an exception in this legislation which allows for disclosure without consent if there is a serious *and* imminent risk. However, as noted by the Australian Law Reform Commission, there are circumstances particularly with predictive testing where the imminent element is not present, yet there is a serious risk to health in respect to genetic relatives. In response to this the Privacy Act was amended in late 2006 to remove the *imminent* requirement for disclosure of genetic information to genetic relatives provided there was a serious risk to the person's life, health or safety.

Resources

The *Privacy Legislation Amendment Act 2006* is available at **www.comlaw.gov.au/ComLaw/Legislation/Act1.nsf/all/search/592A1E3B62096FD6CA2571ED0012E038**

The ALRC & AHEC report Essentially Yours (2003) discusses privacy concerns at **www.austlii.edu.au/au/other/alrc/publications/reports/96/**

For this amendment to become operational it was necessary for the NHMRC to develop guidelines for health professionals working in the private sector to explain the circumstances in which this disclosure without consent could take place. These guidelines then needed to be approved by the Privacy Commissioner. They were approved on 15 December 2009 (see **www.nhmrc.gov.au/publications/synopses/e96syn.htm**).

The 2006 amendment to the Privacy Act has the following clinical implications (Otlowski 2007):

- it deals with the Commonwealth Act and so is only relevant to health professionals in the private sector; to cover health professionals working in the public sector, comparable changes to State and Territory legislation will be needed as well as changes to the Information Privacy Principles
- it does not mandate that health professionals must disclose information in these circumstances
- it only considers privacy issues and so health professionals are still bound by their common law obligation of confidentiality.

Reasons for not disclosing genetic information

In general, family members who are informed of their potential risk and the options available to them appreciate the approach and the underlying concern for their welfare. However, it cannot be assumed that everyone will wish to know.

Sometimes, family members have stated that they do not want to discuss the family's illness because of the problems and difficult decisions that are associated with it and the emotional consequences of talking about them. For example, they may find it offensive to be approached with information about the availability of prenatal diagnosis. In such circumstances, it would fail to respect that person's autonomy by insisting on the provision of information.

A more common situation is that family members' views are not known, or that they dislike discussing health matters in general. If people are kept ignorant of their situation, they will have no opportunity to consider the problem and to decide how to proceed. There is a strong argument for informing such people in a sensitive way, almost always through a family member with whom they relate well. In particular circumstances it may be more appropriate for a health professional to undertake the task, having been introduced by a family member when possible and having had permission from the person for contact to be made.

Genetic information may have implications other than health implications. For instance a diagnosis of a genetic disease or identification of increased risk for a disease may affect whether a person is eligible for financial services such as a mortgage or other loan and personal insurances such as life, income protection or disability insurance. A person might make a reasonable choice not to know their genetic risk status for disease until some time after matters of that kind are resolved. A parent might make a reasonable decision not to have a child tested, or him or herself tested, because such information about the child or about the child indirectly through testing of the parent, may limit those opportunities for the child in the future.

Deceased individuals

Processes for the handling of genetic information about, or material from, a deceased individual vary across jurisdictions. In the absence of instructions, it may be released to family members with the consent of the senior available next of kin. In general, family members will request genetic information because it is of potential significance for their future health and/or that of their children. Caution should be exercised before releasing information not related to health care (e.g. paternity or maternity information).

2.2.2 Non-genetic relatives

Non-genetic relatives (e.g. spouses, partners or those related by marriage) are not at increased risk of developing the genetic disease. However, it may be appropriate that they be informed if their present or future children could inherit the disease. As with genetic relatives, individuals will usually provide the appropriate information to the relevant people. Health professionals should not release such information to relatives who are not genetic relatives without the consent of the person to whom the information relates.

2.2.3 Misattributed paternity or maternity

Most cases of genetic testing will not detect non-paternity or non-maternity. This is because most genetic testing is looking for a specific mutation and the absence or presence of that mutation in the individual being tested will not necessarily reveal non-paternity or non-maternity. However, it might be revealed in certain testing situations. If the genetic test and clinical context are such that non-paternity or non-maternity could be identified this matter should be discussed.

Misattributed paternity may also be identified with non-genetic tests, such as if a child is blood-typed and shown not to have inherited a paternal blood type. There are some settings in which the genetic testing process involves tracking inheritance of genetic changes in a family rather than testing the gene itself (linkage analysis).

It is important to note that there are plausible, albeit rare, biological processes which could account for suspected cases of non-paternity or non-maternity. Non-paternity or non-maternity may be the most likely explanation, but expert advice should be sought before concluding that it is the correct explanation.

In situations in which non-paternity or non-maternity has been identified, possible courses of action may include: not revealing the misattributed paternity or maternity; revealing it to the mother alone; revealing it to the mother and father; and revealing it to the father alone. Non-paternity or non-maternity should be disclosed in only the most exceptional circumstances, as this may cause serious harm to individuals and families.

Examples

A man has genetic testing to determine the presence of a specific mutation in the PS1 gene which has been detected in his father who is showing clinical symptoms of early onset Alzheimer disease. As mutations in this gene show an autosomal dominant pattern of inheritance (there is a 50% chance the man will inherit the mutation and there is a 50% chance he will not inherit the mutation), the absence of the mutation does not mean that this man is not his father's son. Alternatively the presence of a mutation in a son and not the father or mother does not definitively indicate non-paternity or non-maternity. This may be because there is a high incidence of de novo mutations in this particular gene.

Conversely, there are cases of genetic testing in which non-paternity or non-maternity could be identified. It is more likely that misattributed paternity or maternity will be detected in genetic testing for autosomal recessive diseases. For example, ß-thalassaemia is an autosomal recessive disease in which a man who is homozygous for the disease should have a child who is at the least heterozygous (a genetic carrier) for ß-thalassaemia. If the child is not a carrier then this would probably be due to non-paternity—assuming that blood samples tested were the correct ones. It is important to note that mislabelling or switching of blood or DNA samples remains the most common cause of laboratory error and should always be considered before assuming misattributed paternity or maternity.

2.2.4 Adopted children and children conceived with donated gametes

The genetic status of adopted children may have significant and long-term medical implications for them and their adoptive and biological parents. Occasionally an adopted child will be the first person in the biological family to manifest symptoms of a genetic, and potentially inherited, disease. It will then be appropriate for the adoptive parents to try to inform the biological parents. The confidentiality provisions of State and Territory Adoption Acts are relevant in such situations.

Adoptive parents receive certain personal and family health information about a child's biological parents, primarily to assist them in making provision for the future health care of the child. Providing such information could potentially influence whether or not the adoption proceeds. Medical information may be provided upon request so long as it does not identify the birth parent/s. If the result of a predictive genetic test on a birth parent is available it may be provided to the adopted parents, either in a non-identifying form to protect the identity of the birth parent or with the birth parent's consent.

Examples

Some diseases such as cardiomyopathy are present in the general population as sporadic non-familial disorders. They can also be caused by a mutation in any one of a number of genes. Genetic testing to identify the causative mutation can be expensive, and it may be restricted to situations in which a number of genetic relatives have the same cardiomyopathy. This limitation is in place because it is more likely the affected genetic relatives have a familial form of cardiomyopathy and that genetic testing will identify the causative mutation. However, an adopted person does not necessarily have information about the diseases affecting genetic relatives in the birth family and may not be eligible for such testing. The result of such testing may be of great clinical significance for the adopted patient as well as his/her children.

2.3 Non-consensual genetic testing

The ALRC/AHEC Report *Essentially Yours* (ALRC &AHEC 2003) recommended the creation of a new criminal offence for non-consensual genetic testing. In November 2008 the Commonwealth Government released a discussion paper *Non consensual genetic testing* to seek public comment. The discussion paper defines non-consensual genetic testing as: "taking bodily samples and genetically testing them without the knowledge or consent of the individual from whom they have been obtained" (e.g. saliva left on a glass or cheek cells left on a toothbrush). No further information about the status of this model law was available in late 2009. In the UK, a new law came into effect in 2006 creating the offence of 'DNA theft'.

The issue of non-consensual testing is relevant in both medical and non-medical settings. As noted above, autonomy is a key principle in considering ethical requirements associated with genetic testing, and a person should not have a genetic test without his/her consent. Non-consensual genetic testing is also a consideration in parentage studies; tests for paternity should only be performed with consent. With the advent of direct to consumer (DTC) testing (see Section 7.1), the collection of a sample for genetic testing is left to the consumer requesting the test. The laboratory is unable to confirm that the sample actually came from the consumer requesting the test. In the context of medical testing, there is independent professional oversight of the sample request and collection to ensure that sample is collected from the person named on the request form; there is no such oversight in the context of DTC testing. It is important that the legal status of non-consensual genetic testing in Australia is clarified.

Resources

The discussion paper and related information can be found on the Attorney General's Department website at **www.ag.gov.au/www/agd/agd.nsf/Page/Modelcriminalcode_Non-ConsensualGeneticTestingDiscussionPaper**

2.4 Potential misuse of genetic information

To inform risk assessment, there are often greater pressures to discover, gain access to and use genetic information than is the case for traditional personal or family health information. The predictive nature of genetic testing makes it of particular interest in situations where information about a person's future, even though imprecise, could be incorporated into decision-making involving commercial interests (e.g. life insurance or employment; see Sections 7.4 and 7.5). Its novelty also creates a risk that both the information and its implications will be misunderstood by health professionals, the families of those tested, and others in the community who have access to the information, and as a consequence, that it will be misused. Community and professional education, and the ready availability of information when needed, can minimise misunderstanding of, overreaction to, and misuse of genetic information.

Resources

These issues are considered at length in ALRC/AHEC Essentially Yours (ALRC & AHEC 2003) at **www.alrc.gov.au/inquiries/title/alrc96/index.htm**

3 Regulatory framework

Governments in Australia and overseas have increasingly recognised the need for regulation to ensure the quality of health care services provided, including the growing field of medical genetic testing, and to control the utilisation of medical resources to contain costs.
This chapter provides a brief summary of regulatory considerations for medical genetic testing in Australia as they apply in 2009, bearing in mind that the regulatory framework is changing.

3.1 Funding of genetic tests

Most pathology tests attract a Medicare rebate provided that they have been requested by a registered health professional and the test is carried out in a National Association of Testing Authorities (NATA)/Royal College of Pathologists Australia (RCPA) accredited laboratory. However, only a small proportion of funding for genetic tests in Australia comes from Medicare. Only 1% of the different types of genetic tests provided in 2006 were funded by Medicare; these high volume tests accounted for only 25% of the total number of assays (RCPA 2008). The majority of tests are paid for by the State and Territory health departments, using a range of mechanisms including cost-recovery. Some genetic tests are only available if the patient pays directly. Other genetic tests may only be available through overseas laboratories.

Resources

The genetic tests rebated by Medicare are listed at
www.9.health.gov.au/mbs/search.cfm?cat1=147&cat2=156&cat3=&adv=

3.2 Evaluation of tests

3.2.1 Evaluation of tests for MBS funding

Genetic tests undergo the same evaluative process as more conventional pathology tests before they can be paid for via Medicare. This evaluation of effectiveness, safety and cost-effectiveness is managed by the Medical Services Advisory Committee (MSAC) of the Australian Government Department of Health & Ageing. This process does not necessarily examine ethical, legal or social issues.

Resources

Details about the assessment process used by MSAC can be found at **www.msac.gov.au/**

There is active debate internationally about the best way to evaluate the efficacy of single-gene genetic tests. A comprehensive model involving assessment of the analytical validity, clinical validity, clinical utility, and ethical legal social issues associated with a test (ACCE) has been proposed. Not surprisingly, multifactorial diseases that involve multiple genes are even more challenging in terms of assessment of efficacy.

Resources

The ACCE approach is described at **www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm.**
A modified ACCE assessment has been proposed (Burke & Zimmern 2007) available at
www.phgfoundation.org/pages/work7.htm#acce

The formal evaluation of the utility of a genetic test does not necessarily translate into appropriate use of the test in clinical practice. The Medicare Benefits Schedule (MBS) specifies the indications for the genetic tests listed to limit funding of the test to these clinical settings. There have been few assessments of whether health professionals comply with this requirement.

Commentary

Mutations in the HFE gene cause hereditary haemochromatosis, one of the most common genetic disorders among Caucasians. Genetic testing of the HFE gene is rebated by Medicare (item 73317) under the following conditions:

(a) the patient has an elevated transferrin saturation or elevated serum ferritin on testing of repeated specimens

(b) the patient has a first degree genetic relative with haemochromatosis

(c) the patient has a first degree genetic relative with homozygosity for the C282Y genetic mutation, or with compound heterozygosity for recognised genetic mutations for haemochromatosis.

One Australian study found that only 50% of the HFE genetic tests requested fell within the Medicare indications (Gillett et al 2007) available at **www.mja.com.au/public/issues/187_06_170907/gil11340_fm.html**

3.2.2 Evaluation of risk of tests

A unique feature of genetic tests is that any one test can be used for multiple purposes with different levels of risk. For example, the same genetic test could be used to:

- screen a population for at-risk individuals (screening)
- confirm a diagnosis in a patient with clinical features of a genetic disease (diagnostic)
- test asymptomatic genetic relatives to predict risk of developing the disease in the future (predictive) or of having an affected child (carrier).

The purpose of the test in a specific situation determines the level of risk of the test (including medical, psychological, social, and ethical risks) and the associated consent process. NPAAC sets standards for medical testing laboratories in Australia, and it has defined two levels of genetic test (NPAAC 2007). Level 1 genetic tests carry similar risks (and require similar consent) as other medical tests. These are typically diagnostic tests, medical screening tests, or tests of cancer tissue (i.e. somatic cell testing) in which the genetic test is just one component of an accepted medical testing process. Level 2 genetic tests are those associated with interpretive, ethical, or consent issues that are peculiar to the identification of a heritable mutation in an apparently unaffected person. These are typically predictive genetic tests. According to the NPAAC Standard, a Level 2 test requires specialist knowledge for the test to be requested and professional genetic counselling to precede and accompany the test.

Resources

For more information on NPAAC standards, refer to **www.health.gov.au/npaac.** The Classification of Human Genetic Testing – 2007 Edition document can be found at **www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-HumanGenTest.htm**

3.3 Education and professional standards

Australia does not have a national curriculum in genetics for trainees in healthcare disciplines. There has been no published assessment of the genetic competencies of new medical graduates in Australia. Studies overseas indicate that new medical graduates have a poor understanding of genetics and are ill-prepared to utilise contemporary genetic testing well (Baars et al 2005a, 2005b). It is likely that the situation is the same in Australia.

Adequate training in genetics is essential for clinical health professionals and laboratory scientists/pathologists. The quality of services provided by genetic testing laboratories is strongly associated with the training and qualifications held by the laboratory director (McGovern et al 1999). The need for additional resources for training in genetics for current and future healthcare professionals is recognised in the UK and the USA (see **www.geneticseducation.nhs.uk** and **www.nchpeg.org**).

The education of the medical workforce was a focus of the ALRC/AHEC Essentially Yours inquiry into the impact of genetic information on privacy and discrimination, as well as ethical and other oversight of medical and scientific research, clinical practice, and the collection and use of genetic databases (ALRC & AHEC 2003). In response to this, the Human Genetics Society of Australasia (HGSA) has produced a document detailing core capabilities in genetics for medical graduates which represents an important step in ensuring that the next generation of health professionals will take on the challenges of genetic and genomic-based medicine. Implementation of the core capabilities will require acceptance by all universities that train medical students.

The training and accreditation of specialist clinical geneticists is undertaken by the RACP. The RACP works closely with the HGSA in determining training requirements and assessment. Certified genetic counsellors are required to have a postgraduate qualification in genetic counselling to receive Part 1 Certification from the HGSA. Genetic counsellors who have Part 1 are called associate genetic counsellors. Part 2 Certification is obtained after completing a logbook of long cases under supervision. Medical specialists in laboratory medicine are accredited by the RCPA. Medical scientists are certified by the HGSA on the basis of academic qualifications, documented experience, and examination.

Commentary

For the purpose of this document the terms genetic counsellor and professional genetic counselling equates to a HGSA certified genetic counsellor (Fellow of the HGSA - FHGSA). A FHGSA genetic counsellor is a health professional with specific training in genetics and counselling who can provide information and support to individuals or families who may be concerned about or have a genetic disease in the family.

Resources

HGSA has recommended a set of core capabilities that should be achieved by all medical graduates, see **www.hgsa.com.au/images/UserFiles/Attachments/CorecapabilitiesingeneticsforMedgrads1.pdf**

For further information on training and accreditation see:

Specialist clinical geneticists (RACP) at **www.racp.edu.au/amtrain/spec/s_cgen1.htm** and **www.racp.edu.au/training/paed2003/advanced/vocational/genetics.htm**

Medical specialists (RCPA) at **www.rcpa.edu.au/Pathology/Disciplines/GeneticPathology.htm**

Medical scientists (HGSA) at **www.hgsa.com.au/Index.cfm?pid=111447**

Genetic counsellors (HGSA) at **www.hgsa.com.au/Index.cfm?pid=111440**

3.4 Accreditation of medical laboratories

Laboratory practice is highly regulated, with quality standards established by NPAAC having to be met for a laboratory to gain accreditation. Laboratories are assessed against the NPAAC standard in a program managed by NATA and RCPA. NATA uses the Australian and international standards (AS ISO15189 for medical laboratories and ISO17025 for non-medical laboratories [see Appendix C]) as the basis for their assessment. The Australian standards are set by NPAAC and constitute a variety of standards addressing general and specific features of medical testing.

Commentary

For further information on accreditation see **www.nata.asn.au/go/accreditation/how-to-become-accredited**

The standard that is specific for genetic testing can be found at **www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-nad.htm**

A key element of laboratory quality and accreditation is the supervision provided in that laboratory. The NPAAC requirements for laboratory supervision is currently undergoing significant review and will be released for public consultation in 2010, see **www.health.gov.au/internet/main/Publishing.nsf/Content/health-npaac-docs-supervision2007.htm**

At present, laboratory accreditation is not always mandatory in Australia. This means that an unaccredited laboratory is legally allowed to provide a genetic test for medical purposes. Accreditation is required if a laboratory seeks a Medicare rebate for medical testing of any type. In other words, accreditation of medical genetic laboratories is currently dictated by the funding mechanism rather than a commitment to accurate test results. In 2006, 17% of all types of tests were available as non-accredited tests and were presumably funded by sources other than Medicare (RCPA 2008).

Commentary

The fact that laboratory accreditation is principally driven by issues of funding, rather than a fundamental commitment to quality, has drawn attention from a number of sources. The ALRC/AHEC Report Essentially Yours (ALRC &AHEC 2003) recommendation 11-1 provides that:

> In order to complement existing pathology laboratory accreditation arrangements, the Commonwealth, States and Territories should enact legislation to require laboratories to: (a) be accredited for any genetic test that they conduct for medical, diagnostic or treatment purposes; and (b) comply with the relevant accreditation standards. The legislation should make provision for exemptions in appropriate circumstances, such as for genetic tests performed by research laboratories.

This recommendation has been supported by legal review of medical testing in Australia which is funded by sources other than Medicare (see **www.healthyactive.gov.au/internet/main/Publishing.nsf/Content/health-pathology-PhillipsFoxReview.htm**). These recommendations are currently being considered by State and Federal Governments.

One of the key requirements of an NATA/RCPA accredited medical laboratory is that tests are only provided in a medical context, and must be requested by and reported to a registered health professional. This essentially precludes an accredited laboratory from soliciting or providing genetic tests directly to consumers. On the other hand, a laboratory providing DTC testing does not require accreditation to provide such tests (unless the tests are rebated through Medicare).

NATA/RCPA does not accredit medical laboratories outside Australia. Overseas laboratories providing genetic testing may be accredited by a local agency, but it may be difficult to determine the type of accreditation and how it was gained. There is no guarantee that accreditation provided overseas is equivalent to that provided by the NATA/RCPA process.

Resources

For further information on NPAAC requirements see **www.health.gov.au/internet/main/publishing.nsf/Content/npaac-nucleic-acid-toc~npaac-nucleic-acid-diag~npaac-nucleic-acid-gen**

3.5 Regulation of genetic tests

In addition to accreditation of the laboratory which provides the test, there is also a regulatory process that applies to each test provided by a laboratory. Under Australian law, genetic tests are considered to be therapeutic goods and need to comply with the *Therapeutic Goods Act 1989*. This Act is administered by the TGA (see **www.tga.gov.au**).

Under the Act, genetic tests are placed in one of two categories. If a genetic test kit contains material of human origin or is designed for self-testing (e.g. for home use), the kit must be listed on the Australian Register of Therapeutic Goods (ARTG) which is managed by the TGA (see **www.tga.gov.au/docs/html/artg.htm**). The TGA must be provided with evidence of good manufacturing practice, product information, instructions for use and any promotional material for listable genetic tests.

Most genetic tests provided by medical testing laboratories would not fall within the scope of the ARTG because they do not contain human materials and are not developed for home use. Nonetheless, genetic tests must still comply with labelling requirements, relevant standards and the advertising provisions of the Act. In addition, laboratories are required to report any problems such as serious adverse events.

The regulation of pathology tests by the TGA is being reviewed. Under the proposed new framework for regulation, all medical tests will be regarded as '*in vitro* diagnostic devices' (IVDs) and will be regulated by the TGA. It is proposed that the TGA requirements would be comparable to the NPAAC in-house IVD standard currently used by NATA/RCPA to accredit laboratories, and which will continue to be an acceptable way of meeting TGA requirements for in-house IVDs. This regulatory oversight would then apply to **all** genetic tests, irrespective of the accreditation status of the laboratory or how the test was funded. It would become illegal to provide a medical genetic test that did not comply with the requirements of the TGA. This outcome would bring all genetic tests provided by public and private sector laboratories into the one regulatory framework, and require the same standard of accreditation for all genetic tests.

Resources

The TGA Forthcoming (new) regulatory framework for in vitro diagnostic devices (IVDs) is available at **www.tga.gov.au/ivd/forthcoming.htm** Regulation of direct to consumer (DTC) genetic tests is considered in Section 7.1.

Part B: The practicalities of genetic testing

4 Before genetic testing is ordered

This chapter is intended to assist health professionals to:

- provide information or genetic counselling to patients before they make a decision about genetic testing
- ensure that, if the patient decides to proceed with a test, he or she makes a free and informed choice
- prepare patients for the test and the results.

This chapter predominantly relates to genetic tests for heritable genetic variants. Tests for somatic (non-heritable) genetic variants are briefly dealt with in Section 4.5.4.

Commentary

Tests for somatic genetic variants are typically used in evaluating tumour tissue, and carry the same implications as other diagnostic tests in this setting. These tests determine the characteristics of a tumour and help define prognosis and appropriate therapy. Somatic variants are, by definition, non-heritable and hence these investigations do not carry implications regarding the risk of further primary cancers in the patient or in genetic relatives. Somatic genetic tests need to be assessed for their validity and utility, just as any new investigation needs proper evaluation. But somatic genetic tests do not raise ethical, legal or social issues that require special consideration.

4.1 General principles for providing information

The following points are relevant to each stage of information provision involved in decision-making about genetic testing. As genetic information is novel and can be complex, it may be important to:

- ascertain people's current level of knowledge and their ability to understand the information needed to make an informed decision
- provide information in a form and manner that is clear and concise, and accords with the person's circumstances, personality, expectations, beliefs and fears, values, cultural background and any experiences of genetics (including a disease in the family)
- provide information with due regard to age, level of maturity, education, intelligence and emotional state
- consider the content and scope of the information, including the order in which information is presented
- allow adequate time for discussion, as individuals have different levels of understanding and informational needs
- provide practical help (e.g. reviewing technical information about the test, being someone with whom matters can be discussed as people reflect on the decision to be made in light of their personal situation and the available medical information)
- repeat key information, and allow the person time to make a decision, encouraging reflection, questions and consulting with family and friends

- assess whether or not the person has understood the information provided by paying attention to his/her responses
- encourage patients to restate information in his/her own words, correct and clarify misunderstandings, and offer ample opportunities for questions and answers
- assess whether the patient can apply the information to his/her personal circumstances, and make decisions
- consider the form in which information is provided (e.g. verbally, audiotape, digital, electronic, diagrams, written); it is often helpful to provide information in a number of ways and provide written information for the person to take home
- provide information in the patient's preferred language; determine whether an appropriately trained health interpreter is required and whether written, audiotaped, electronic or digital materials need to be translated into another language.

Resources

There is a variety of general educational resources for the lay audience about genetic testing and the medical, ethical, and social issues arising from genetic testing, see:

www.genetics.edu.au

www.hhs.gov/familyhistory/respachealth.html

https://familyhistory.hhs.gov/fhh-web/home.action

www.ornl.gov/sci/techresources/Human_Genome/home.shtml

www.accessexcellence.org/AE/AEPC/NIH/index.php

https:/ehrweb.aaas.org/ehr/books/index.html

More specific information about particular genetic diseases and support groups can be located at many sites, including www.agsa-geneticsupport.org.au/home and www.genetics.edu.au/

4.1.1 Providing genetic information or genetic counselling

To provide genetic information or genetic counselling, the health professional should be appropriately qualified (e.g. as a medical practitioner or genetic counsellor), knowledgeable about the area in which he or she is counselling, able to communicate effectively, aware of the consequences for individuals and families of genetic test results, and able to deal with emotional responses to stressful information.

Providing information is not the same as genetic counselling

- **Information giving** is primarily an educational process (Kessler 1997), whether by explanation from a health professional, through printed/audiovisual resources, or both. Training as a genetic counsellor is not required for those whose role is limited to information giving (this may be appropriate for decision-making about diagnostic testing, and before genetic carrier testing in populations where the group to be tested has been consulted and supports the program).
- **Genetic counselling** encompasses both information giving with discussion and exploration of the implications for the individual and their family in a contextual framework that is unique for each person. For this, specific training and experience in counselling is required. Genetic counselling is generally required before and after predictive genetic tests, following a positive genetic carrier test and following an abnormal result on a prenatal diagnostic or screening test. Genetic counselling should also be recommended for decision making about tests likely to provide uncertain results and/or to have significant implications for the patient and their family.

4.2 Assisting the patient to make a decision about genetic testing

People may be referred for genetic counselling or testing without a clear understanding of the reason for referral, the issues that might be discussed, or what information the test can provide. The health professional should not assume that someone has come for a test, or even to discuss a test (particularly with prenatal testing).

The role of the health professional is to assist individuals, couples and families make decisions that are genuinely their own and appropriate to their personal situation. They do this by:

- clarifying what the person wishes to discuss and how much he or she already understands
- discussing alternatives and consequences of the various options (e.g. getting a second opinion about testing, not taking the test at all, postponing the test, or storing DNA for later testing)
- discussing supports available, including genetic counselling (which will vary according to the circumstances of the testing) but also the opportunity to bring a partner, family member or friend to genetic counselling sessions
- encouraging both members of a couple to participate in genetic counselling about reproductive issues, including prenatal testing
- explaining that testing is voluntary and it is possible to withdraw from the testing process at any stage, even after the testing has been done.

Examples

A 33 year old woman has antenatal maternal serum screening during her first pregnancy for Down syndrome (trisomy 21) and neural tube defects (spina bifida). The first trimester screening test is abnormal for Down syndrome, placing her at 5% risk of carrying a fetus with trisomy 21. She is then referred for a diagnostic test (genetic studies of cells cultured from a chorionic villous sample [CVS]). During the pre-CVS discussion provided by the obstetrician, it becomes clear that the woman had not considered the consequences of an abnormal maternal serum screen, and the possibility that a prenatal diagnosis of trisomy 21 might lead her to consider termination of the pregnancy. She and her partner decide to proceed with the CVS and the genetic test on the basis that they would consider termination of pregnancy for a fetus with trisomy 21. The molecular genetic test determines the number of copies of each chromosome. However, the fetus is found to have Klinefelter syndrome (47, XXY), a condition with much milder features than trisomy 21 yet associated with learning difficulties and infertility (both trisomy 21 and sex chromosome abnormalities become more likely with increasing maternal age). The ability of this couple to make decisions that are autonomous will depend on their understanding of the tests undertaken and the conditions that might be identified. The increasing anxiety induced by the progression of abnormal tests would make it progressively more difficult for many couples to absorb and utilise complex information for decision-making. This makes it all the more important that patients understand the potential consequences of test results before they agree to having the test performed.

4.2.1 Understanding the health professional–patient relationship

There is an imbalance of knowledge and power between the health professional and the person making the decision, and the health professional is in a position of trust. As a result, health professionals must be aware that they can easily and sometimes unknowingly influence decisions. Sometimes, when testing is clinically indicated it will be their role to recommend genetic testing and to provide information and counselling. At other times, information and counselling should be given in a way that is not directive. This can be difficult and, when considered necessary, it may be appropriate for the health professional to arrange a separate counselling session for the patient with another health professional. This allows the person to receive information from several people with different backgrounds, attitudes and experience.

Some people will do what they perceive, accurately or inaccurately, the health professional would want them to do. Sometimes, a person may find it hard to make a decision, and will genuinely want and ask for advice from the health professional. Consideration should be given to the response to such a request. In general, health professionals providing genetic counselling should assist people to make a decision which is truly their own and should avoid telling them what they should do. Reflection, discussion with a friend or family member and further counselling sessions may help people to come to a decision. However, if the health professional decides to provide direct advice, the professional will need to be well-informed about the circumstances of the person, and advise with the best interests of the person uppermost.

Commentary

The uptake of antenatal screening for Down syndrome (trisomy 21) is influenced by multiple sources including the mother and partners opinions, the attitudes of the healthcare professionals involved, written information and experiences of family and friends (see Jacques et al 2004; Park and Mathews 2009).

There may be circumstances when it is not appropriate for the professional who provides health care to a person, or family, to act as counsellor when it comes to making decisions about genetic testing. For example, a doctor who is treating a child with a serious inherited disease may view the disease as treatable and may find it difficult to avoid indicating an opinion about what the family should do when the parents ask about the possibility of prenatal diagnosis for the next pregnancy. In addition, some parents may feel uncomfortable about raising this matter with their doctor, as it could appear that they do not value their existing child or the care provided by the doctor. Health professionals who do not wish to discuss prenatal testing themselves (for whatever reason), or feel unable to do so in a dispassionate way, should offer families referral to another appropriate health professional.

Examples

A three year old girl was diagnosed with cystic fibrosis (CF). Genetic testing identified a common mutation in both the paternal and maternal copies of the CFTR gene responsible for this autosomal recessive disorder. Both parents were then confirmed by genetic testing to be carriers of the mutation. After a discussion with the daughter's paediatrician, the couple elected to have prenatal diagnosis during the next pregnancy. At 10 weeks gestation, the woman had a chorionic villous sample collected and sent to the laboratory for analysis. The result was due in 10 days. While the parents were waiting for the result, their affected daughter was admitted to hospital with pneumonia, requiring treatment with intravenous antibiotics, physiotherapy, and supplementary oxygen. The nursing staff knew the family from previous admissions and noted that the parents were not providing as much emotional support for their daughter as they had on previous admissions. This had not been noted by the girl's paediatrician. In discussion with a social worker, the parents spoke of their sense of conflict in considering termination of pregnancy if the fetus had two mutated CFTR gene copies while providing emotional support for their daughter who was being treated for the consequences of having the same abnormal genes. The fact that the paediatrician was instrumental in both sustaining their daughter and in their decision-making about prenatal diagnosis made it difficult for them to address these issues with the paediatrician. After discussion between the parties involved, it was decided that the further management of prenatal diagnosis in this family would be managed by another specialist and not the daughter's paediatrician.

4.2.2 Can a health professional decline to order a genetic test?

Occasionally, a genetic test will be requested by a legally competent adult but the health professional may decline to perform the test for reasons such as the following:

- the individual might come to harm
- it is considered that the individual cannot give fully informed consent because of his/her emotional state or apparent coercion
- the individual refuses some aspect of an established testing protocol, considered to be an important part of the process, such as pre-test counselling
- for logistic reasons or due to resource issues the health professional is unable to provide the test
- the health professional considers that testing is not appropriate from a medical perspective
- the health professional believes that testing is inappropriate from his/her own ethical perspective.

In the first three of these situations, the wish of the patient competes with the concern the health professional has for the patient's well-being and/or perceived capacity to understand matters that are important for making the decision. Professional judgement, which acknowledges the patient's choice but gives due emphasis to the health professional's duty of care, is required.

It would generally be inappropriate to provide testing simply because it is requested, without considering the potential consequences. On the other hand, health professionals should think carefully before refusing testing, especially if there is a possibility that their perception of the patient's capacity to make a free and informed choice, or the likelihood of harm as a result of testing, might be incorrect. When a health professional forms the view that a person's capacity to give informed consent is impaired by his/her emotional or mental state, referral to a psychiatrist or other appropriate health professional should be offered and testing postponed. Discussion with colleagues may assist with decision-making and in some circumstances, referring the patient for a second opinion will be appropriate.

In the last two situations, the priorities of the patient and health professional differ. In the counselling process it will be important for the two parties to discuss these differences. Once again, discussion with colleagues and consideration of referral of the patient to another health professional may be appropriate.

4.3 The consent process

If a patient decides to proceed with genetic testing, consent is required, though it may be implied, verbal, or written and with or without pre-test counselling, depending on the context. Details and information required during the consent process vary according to the circumstances; for example, consent to perform a simple diagnostic test is much less complex than consent to perform predictive genetic testing for a disease for which there is no prevention or treatment (this is generally undertaken by a specialist clinical genetics service).

The aim of the consent process is to enable persons considering testing to make an informed decision based on consideration of what is likely to be the best possible outcome according to them. Free and informed choice is an essential element of giving consent. Health professionals should avoid counselling in a way that might direct the individual's choice, and must not use deliberate deception or coercion.

4.3.1 Written, verbal or implied consent?

Consent for diagnostic genetic testing is usually given verbally or is implicit in the request for diagnosis and management of the problem, as is the practice when diagnostic medical testing uses other technologies and takes place in the context of the doctor–patient relationship.

However, it may be advisable to obtain written consent when testing symptomatic individuals if the test may give an uncertain result, or a certain result with uncertain implications. Written consent is also required for genetic tests which raise particular issues regarding complexity or ethics. As noted above, NPAAC has categorised genetic investigations according to the need for formal pre-test counselling and consent. The consent form should provide a record of the matters involved and discussed. The document can provide a framework for discussion with the patient, thereby reassuring both health professional and patient that relevant issues have been addressed.

Consent for genetic carrier testing in families in the context of a known family mutation may be given verbally but, because some of the consequences are more complex and far reaching, written consent is often preferable.

Genetic material obtained for clinical purposes can only be used for research if approved by a HREC in accordance with the *National Statement* (**www.nhmrc.gov.au/publications/synopses/e35syn.htm**).

According to the NPAAC standard, genetic tests and screening tests (e.g. neonatal screening) are deemed to be the same as other medical tests, requiring the same degree of informed consent etc, unless the test fulfils one or more of the criteria listed below. The pre-test genetic counselling and written consent is required in any of the following situations:

- Guidelines developed by the NHMRC (see **www.nhmrc.gov.au/guidelines/health_guidelines.htm**) or a national medical specialty college or society recommend pre-test genetic counselling and written consent.
- The specimen being tested is from a clinically affected child being tested for a disorder that typically presents in adulthood.
- The specimen being tested is from an apparently unaffected child or fetus when testing for a mutation already defined in the family.
- The specimen for testing is from a clinically unaffected adult and the test is predictive of a disease for which interventions are of limited efficacy or carry substantial risks or costs.

Commentary

The NPAAC Standard regarding categorisation of genetic tests can be found at **www.health.gov.au/internet/main/publishing.nsf/Content/2B242187AA443368CA257371001176A8/$File/Classification%20of%20Human%20HumGenTestSept07.pdf**

4.3.2 Circumstances in which formal consent may be waived

In medical processes there is always some form of consent, whether written or implied. In the context of newborn screening the level of consent sought may be minimal. The parent/s are provided with an information pamphlet before verbal consent is sought and recorded in the medical record. The test is not performed if consent is refused, though the parent/s will usually be referred to an appropriate health professional to discuss the implications of refusal for the child. Refusal to provide consent is documented on the medical record and signed by the parent/s (GEM Consortium 2007). A pilot project seeking written consent is currently being trialled in Victoria. The conditions screened for vary between State and Territories though usually include cystic fibrosis, phenylketonuria, galactosaemia, primary congenital hypothyroidism and rare metabolic conditions (GEM Consortium 2007).

Commentary

The Genetics Education in Medicine (GEM) Consortium was contracted by the Commonwealth Government to develop a national educational resource on genetic medicine for Australian General Practitioners. The outcome of this project is Genetics in Family Medicine: The Australian Handbook for General Practitioners 2007 (GEMS). GEMS is located on NHMRC's eGenetics subsite at **www.nhmrc.gov.au/your_health/egenetics/practitioners/gems.htm**

Consent for the testing of stored genetic material, as part of a research study, may be waived in the circumstances set out in the *National Statement*, in the sections on Use of Human Tissue Samples and Human Genetic Research **www.nhmrc.gov.au/publications/synopses/e72syn.htm**.

4.3.3 Genetic testing in minors

Genetic testing of minors raises important considerations, particularly in relation to capacity to understand the implications of testing and provide informed consent. Determination of whether consent is required from the parent, the child or a combination of both should be based on consideration of age of consent (which varies between States and Territories) and capacity to understand the information provided. Children have developing levels of maturity, from being unable to understand the implications of testing, to understanding some relevant information, to understanding information but not being old enough to provide proper informed consent.

In clinical practice, there are two extremes: the child does not understand the information provided and parents are responsible for consent; and the child is considered 'mature', understands the information provided and can legally give consent. In between these two extremes is a considerable grey area where consultation with relevant health professionals is required in order to make an appropriate decision.

Predictive genetic testing

Any request for predictive genetic testing of a child from a person with parental responsibility should be discussed with experienced health professionals who can assess the family situation, nature of the disease, possible medical or other benefits and implications of testing for the child and other family members. The vulnerability of children must be recognised; as must a health professional's need to be satisfied that due care has been taken when making decisions on their behalf. Those requesting testing should be encouraged and assisted to make an honest assessment of their reasons for doing so and to consider carefully how the test might directly or indirectly benefit the child. Relief of parental anxiety (and occasionally a child's anxiety) is considered insufficient reason for proceeding at this time, in the absence of guiding research.

Resources

The policy of the Human Genetics Society of Australasia regarding testing of children can be accessed at **www.hgsa.com.au/images/UserFiles/Attachments/Pre-symptomaticandPredictiveTestinginChildrenandYoungPeople.pdf.** It is recognised that the psychosocial consequences of predictive genetic testing of children have yet to be documented (Duncan & Delatycki 2006).

Risks of predictive testing in minors

- The child may have increased anxiety and distress related to the anticipation of developing the disease.
- Removes the child's right to decide whether to be tested as an adult.
- Children are often not able to choose whether they want to share this information with their parents or guardians.
- The information may alter parent-child or sibling-sibling relationships.
- The test result may lead to diminished self-esteem and difficulties with future interpersonal relationships.
- The test result may have implications for life insurance and employment.

Deferral of testing

If testing is deemed not to be in the child's best interests, it should be deferred until the child reaches an age at which the child can give consent in his/her own right; the age of consent to medical procedures varies in different States and Territories, and the law also provides for consent by mature minors. Generally, children 16 years and older may give consent but this is often directed to medical treatments that have an immediate impact.

When an older child or adolescent requests predictive testing

It may be difficult to reconcile the legal and ethical positions when an older child or adolescent (so-called mature minor) requests predictive genetic testing but is not old enough to give legally effective consent. In such circumstances, it is appropriate to involve an expert in assessment of maturity in adolescents (e.g. an adolescent psychologist or psychiatrist).

When young people give their consent, testing is legally permissible as long as the parents or guardians give their consent too. When young people do not wish to involve their parents, it may be advisable to postpone testing until the age at which legally effective consent can be given, provided that their health is not compromised.

When testing is performed with the consent of all involved, results are usually given in the presence of the young person and his/her parents or guardian. If the young person wishes to keep the result private, it may be appropriate to respect this wish. Health professionals should be aware of legislation in their State or Territory that relates to the age of consent to, and definitions of, medical procedures and treatment, and consent by mature minors.

Examples

The 16 year old daughter of a man with severe Huntington disease approached her general practitioner for genetic testing to clarify her genetic status and risk of disease. This is an autosomal dominant disease, and she was at 50% risk of inheriting the mutation responsible for her father's condition and of developing the disease. The daughter had no obvious features of the disease, and stated that she simply wanted to know her risk of developing Huntington disease. The general practitioner was concerned that genetic testing was not in the best interests of the daughter because of the combination of her father's disease and her level of maturity. She referred the daughter to a genetic counselling service for further advice and assessment. The genetic counsellor met the daughter and noted that, according to the local legislation, the daughter was old enough to make her own decisions in relation to medical care. Nonetheless, the counsellor was also concerned that it was not in the best interests of the daughter to be having the test. These concerns were discussed with senior colleagues and with the daughter at a series of appointments. The genetic counsellor also provided support for the daughter as she dealt with her father's deteriorating health. This professional relationship was maintained over a period of 18 months. By the end of that period the genetic counsellor, her senior colleagues, and the daughter agreed that genetic testing to clarify the daughter's genetic status was appropriate, and this was arranged by the genetic service.

When predictive genetic testing of a child is clinically recommended

In some circumstances it may be appropriate for a doctor to recommend predictive genetic testing of minors including where there is a highly effective intervention that can prevent a serious future health problem, or where there is an effective surveillance program.

Examples

A 13 year old boy has a paternal family history of familial adenomatous polyposis (FAP) due to a familial mutation in the APC gene responsible. This is an autosomal dominant disease in which hundreds of polyps form in the colon during the teenage years. Any one of these polyps can become a cancer, and so close colonic surveillance is recommended. The boy is at 50% risk of inheriting this mutation. Genetic testing to look for the family mutation is recommended by the age of 12 to determine if the boy needs a colonoscopy to document his current disease state and plan further surveillance, or if he can be discharged from follow-up because he has not inherited the family's mutation. However, his father had died of colorectal cancer and his mother was frightened that her son would suffer the same fate. She ignored requests from the boy's paediatrician and clinical genetics service to meet and discuss these issues. Eventually the family general practitioner was able to engage her on these matters, providing her with evidence that early surveillance is the key to a good outcome in this disease. She subsequently brought the boy to an appointment to discuss predictive genetic testing.

Occasionally, parents may be unwilling to give consent to genetic testing following extensive counselling, or refuse consent for treatment after testing shows the child to have inherited the gene mutation. If the case for genetic testing is very strong, and the doctor considers that the parents are not acting in the child's best interest, application can be made to displace the parents' authority by legal proceedings, so that a court can decide the matter. This approach may address the medical issues associated with the genetic test result but can also be associated with significant disruption in the family and in the relationships with health professionals. It would be important to discuss such situations with experienced colleagues prior to making an application to the court.

Ensuring genetic information is passed on to children at an appropriate time

If predictive genetic testing is undertaken in children too young to provide effective consent, there should be mechanisms to ensure that the genetic information is passed onto them when they are old enough to understand it and its implications for them. Certain events (e.g. separation of parents) can lead to the failure to inform children at the appropriate time.

Genetic carrier testing in minors

The psychosocial consequences of genetic carrier testing of children are largely unknown (Duncan & Delatycki 2006). Genetic carrier testing of children for an inherited autosomal or X-linked recessive disease or balanced chromosome rearrangement also impairs the child's autonomy and the possibility of informed choice at an older age. However, the result of genetic carrier testing generally has no implications for the future health of the child. It provides information about the chance that the child, once an adult, could have children affected by the disease (Borry et al 2005). Research is required to determine the benefits and harms that might result from such testing. Parent groups see genetic carrier information to be different from information predicting the later onset of a disease and their views should be given due weight and be respected (Barlow-Stewart et al 2004). They argue that there may be benefit to children if they have the opportunity to learn about and come to terms with the information gradually over time, in parallel with other aspects of development and in the context of family discussion and support.

4.3.4 People with reduced capacity to give informed consent

Special consideration needs to be given to predictive genetic testing of those with reduced capacity to provide informed consent, for whatever reason. The health professional should try to ensure that the information presented is understood by the person to be tested and is correctly interpreted. A family member, friend, legal guardian or professional advocate should be present, depending on the nature and degree of disability and whether the person is legally able to give consent. The motivation for requesting testing should be explored as coercion is perhaps more likely in this setting. The perceived benefit to the family may have to be considered in addition to those for the tested person alone (e.g. when testing is requested to inform decisions about future care needs and to make provision for them).

4.3.5 Genetic testing and Indigenous peoples

"Indigenous peoples have the inherent and inalienable right to freely determine what is best for them and their future generations in accordance with their own cultures and world views." (**www.treatycouncil.org**).

Genetic testing relating to Indigenous peoples (individual or population level) is complex and may be considered controversial by some because of historical attempts at racialisation and theories of inferiority, as well as issues of ownership, patentability, benefit sharing and perceived disregard for free, prior and informed consent linked to cultural frameworks and language barriers.

Professionals associated with genetic testing should be able to express their respect for Indigenous perspectives through "a rigorous understanding of the meaning of equitable negotiation of consent" (Dodson and Williamson 1999).

Many Aboriginal and Torres Strait Islander peoples do not identify English as their first language. Consent for referral, counselling and testing should take into consideration the potential requirement for skilled interpreters to relay concepts that may not have a direct translation, and consultations should allow sufficient time to accommodate detailed translation and explanation as required. Written confirmation of consent is preferable to a verbal agreement, particularly when an interpreter has been engaged to facilitate communication. It may also be appropriate to have a family member or other support person involved in the discussions.

Indigenous populations often share common beliefs regarding origin, cultural affinities and linguistic characteristics that transcend genetic determinants (Mgbeoji 2007). Health professionals, clinical geneticists and genetic counsellors should consider the concerns of Indigenous peoples about the laws and ethics of genetic testing, as well as the spiritual and historical issues (Berg 2001).

An ethical approach to genetic testing for Indigenous peoples (and in fact all populations) should incorporate:

- protection from racial discrimination
- preservation of human rights
- free, prior and informed consent
- retention of cultural self-determination (Mgbeoji 2007).

Commentary

An example of a genetic disease which is particularly prevalent in certain Indigenous communities in the Northern Territory is Machado Joseph disease (MJD). This is a neuromuscular degenerative disease which is inherited in an autosomal dominant manner. This disease was initially referred to as 'Groote Eylandt Syndrome', but genetic testing has shown that affected patients have a trinucleotide repeat mutation in the gene responsible for MJD. For more information refer to **www.mjd.org.au**

4.3.6 People from culturally and linguistically diverse backgrounds

Special care must be taken when obtaining consent from people from different cultural backgrounds. In these situations, it may be appropriate to involve a supporter to accompany and advise the person. This could be a family member or friend but in some cases, an independent advocate will be best.

Qualified interpreters and culturally appropriate materials should be available for people from culturally and linguistically diverse backgrounds. Where this is not possible, telephone interpreter agencies can provide relevant services. However, not all cultural groups welcome the involvement of non-family members in such circumstances and health professionals need to be aware of and sensitive to this possibility (NHMRC 2004).

Resources

The Multicultural Disability Advocacy Association (MDAA) has produced a useful information sheet on using interpreters successfully at **www.mdaa.org.au/faqs/interpreters.html**

In some circumstances, when testing populations with a distinct ethnic, cultural or religious background, it is important to seek approval from and engagement with the community as well as the individuals.

4.4 What type of information should be provided?

The information to be provided will vary depending on the type of genetic test to be performed, the specific situation and the needs of the patient. The consent form may include information that is directly relevant to the testing situation and which requires specific consent, with an information leaflet covering other matters. The following information may be appropriate:

- The test result may be in the form of a probability rather than a certainty of developing, or not developing, the disease. In general, the test result will provide probabilistic information about age of onset, severity or symptoms.
- The method of communication of the result to the person tested in terms of who it is done by and in what form. For predictive testing, results should be communicated by the health professional at a consultation and confirmed in writing. By contrast, following pre-test genetic counselling, the result of a genetic carrier test could be provided by telephone or letter unless the health professional perceives that the person tested will require post-test counselling and support.
- The test result will be confidential and that the person requesting the test can determine who can have access to it and who can know that the test has been performed.
- The involvement of the person having the test in terms of any medical procedures and the number, nature and sequence of appointments and the estimated time to obtain a result.
- The costs involved.

- Information about the disease for which the patient is being tested, including:
  - the clinical features and their variability
  - the range of age of onset
  - the potential impact of the disease, including pain and suffering, disability, participation in everyday life, education, employment, marriage and having children, life expectancy and the support given by society to affected individuals (e.g. financial assistance, services to address disability, help in the home, respite care and community support groups)
  - the pattern of inheritance, and the genetic basis of the disease in as much as it is known
  - that the information given about the probability of developing the disease may be the best available at the present time, it may change after further research
  - the availability of risk-reducing, prevention strategies or treatment
  - whether prenatal testing or pre-implantation genetic testing is possible.
- Information and contact details of genetic support groups/lay organisations. Such groups will often be able to provide additional information about the physical, emotional and social implications of the disease.
- Information should be provided about the implications of a medical genetic test result for future uptake of risk-related insurance such as life or income protection.
- As germline DNA is shared with genetic relatives, the person should be informed that the results may impact on the future health of genetic relatives who may need to be offered testing.
- Storage of the DNA sample in the testing laboratory.

Commentary

Talking about 'risks' is not simple. It is clear that many people find it confusing to deal with possibilities rather than certainties. Even if something is very likely to happen, there is still the possibility that it may not. A rare but serious problem may be of more concern than a common but less serious one. Risks can also be presented in different ways, including percentages (50%), odds (one chance in two), words (equal chance of happening or not happening), or as graphs. Risks can also be presented as 'the risk in the next year' or as 'the risk by the time you reach a certain age'; we use both methods in this Information Paper.

It can be helpful to present risks in different ways, or from different perspectives, to assist the patient get a clearer understanding of the accuracy of a risk estimate, and the limitations inherent in risk estimates (see O'Doherty & Suthers 2007).
www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=14512488

4.5 Test-specific considerations

Patients should also be provided with information that is specific to the test being considered.

Resources

Specific information about a gene test and the associated disease can be found at

www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests

www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM

It is important to note that these sources are not necessarily comprehensive and do not necessarily reflect clinical practice in Australia.

4.5.1 Diagnostic genetic testing

Even if a diagnostic genetic test identifies a germline mutation that may also be present in genetic relatives, this conclusion may have been reached through clinical findings alone (e.g. family history). However, diagnostic testing can raise special ethical issues.

Examples

A patient with medullary thyroid cancer, and no family history of this disease, may have an underlying heritable mutation in the RET gene that is responsible for the cancer and places other genetic relatives at high risk of this disease.

- If there is little clinical evidence that the patient has a familial disease, the ethical consequences of the test e.g. implications for genetic relatives, may not be known until the report is issued.

Examples

A strong family history of breast and ovarian cancer may be sufficient to indicate that a woman with breast cancer is likely to have familial breast cancer, and is at high risk of developing further breast and ovarian cancers. However, if she has not inherited the family's BRCA1 mutation, her risk of developing further breast or ovarian cancer is substantially reduced.

- Genetic testing can provide a risk assessment that is more accurate than clinical assessment alone, if it identifies a mutation responsible for a familial disease and allows genetic relatives to clarify their own risk of disease.

Examples

Approximately 2% of physically normal boys with intellectual disability have a specific mutation in the FMR1 gene (fragile X syndrome). However, there is a common variant of this mutation that does not cause intellectual disability but is associated with the development of a progressive neurodegenerative disease in late adult life. Testing of an affected boy may not identify the underlying genetic basis for his intellectual disability, but might identify an unexpected risk factor for late-onset neurological disease both in the boy and his genetic relatives as well as the risk for other genetic relatives to have fragile X syndrome itself.

- Identifying a mutation in a gene does not necessarily mean that the mutation is the cause of the disease; in other words, genetic analysis may identify a mutation in the gene that is unrelated to the patient's presenting complaint.

4.5.2 Predictive genetic testing

Generally, predictive tests should be accompanied by pre- and post-test genetic counselling from a person experienced in this field. Some ethical issues in relation to predictive genetic testing are outlined below.

A predictive genetic test result can reveal the genetic status of another individual without that person's permission.

In these situations the person may be made aware of their genetic status in a situation that is not supported by genetic counselling. This is most likely to occur in parent/child relationships or in identical twins. In a parent/child situation, the parent should be informed about the child's wish to have testing and have the option of being tested first. Some parents will prefer their child to be tested in the first instance to reduce the chance that they (the parent) will be found to have the familial mutation, albeit indirectly.

Examples

A man has a rare autosomal dominant disease and the causative mutation has been identified. His daughter is asymptomatic and does not wish to know her genetic status. However, her child (the man's grandson) has predictive genetic testing for the disease. If the grandson has inherited the familial mutation, his mother must also have inherited it. Her genetic status is revealed without her being tested.

Identical twins have almost identical genomes and will have the same result for virtually any test for a heritable genetic variant. In a situation where one of identical twins seeks testing for a heritable mutation and the other twin does not wish to know his/her genetic status the central ethical issue is whether one twin's right to know takes precedence over the other twin's right not to know (Heimler & Zanko, 1995). Some argue that the right to know outweighs the right not to know and therefore testing should take place. Others argue that the two stands are equally valid and that testing should not proceed as the twin who does not wish to know is in danger of harm by finding out his or her genetic status without appropriate counselling. This situation is often handled by attempting to have face-to-face discussions with both twins; if testing proceeds, the twin who does not wish to know his or her genetic status is offered pre-test counselling to minimise the risk of harm.

Some argue that if there is a reproductive decision resting on the result of the predictive genetic test, that the test should always proceed irrespective of the wishes of the other person (Maat-Kievit et al 1999).

Adverse outcomes from predictive genetic testing

Adverse outcomes have not been as frequent as some anticipated prior to the availability of predictive genetic testing. For example in Huntington disease predictive genetic testing, about 2% of those who test gene positive experience a 'catastrophic event', defined as suicide, attempted suicide or hospitalisation for depression and/or anxiety within 12 months of receiving the test result (Almqvist et al 1999). Less severe adverse events such as relationship difficulties or negative psychological impact such as depression and/or chronic anxiety are more common and are also not usually long term. For example, those shown to have inherited a familial cancer predisposing mutation found that anxiety for people who have had genetic testing usually lessens over 12 months to the level that is normal for them (Meiser et al 2002; Dunlop et al 1997).

4.5.3 Genetic carrier testing

Genetic carrier testing can raise issues as the definition of carrier status implies that genetic relatives may also be carriers. Testing can also raise issues of reproductive options and techniques, such as:

- pre-implantation diagnosis and the consequential non-use of embryos which have inherited a disease-related mutation
- prenatal diagnosis and decisions about whether or not to continue a pregnancy if the fetus has inherited a disease-causing gene mutation(s).

Commentary

The term 'carrier' is used to describe a person with one mutated copy of the gene. It is used in different ways in different contexts.

When considering autosomal recessive and X-linked disorders, carriers of the causative mutation are typically unaffected and not at significantly increased risk of developing the disease. However, they may be at significantly increased risk of having a child who is affected with the disease. For example, cystic fibrosis is an autosomal recessive disorder, and the affected child's parents are usually both carriers of mutations which cause the disease. On the other hand, males have only X chromosome and will develop an X-linked recessive disorder if they have a mutation on that chromosome e.g. as in males with haemophilia A. A woman is said to carry an X-linked mutation because she has a second X chromosome with a working (normal) copy of the gene.

When considering an autosomal dominant disorder, the term 'carrier' applies to a person who has one working and one mutated copy of the gene. The carrier may be affected with the disorder. For example, a woman may carry a mutation in the gene responsible for myotonic dystrophy, and exhibit clinical features of that disease. Alternatively, the carrier may be unaffected but remain at high risk of developing disease in later life. Some carriers of the mutation which causes myotonic dystrophy remain asymptomatic for many years. A carrier may remain unaffected because of the sex-limited nature of the disease. For instance, a man may carry a mutation which causes familial ovarian cancer but he will not develop that particular disease, but he could pass the mutation onto his daughter.

4.5.4 Somatic and pharmacogenetic testing

Traditionally somatic genetic testing has not been the primary focus of clinical genetics practice. However, somatic mutation testing is gaining prominence as it offers insights into how some cancers behave and respond to treatment. As well as targeting treatments somatic genetic testing can indicate disease prognosis. When considering somatic genetic testing for a patient it may be useful to consider the availability of suitable treatment options.

The tailoring of individualised drug therapies using genetic testing is commonly referred to as pharmacogenetics. Individual differences in response to drugs are often genetically determined. Some considerations before ordering a pharmacogenetic test are:

- Some pharmacogenetic variants are found more commonly in certain racial or ethnic groups than others. The use of race as a surrogate pharmacogenetic test, or of a pharmacogenetic test as a surrogate for racial identity, raises ethical concerns. This type of genetic based information should be used with care and appropriately, to avoid stigmatisation and discrimination.
- The change from current practice towards what is now popularly termed personalised medicine will significantly alter the way pharmaceutical companies develop drugs and design clinical trials. This is likely to lead to more drugs being approved by the regulators, but with smaller target markets, identified by companion pharmacogenetic tests rather than marketing material.

Examples

One example of somatic and pharmacogenetic testing which has been successful in optimising cancer therapy is HER2/neu gene status and response to the drug herceptin in breast cancer. The drug herceptin is an antibody that targets overexpression of HER2/neu protein observed in approximately one-third of patients with breast cancer. Consequently patients are prescribed herceptin (an expensive drug with significant side effects) only if their tumour has been shown to overexpress HER2/neu.

5 Ordering a genetic test

This chapter is intended to assist health professionals involved in the ordering of genetic tests to:

- determine the best test to answer the clinical question
- assess the characteristics of a test
- identify laboratories where the test may be performed
- provide patients with accurate information on the storage, access and use of samples and information.

The information below assumes that a process of information provision and informed consent has already taken place, including offering the patient genetic counselling as appropriate, considering factors that may compromise the process and providing suitable information about the specific test involved.

5.1 Who is involved in ordering a genetic test?

The jurisdiction-based approach to funding genetic tests (see Section 3.1) has led to various practices regarding who can order DNA tests. In some jurisdictions, specialist clinical geneticists (employed in the public sector) are the only health professionals allowed to order genetic tests. This approach has allowed control on the types and numbers of genetic tests being ordered. However, it is not viable or appropriate in the long-term as the diversity (in terms of disciplines covered) and volume of genetic tests increases. By 2006, 25% of the volume of genetic tests ordered across Australia were Medicare–rebated (RCPA 2008) and were ordered by a wide variety of health professionals in the public and private sector.

A genetic test to confirm diagnosis of some diseases can often be managed by the GP. Even predictive genetic testing, which may be more appropriately ordered by a specialist clinical geneticist, inevitably involves the GP who is responsible for the patient's (and family's) long-term care. Considerable training and continuing education are required to ensure that GPs and specialists other than clinical geneticists who order genetic tests, or deal with patients/families having genetic tests, are aware of the implications of a genetic test and have some knowledge on how to interpret the result of the test.

The role of the specialist clinician is also evolving. Inevitably, as there is increasing familiarity with the genetic basis for various diseases that are managed by specialists such as cardiologists or oncologists, the specialists will become more skilled in understanding the validity and utility of tests for heritable variants in managing the patient's disease. However, such test results may also carry significant implications for the patient's genetic relatives, and the specialist may not have the necessary time or experience to manage these consequences of the initial genetic investigation. For this reason, a formal association between specialists and genetic counsellors will be important to manage the familial aspects of genetic test results.

Like all other medical tests, it is not appropriate for practice staff (e.g. nurses or practice managers) to be directly involved in requesting tests or delivering results to patients.

There is also rapid expansion of genetic testing of cancer tissue (somatic cells). The volume of such testing rose by 23% from 2006 to 2007 (RCPA 2008). These assays for non-heritable mutations will generally be ordered by specialist clinicians involved in cancer management, and they do not carry the ethical implications associated with testing for heritable variants.

5.2 What is the best genetic test to answer the clinical question?

Clinical assessment and documentation of the family tree are usually the starting points for diagnostic genetic testing as they define which gene or genes should be studied. Identifying the mutation causing the disease will be straightforward if only one gene can cause the disease, if that gene has been identified and if only one or a small number of mutations in that gene cause the disease.

In most cases, however, testing is much more complex, because different mutations can cause the same genetic disease in different families, and diseases can be caused by multiple mutation mechanisms. The result of this complexity is that laboratories often screen genes for mutations, or test a small number of known common mutations, rather than offering a single test for each disease.

Choosing the best genetic test to answer the clinical question involves consideration of the following questions:

- Is a genetic test most appropriate or is there a better non- genetic test available?

Examples

One example of somatic and pharmacogenetic testing which has been successful in optimising cancer therapy is HER2/neu gene status and response to the drug herceptin in breast cancer. The drug herceptin is an antibody that targets overexpression of HER2/neu protein observed in approximately one-third of patients with breast cancer. Consequently patients are prescribed herceptin (an expensive drug with significant side effects) only if their tumour has been shown to overexpress HER2/neu.

- Which gene/s should be screened? What is the prior probability of a particular gene being involved?
- Which mutations are being searched for?

Commentary

In Australia, approximately 75% of causative mutations in the CFTR gene causing cystic fibrosis is a single mutation (F508), the top three mutations account for 80%, the top ten mutations make up 83%, the top sixteen make up 83.7% and hundreds of different mutations account for the remaining 16.3%. So how many different mutations should be part of routine testing? Different states in Australia routinely screen between 5 and 16 mutations.

- What is the availability and cost of the test?
- How long will it take to get a result? This is referred to as the 'turnaround time' and will vary depending on the urgency of the test and to some extent the resources available in the DNA testing laboratory.
- What ethical and regulatory issues might arise in relation to this test?

While they are often more ethically complex, selecting a genetic test in predictive and carrier testing is simpler, provided the mutation causing the disease has been identified in an affected genetic relative (who may be symptomatic or a carrier). If the family's specific mutation is known, a specific test can be developed to identify it. If it is not possible to identify the specific mutation responsible for the disease (i.e. because the gene has not yet been identified, or because the technology fails to detect the mutation), an indirect method such as genetic linkage may be feasible to infer the presence or absence of a mutation in genetic relatives.

5.3 What are the characteristics of the test?

Assessment of the characteristics of a test needs to address three distinct but related considerations.

The *analytic validity* of the test refers to the ability of the test to correctly identify a mutation, or the absence of mutations, in the gene being tested. It principally relates to technical aspects of the laboratory's analysis.

Commentary

In some situations, a test needs to have a very high degree of accuracy to provide analytical validity. For example, DNA sequencing requires the correct identification of each nucleotide in a DNA sequence. Any error in assigning a nucleotide would be interpreted as an abnormality in the patient's DNA sequence, with projected abnormalities in the protein derived from that gene. In other situations, the test does not need to provide such a high degree of accuracy and can still provide analytical validity. For example, fragile X syndrome is due to an expansion in a triplet repeat at the end of the FRAXA gene. In affected children, the expansion is typically 2-10 times longer than that found in unaffected children. A test does not need to indicate the precise degree of expansion to provide analytical validity; the degree of expansion (above a certain threshold) provides little further information.

The *clinical validity* of the test refers to the performance of the test in a specific clinical context. Some of the key factors determining the clinical validity of a test are the prior probability that an affected patient has a mutation in the gene being tested, the frequency of mutations of this gene in the general unaffected population, and the frequency of mutations of this gene in patients with similar diseases. This assessment should include evaluation of:

- **clinical sensitivity**—the proportion of patients with the disease who have an abnormal genetic test result
- **clinical specificity**—the proportion of people who do not have this particular disease who have a normal genetic test result
- **false-positive rate**—the proportion of patients who typically have this test who have an abnormal test result but do not have the specific disease
- **false-negative rate**—the proportion of patients who typically have this test who have a normal test result and do have the specific disease.

Commentary

Familial mutations in the TP53 gene can cause breast cancer, but such mutations account for less than 1% of all cases of breast cancer. Hence genetic testing of TP53 will generally be of low clinical validity in women with breast cancer because the great majority of affected women will have a normal test result.

The clinical utility of the test involves considering whether the result of the test could alter decision-making by the requesting health professional or the patient. A test may have a high degree of analytical and clinical validity, but have little clinical utility in a particular context.

Commentary

Somatic mutations in the APC gene are a very common feature of colorectal cancers. This gene is implicated in the pathogenesis of most colorectal cancers, and there are methods for accurately identifying these somatic mutations. A genetic test for somatic mutations in the APC gene could have analytical validity and clinical validity. However, there is no evidence (as yet) that identifying somatic mutations in this gene make any difference to the advice or treatment provided to the patient. Such a test would not have clinical utility. Of course, this lack of clinical utility would change if treatment became available that was specific for colorectal cancers with or without somatic mutations in the APC gene.

A genetic test for heritable variants may raise a variety of ethical, legal, and social issues. These should be considered prior to the implementation of the test so that the necessary education, consent processes, and management protocols can be put in place.

5.4 Who performs genetic tests?

In Australia, there are different types of laboratories providing genetic tests. These are summarised in the table below. For more information on which Australian laboratories perform which genetic tests refer to the RCPA's Catalogue of Genetic Tests and Laboratories: **http://genetictesting.rcpa.edu.au/**

Laboratory	Tests offered	Links with health professionals	Funding
Specialist genetic testing laboratories in the public hospital system	The majority of medical genetic testing is provided by public sector laboratories	Many of these laboratories have links to clinical genetics services	Predominantly State/ Territory funding Private patients billed directly where not funded through Medicare
Pathology laboratories in both the public and private sector	A range of medical tests including genetic tests	Usually these laboratories do not have a strong link with clinical genetics services	Mixture of State/Territory and/or Commonwealth funding Also fee for service
Private laboratories that specialise in genetic testing	Very few in Australia	Usually these laboratories do not have a strong link with clinical genetics services	Funding is predominantly fee for service
Direct to consumer (DTC) marketing laboratories	Most laboratories provide various combinations of medical and/or quasi medical tests	All DTC genetic testing laboratories advertise directly to the public through the internet	Fee for service Less than 10 of these laboratories in Australia and none so far offer DTC tests for medical conditions
Research laboratories	Tests are usually developed or used as part of a research protocol	Variable	Provided as a consequence of research work Generally funded by research grants

There are several additional considerations when considering who will perform the test:

- *Local versus distant laboratory* – for some genetic diseases, the volume of tests to be performed and the relative ease of interpretation of results, makes it easy to justify having multiple laboratories able to offer this testing. For other diseases, the rarity of the disease and complexity of analysis and interpretation makes a strong case for only a few regional laboratories providing such a service. For even rarer diseases, one or two national reference laboratories would be appropriate. There are many genetic diseases for which no laboratory in Australia offers testing, and this adds a layer of complexity to the testing process because by sending the genetic test overseas the regulatory requirements operating in Australia (particularly accreditation standards) are not always enforceable.
- *Accredited or not* – while most diagnostic laboratories offering genetic testing in Australia are accredited to the NATA/RCPA ISO 15189 standard, most research laboratories are not. Therefore, results that they provide should not be used in clinical decision-making. This can potentially put pressure on local diagnostic laboratories to develop 'one-off' tests to validate the test result from a research laboratory.

- *Turnaround time (in relation to need)* – Most genetic tests have turnaround times of days to months. While this is not a clinical problem if the test result will be used for non-urgent decision-making, in some situations (e.g. prenatal diagnosis or pharmacogenetic testing) a rapid turnaround time is essential. This is difficult, as most genetic tests across Australia are low volume (less than 100 assays per year), and 17% of laboratories do less than 100 genetic assays of any type each year (RCPA 2008). Prenatal diagnoses are particularly challenging in this regard because they take priority and potentially disrupt turnaround times for other tests provided by the laboratory.
- *Financial implications and financial consent* – For the limited range of genetic tests rebated by Medicare, or provided by a public sector laboratory in a State or Territory that offers that test, there is no barrier in relation to cost that might limit the patient's access to that test. However, only 13% of the types of genetic tests were provided in four or more States or Territories in 2006, and no genetic test was provided in all States and Territories (RCPA 2008). Public and private patients living interstate may be required to pay the cost of the test. While their public healthcare provider might pay for the test, a private healthcare provider is unlikely to pay for the investigation. Unfortunately, there are no data available regarding the funding of testing provided across State and Territory boundaries in Australia.

5.5 Storage, access and use of samples and information

5.5.1 Storage of and access to genetic test results

It may be appropriate to discuss the following with the person tested:

- where the test result will be stored
- the intended duration of storage
- who will have access to the result (in general, those who arranged the testing, the laboratory personnel who performed the testing, those who transmitted the result to the tested individual, those who were authorised by the tested individual to have access to the test result and those who are responsible for storage of the medical record)
- who is responsible for retention and integrity of the information, and for its confidentiality and privacy
- the procedure for accessing the information
- whether correction of the test information can be sought if re-tested and an error is detected
- whether a record of genetic information can be deleted.

Commentary

NPAAC has minimum standards for the retention of samples and records of testing. The minimum time for retention of genetic test results is 100 years. Samples for genetic testing need to be retained for up to three years depending on context, see **www.health.gov.au/internet/main/Publishing.nsf/Content/0392138A9970DFD1CA257371000D9200/$File/RetenLabRecSept07.pdf**

The following should also be explained as appropriate:

- It may be prudent to advise the patient to reveal the test result only to persons in whom the patient wishes to confide and who can be trusted to keep the information confidential.
- The laboratory professional may be approached by other family members for access to the results of genetic testing or to stored genetic material. The circumstances in which the person tested authorises the laboratory to release information should be defined, including what is to happen after his/her death. It may be possible to meet the needs of other family members while preserving the confidentiality of the person tested.

- The person tested should specify which, if any, of his/her medical advisers should be provided with the test result. This applies particularly for predictive and genetic carrier testing. Diagnostic genetic test results would normally be provided to the health professionals caring for the person tested.
- The person tested should be asked for permission for the result of a predictive genetic test to be provided to the health professionals caring for him/her if circumstances arise that make it impossible for him/her to give consent e.g. the onset of symptoms of a dementing disease for which predictive genetic testing was performed many years earlier. Such information could be important for planning the person's treatment.
- Circumstances in which a government agency can seek disclosure of the information or where the law may require or authorise disclosure without the person's consent.

While uncommon, a person may withdraw even after the test result is available though not yet delivered. When a person withdraws, he/she should be asked for instructions regarding disposal or subsequent use of the information and genetic material collected for testing.

Commentary

NPAAC has minimum standards for the retention of samples and records of testing. The minimum time for retention of genetic test results is 100 years. Samples for genetic testing need to be retained for up to three years depending on context, see **www.health.gov.au/internet/main/Publishing.nsf/Content/0392138A9970DFD1CA257371000D9200/$File/RetenLabRecSept07.pdf**

5.5.2 Storage and subsequent use of DNA sample

In general, laboratories will store genetic material for a period for substantiation or validation of the result, to comply with accreditation or legal requirements. If genetic material is to be stored for reasons other than standard laboratory practice or legislative requirement, individuals should be informed that this is proposed or will occur. Their consent should be sought if storage is not mandated, and they should be told:

- why the material is to be stored
- the nature of the material to be stored
- where the material is to be stored
- the intended duration of storage

Commentary

It may be necessary to store some genetic samples for longer than others. For example, samples that may be beneficial for the testing and diagnosis of other genetic relatives (cascade testing), such as BRCA samples in which a specific mutation has been detected, may be kept for longer than a sample used to confirm the clinical diagnosis of cystic fibrosis in an individual.

- who is responsible for retention and integrity of the material, and for its authorised use
- that in Australia the genetic material tested becomes the property of the testing laboratory from a strictly legal perspective
- that the laboratory will store the material in accordance with current practice but cannot guarantee its viability for future use
- who will have a right of access to the material
- the procedure for gaining access to the material.

If stored genetic material is to be re-tested in light of new knowledge or new technology, as an extension of the original laboratory service, there will be an obligation to state this on the consent form and for the person tested to keep the requesting doctor informed of his/her contact details and for the laboratory to inform the requesting doctor about information arising from the re-testing.

These issues may be handled differently when it comes to Newborn Screening Programs. Since these are undertaken by the various State and Territory health departments, there could be differing requirements for consent, storage and use of the newborn screening cards that provide the DNA source. This is presently under consideration and discussion through the Australian Health Ministers' Advisory Council (AHMAC). If samples are to be used for research, see Section 7.7.

Commentary

The length of time that newborn screening cards are stored for varies according to State and Territory policies. Currently newborn screening cards are held indefinitely in Victoria, for 50 years in Queensland, South Australia, Northern Territory and Tasmania, for 18 years in New South Wales and the Australian Capital Territory and for two years in Western Australia (National Public Health Partnership 2002).

6 Providing the results of a genetic test

The analysis, interpretation and delivery of a test result occur in a number of stages. This chapter outlines considerations for:

- the laboratory professional in analysing the test result
- the health professional in interpreting the result
- the health professional in delivering results to patients and family members.

All those involved in genetic testing should be aware of the most up-to-date resources that are suitable to assist laboratory geneticists and referring health professionals in their interpretation of genetic test results. Three relevant web-based resources are:

- RCPA Catalogue of laboratories providing genetic testing at **www.genetictesting.rcpa.edu.au**.
- US National Centre for Biotechnology Information catalogue of genetic tests with reviews of genetic disorders at **www.genetests.org**.
- Lab Tests OnlineAU at **www.labtestsonline.org.au**, directed at the 'health consumer', that provides useful clinical data on various tests or diseases but less detailed information on genetic tests.

6.1 Analysis of the test result by the laboratory professional

The laboratory professional interprets the analytical result and provides this interpretation in the test report. This is the analytical interpretation, and it may be a complex process involving detailed review of publications, databases, family history information, and sequence analysis programs. For example, the consequences of a change in DNA sequence in relation to RNA sequence, protein structure, and protein function must be determined and validated:

- variations in DNA sequence that disrupt the formation of a protein (e.g. truncating mutations) are typically (but not universally) pathogenic
- variations in DNA sequence that alter one amino acid for another in the resulting protein (ie missense mutations) may be benign or pathogenic, and it is often difficult to determine the biological consequence
- variants that are individually benign may be pathogenic if they occur together in the same gene.

This interpretation must then be presented to the requesting health professional to facilitate understanding and subsequent decision-making. There are challenges in this process, ensuring that the health professional interprets the genetic test result correctly and that the novelty of a genetic test does not obscure the consequent decision-making.

Commentary

A report is not always a secure means of transferring information from a diagnostic service to the health professional. Information that is essential for decision-making is often missing from reports and medical records, and health professionals often fail to identify these deficiencies (Lau et al 2004). Even when the necessary information is provided, health professionals frequently misinterpret histopathology reports (Powsner et al 2000) and reports of genetic testing (Giardiello et al 1997).

Tests may be used inappropriately to determine choice of medication rather than dose of medication. Pharmacogenetic testing to identify a patient who should receive low-dose azathioprine (rather than standard dose) may be used by the health professional to deny the patient this effective medication (Ansari et al 2003).

Resources

The Royal College of Pathologists Australasia has developed guidelines (**www.rcpa.edu.au/static/File/Asset%20library/public%20documents/Policy%20Manual/Guidelines/Guidelines%20for%20reporting%20molecular%20genetic%20tests%20to%20medical%20practitioners.pdf**) for the reporting of medical genetic tests. This details the information that should be considered by laboratory professionals when providing a report to the requesting health professional. The guidelines include examples of laboratory reports that may be appropriate in different clinical settings.

6.2 Interpretation of test results by the health professional

The health professional interprets the analytical result and interpretation in the light of the clinical context and the decisions that need to be made. In making both the analytical and clinical interpretations of a genetic test, it is important to draw a distinction between the genetic variant identified (genotype) and the functional outcome (phenotype) that this may cause.

Examples

One example of somatic and pharmacogenetic testing which has been successful in optimising cancer therapy is HER2/neu gene status and response to the drug herceptin in breast cancer. The drug herceptin is an antibody that targets overexpression of HER2/neu protein observed in approximately one-third of patients with breast cancer. Consequently patients are prescribed herceptin (an expensive drug with significant side effects) only if their tumour has been shown to overexpress HER2/neu.

Examples

For some mutations and disease, the association between mutation and disease is very strong but this is not a universal phenomenon. Hence, an unaffected woman with a pathogenic mutation in the HTT gene is highly likely to develop Huntington disease at some stage during her lifetime, but she should not be described as having the disease.

6.3 Who should receive the test result?

In the context of medical testing, the report of a test must necessarily be provided by the laboratory to the requesting health professional. The requesting health professional then decides the extent to which the test result is shared with the patient, placed in the medical record, and shared with other health professionals involved in the patient's care. This decision typically rests on the patient's desire for information and confidentiality, organisational policies regarding record-keeping, and the utility of the result for other health professionals providing care. However, as noted in Section 1.4, genetic tests raise additional considerations regarding confidentiality, both for the patient and the family.

The distribution of the test result, either as a copy of the laboratory report or by some other means, is an important consideration for the results of a genetic test. This matter should be explicitly addressed so that competing preferences e.g. not placing the result in the medical record that may provide confidentiality but limit the utility of the test, are recognised and addressed. Laboratories are required to send a copy of all test results to the requesting doctor. If the test had been referred from one laboratory to another for testing, the testing laboratory is required to send a copy of the report to the requesting laboratory; it is not sufficient for the testing laboratory to send a report to the requesting health professional and simply advise the requesting laboratory that the genetic test was undertaken.

Commentary

There should be consideration of the distribution of test results especially in relation to electronic health records. Integrated electronic health records and record linkage pose potential issues in terms of unauthorised access to genetic information. However, in principle electronic health records should be no different from all other medical records and afforded the highest level of confidentiality and limited access.

6.4 Delivering results of tests for heritable mutations to patients and family members

Where possible, the health professional giving a genetic test result should be the health professional who provided the pre-test counselling.

6.4.1 How should information be provided to the patient?

The physical environment in which the patient is being seen should be appropriate for the information being provided. For example, there should be appropriate provision for privacy, comfort, and lack of distraction. Patients could be encouraged to have a partner, family member or friend accompany them for support, particularly where there is the potential for an adverse reaction to the test result. Despite the fact that much information will have been provided before conducting the test, it is important to discuss the disease, implications and treatment options in the context of the actual results. Some considerations include (see also Section 4.1):

- helping individuals/families to comprehend the medical facts related to the test results, including causation and recurrence risks
- distilling information into clear and understandable concepts, restricting the use of medical jargon, considering language that avoids negative connotations (e.g. intellectual disability rather than mental retardation, gene alteration rather than mutation)
- clearly explaining treatment options, strategies to manage the disease and, where relevant, available reproductive options
- outlining implications for family members and strategies to identify and notify relevant people
- providing contact details for support services.

Commentary

It is important to recognise that genetic testing to identify a familial predisposition to develop disease probably represents a unique experience for the patient. Such testing has only recently become available and it is unlikely that the patient will have had a similar experience on which to base expectations. Some patients and family members are surprised by the strength of the positive and negative emotions associated with a genetic test result. It is essential that both staff and patients feel secure in the physical environment in which test results are being provided, and that there is potential support for both staff and patients should the need arise.

6.4.2 Follow-up with patient and affected family members

As discussed in Section 2.2, patients may be asked to communicate aspects of their test results to genetic relatives who may also be affected or are at risk of the familial genetic disease.

When genetic information is to be shared with family members, the most appropriate person to make the initial contact is generally the person who has undergone the genetic test (Forrest et al 2007). There may be difficulties in communication between particular family members, in these cases involvement of another family member as a go-between

may be helpful. The health professional may be able to facilitate the process of family communication by providing written information or agreeing to phone contact from the genetic relatives. In facilitating such communication, the health professional must ensure that legal and ethical requirements regarding privacy and confidentiality are maintained.

In Australia, individuals can refuse to pass on genetic information to genetic relatives without a breach of law. However, in deciding not to disclose such information to genetic relatives, an individual will need to balance carefully his/her right to privacy with the fact that disclosure could lead to the avoidance of a substantial chance of harm to a genetic relative. As discussed in Section 2.2, the changes to the Privacy Act in 2006 allow, in the appropriate exceptional circumstances, for a health professional working in the private sector to release information to genetic relatives without the consent of the person being tested.

Psychological adjustment to genetic test results can occur over a period of time and this should be considered in the ongoing follow up.

6.4.3 Dispute of test results

Dispute of results can occur in relation to the actual positive or negative result of the test, or the interpretation of the result. If a patient disputes the results of a genetic test, the reason for the dispute should be investigated and options for addressing the dispute should be sought by the health professional responsible for ordering the test. As a last resort, if the dispute cannot be resolved, the patient may want to seek a second opinion.

Part C: Other types of genetic tests

This chapter outlines the ethical, legal and social issues associated with direct to consumer testing, and the use of genetic testing to identify health and personal information for purposes other than the direct medical care of the individual.

7.1 Direct to consumer (DTC) genetic testing

Direct to consumer (DTC) genetic tests are tests that are conducted by genetic testing laboratories without requiring a referral from a health professional. The customer wanting a test deals directly with the laboratory; supplying the sample, receiving results and paying for the test.

Several Australian laboratories offer identity-related DTC genetic tests (for example paternity testing), but currently none offer diagnostic or predictive DTC genetic tests for genetic diseases without the test being ordered by a health professional. However, there is a concern that some companies are advertising directly to the public and indicating that if an individual does not have access to a health professional to order the test, the company will provide a list of health professionals able to do so. Since some of the tests offered in these circumstances involve the multifactorial medical conditions such as diabetes, it is difficult to see how most health professionals can order this type of test and then have the knowledge to help interpret the results.

The situation is different when it comes to overseas based companies. A broad range of tests are available via the internet from providers in the USA, including predictive and diagnostic tests for a range of genetic disorders, as well as lifestyle tests such as dermatogenetics and nutrigenetics.

Resources

For further information on DTC DNA testing see **www.nhmrc.gov.au/your_health/issues/genetics/dtc.htm**

A useful resource that provides an overview of what companies in the USA are offering DTC DNA tests is the Genetics and Public Policy Center in Washington DC at **http://.dnapolicy.org/resources/DTCcompanieslist.pdf**

Related tests that raise similar regulatory and ethical issues to DTC tests include:

- direct to public genetic tests (HGC 2007), where someone other than a health professional (e.g. a pharmacist or an alternative medicine practitioner), orders the test and/or interprets the results raised
- tests that can be initiated by the consumer but where the results are formally requested and/or delivered by a health professional who may not have the expertise.

Resources

The Hunter et al (2008) article cogently summarises a number of reasons why DTC genetic testing is not currently useful at **http://content.nejm.org/cgi/content/full/358/2/105**

Regulation of direct to consumer genetic tests

At present, the accreditation of laboratories and regulation of test kits is limited to medical laboratories which provide tests in a healthcare setting. A medical test cannot be provided by an Australian laboratory without the involvement of a health professional in the care of the person being tested. These restrictions do not apply to tests that are provided directly to a consumer by an overseas laboratory. An overseas laboratory can market DTC genetic tests through the internet and provide testing to people in Australia without fulfilling any of the Australian accreditation or regulatory requirements.

Commentary

One of the key requirements of an accredited medical laboratory is that medical tests are only provided in a medical context, being requested by and reported to a registered health professional (see **www.health.gov.au/internet/main/publishing.nsf/Content/npaac-nucleic-acid-toc~npaac-nucleic-acid-diag~npaac-nucleic-acid-gen**).

The proposed involvement of the TGA in the regulation of all medical tests will have implications for DTC testing. The TGA has developed non-binding guidance to assist the use of certain tests, and a number of other options are being considered. A mix of regulatory approaches will be required, including provision of consumer education, strengthening consumer protection legislation, and introduction of ethical guidance for industry.

This multifaceted approach is consistent with the recommendations of the UK Human Genetics Commission (HGC 2003; 2007) and the view of the American Society for Human Genetics (ASHG) (Hudson et al 2007). More stringent regulation would involve restricting advertising or even banning or restricting the DTC tests. While the restrictions described might be options for DTC genetic testing laboratory operating in Australia, they are not practical suggestions for overseas based laboratories.

Ethical, legal and social issues

- While DTC testing may be attractive to consumers who are concerned about their genetic information being passed on to insurance companies, the relative lack of control over sampling in the home raises the possibility of testing that is unauthorised, or performed without adequately informed consent, leading to threats to privacy.
- While laboratory analysis of DTC tests may accurately detect genetic differences, it can be difficult for consumers to understand the scientific uncertainty associated with genetic tests and accurately infer conclusions from the test results; this is relevant to the single gene Mendelian diseases but is particularly the case for predictive testing for multifactorial diseases and those used as the basis for lifestyle interventions.
- Potential risks to consumers include psychological harm from receiving adverse results in the absence of genetic counselling, inability to make appropriate and informed decisions without the involvement of a health professional, and becoming one of the 'worried well' if identified as being even at low risk of developing a potentially life-threatening disease (e.g. heart disease).
- There are concerns regarding the scientific validity and misleading claims of DTC genetic tests, including:
    - testing benefits may be overstated; for example, some dermatogenetics companies claim to provide definitive information on skin health on the basis of genetic tests, although there is limited evidence of the accuracy or utility of these tests in relation to skin care
    - the results of DTC tests may be misleading, ambiguous or inaccurate, as found by a US Government Accountability Office study (US Government Accountability Office 2006 – see **www.gao.gov/new.items/d06977t.pdf**).

Commentary

A recent comparative study of two US-based DTC genetic testing companies in the USA showed that while the accuracy of the raw data was high (99.7% - ie. the laboratories consistently got the same genetic test result), the clinical interpretation of the test result was a major concern. For seven diseases, the two laboratories testing the same five individuals had 50% or less agreement in their clinical interpretation in terms of increased risk, decreased risk and average risk (Ng et al 2009).

Health professionals need to be well-informed and appropriately supported so that they can guide consumers to make informed decisions and help reduce the negative impacts of DTC genetic testing.

Resources

UK HGC Common Framework of Principles (currently draft principles and consultation document) can be found at **www.hgc.gov.au/Client/Content.asp?ContentId-816**

7.2 Lifestyle choices

The range of genetic testing for lifestyle issues is continually expanding as new gene associations are discovered. In Australia, several companies offer services analysing the profiles of genes associated with nutrition, skin care and lifestyle-related conditions. These tests are generally offered through the internet via DTC advertising. In some cases, potential customers need to be referred by their health professionals or company providers who are registered health professionals.

Some of these tests (e.g. nutrigenetic tests) are currently exempt from regulatory oversight by the TGA. However, proposed changes to legislation governing the operation of the TGA will have implications for all human genetic tests.

Presently the philosophy of 'caveat emptor' or 'let the buyer beware' would apply to non-medical genetic tests because health issues are not involved. However, as indicated in the following section, there remain wider concerns about these types of genetic tests.

Ethical legal and social issues

There are issues regarding the scientific validity and misleading claims of DTC genetic tests, including:

- testing benefits may be overstated; e.g. a company might claim to provide definitive information on 'cardiovascular health' on the basis of genetic tests, although the evidence for the accuracy or utility of these tests might be limited or still subject to further research and confirmation. Consequently, the individual might believe (erroneously) on the basis of the genetic tests result that he/she no longer needed to pay attention to established prevention measures e.g. avoidance of dietary factors implicated in cardiovascular disease
- public trust in medical genetic testing will be eroded by continuing false or exaggerated claims for medical and lifestyle type tests.

Resources

The TGA Forthcoming (new) regulatory framework for IVDs is available at **www.tga.gov.au/ivd/forthcoming.htm**

7.3 Genetic relationship testing

7.3.1 Genetic paternity testing

Genetic paternity testing is primarily used as part of Family Law court proceedings or through readily available DTC genetic testing to establish paternity or maternity.

Court-related matters require testing to be carried out in laboratories that follow family law regulations including accreditation by NATA. Accreditation in this instance is to the ISO 17025 standard which is less than that required of medical testing laboratories that undergo accreditation to the ISO 15189 standard (see Appendix C). Commercial kits used by laboratories for paternity testing have been developed for forensic purposes and so have undergone a significant degree of evaluation and assessment. In contrast, for DTC genetic testing there are no regulatory controls and evidence gathered in this way is unlikely to be acceptable to Australian courts.

Ethical, legal and social issues

One of the principle concerns in paternity testing (or relationship testing generally) is that of consent. Testing involves samples from at least two genetic relatives e.g. father and child, and the samples should only be obtained without coercion and with the consent of the person or appropriate parents/guardians. A model criminal offence relating to non-consensual genetic testing is currently being developed (see Section 2.3 for further discussion of the draft model legislation).

7.3.2 Genetic ancestry testing

Family connections and tracking can now be undertaken through genetic testing, and has become another example of the 'recreational genomics' being offered by DTC genomics companies. It has also opened up a broader potential to search for likely genetic relatives overseas or genetic relatives from many past generations.

Ancestry testing services predominantly identify common variations in genes and in non-coding DNA and, on this basis, claim that affinities between individual or ethnic groups can be established. However, research has established only associations between these markers and certain ethnic groups, which vary in strength and reproducibility. Overall, these associations are less relevant to individuals than to large populations.

Ethical, legal and social issues

Ancestry testing is not used for medical purposes, although it has the potential to identify genetic information relating to contemporary genetic relatives without their consent. The rapid growth in this type of testing is raising concern because of its possible impact on a wide range of psychosocial, ethical, legal and social issues, political and health related issues, and the unresolved scientific and non-scientific challenges (ASHG 2008). Consumer protection is an issue, particularly in relation to false advertising and the limitations of testing.

7.3.3 Genetic testing for immigration

Genetic testing for immigration is an extension of paternity testing, and allows DNA evidence to prove relationships that might not otherwise be possible through the usual documentary evidence. This can be useful in assessing visa applications and other migration related decision-making.

Like genetic paternity testing, there are accredited genetic testing kits that allow a range of DNA markers to be tested thereby confirming or excluding relationships. The utility of these

DNA markers depends to some extent on the availability of key individuals in the family and the closeness of the relationship being tested. For example, it is relatively easy to establish the relationship of children if DNA from both parents is available, but harder to establish the relationship of more distant genetic relatives (e.g. cousins).

Ethical, legal and social issues

The ALRC/AHEC Report Essentially Yours (ALRC & AHEC 2003) identified the following key issues in relation to non-medical testing:

- providing documentation and counselling for those who want to use genetic testing for immigration purposes
- chain of custody of these genetic tests to ensure that there is no identity fraud or other manipulation of results
- conducting genetic tests only for the purpose stated
- genetic testing laboratories doing such tests having the appropriate qualifications and accreditation.

7.4 Genetic testing and the life insurance industry

Life insurance companies obtain genetic information by asking questions about the health and causes of death of close genetic relatives, and such information can be used to determine eligibility for life insurance. As genetic testing has become more readily available, insurers view this genetic information as no different from other health information and therefore expect it to be disclosed. If a test has been undertaken the insurer may then request the test result if it is believed the information is relevant to its underwriting decision. Insurers wish to avoid adverse selection, which is the situation where a disproportionate number of individuals at high risk of receiving an insurance payout purchase insurance policies. These developments have raised concerns that unfair discrimination could occur if genetic information is used inappropriately by insurers. In Australia, insurance companies are not in breach of the *Disability Discrimination Act 1992* (Cwlth) if their actions are based on sound actuarial and other relevant statistical data, and the use of genetic information is not unfair discrimination when used in this way.

In Australia, the recommendation of the ALRC/AHEC *Essentially Yours* report (ALRC & AHEC 2003), which was accepted by the Commonwealth Government, is that genetic information is no different to any other information for insurance purposes; that is, the general law on insurance contracts requires mutual disclosure in good faith of all relevant material and information that would help in risk assessment.

The insurance industry has agreed that no insurer will require an applicant or insured person to have a genetic test as part of a policy application. However, under Australian law, applications for life insurance are required to disclose any health or genetic information known by the applicants, about themselves or genetic relatives.

Resources

The insurance industry genetic DNA testing policy is found under IFSA Standard 11 at www.ifsa.com.au/documents/IFSA%20Standard%20No%2011.pdf

Some issues are still to be addressed to ensure that the appropriate use of genetic testing occurs within the industry. These include:

- continuing education of agents in the insurance industry to avoid inappropriate discriminatory use of genetic information
- a clear understanding by customers of the mechanism to lodge complaints if it is felt inappropriate decisions have been made
- ensuring rigorous actuarial assessment of the applicability of a genetic test in the insurance setting – particularly in relation to those genetic diseases with low penetrance
- plain English application and information sheets so that individuals understand exactly what is required of them (as well as the insurance industry).

It is clear that a procedure needs to be set in place to ensure that genetic tests are used appropriately. The expertise for this needs to come from insurance industry bodies working with experts in genetics.

Ethical, legal and social issues

It is possible that some people do not have genetic testing or seek genetic counselling in case the results jeopardise access to life insurance, and this may have a long-term adverse effect on their health.

Commentary

A recent population-based study by Keogh et al (2009) assessed whether knowledge of insurance implications influenced uptake of genetic testing. The study reported that the proportion of participants who declined genetic testing among those informed of insurance implications was more than double the proportion among those without this knowledge. However, it is important to note that this study involved a small sample size with statistical validity and so possible bias cannot be excluded.

People who act as volunteers in genetics research projects need to know that any results provided to them have the potential to adversely affect their ability to obtain life insurance. This needs to be clearly explained as part of the consent process. Volunteers who are not given test results are under no obligation to disclose their participation in the research project unless specifically asked if they had undergone genetic testing. The participant could then explain that they have in the context of a research study but have not received any results. This is unlikely to put them at a disadvantage in relation to life insurance.

Commentary

A justification that has been given for the insurance industry to use information provided by genetic tests is that these same tests are used by health professionals in clinical decision making. Superficially this is the case but the significance of genetic test results in clinical practice is interpreted differently taking into consideration the clinical context. Similarly, the use of genetic test results by the life insurance industry must take into consideration the relevant actuarial evidence about the implications of the genetic test result on life expectancy.

7.5 Genetic testing in the workplace

Health information is used in a number of areas of employment including health screening, health surveillance and other health assessments (see ALRC & AHEC 2003, Chapter 29).

Examples include:

- health screening in the form of medical examinations essential for OH&S requirements when operating hazardous machinery
- health surveillance when there is possible workplace exposure to hazardous materials
- health assessments as part of sick leave applications and workers' compensation examination.

In all of these activities, it is possible that genetic information might provide useful information or might be misused. In the USA, predictive testing for disease risk factors is a particular concern as the employment package for an individual might also include medical insurance. The recent passage of the Genetic Information Nondiscrimination Act of 2007 (GINA) in the USA may now address this concern. Although this is not an issue in Australia since health insurance is community-rated and not part of workplace contracts. Within the employment scenario there are many competing interests including employers' interests, employees' interests and the public interest, and the inappropriate use of genetic information in the workplace is potentially a difficult and growing area of concern.

Commentary

Workplace testing is currently used by the Australian Federal Police and Australian Army, which ask new recruits to volunteer their DNA specimens for storage in case they are needed for body part identification or (in the case of the Australian Federal Police) excluding an officer's DNA profile if there is crime scene contamination. In one case, a negative genetic test result allowed a person, who was thought to have Marfan syndrome on the basis of his height, to be accepted into the Australian armed forces (Barlow-Stewart and Keays 2001).

Ethical, legal and social issues

Ethical, legal and social issues related to genetic testing in the workplace include storage and safeguarding of DNA samples, the potential for samples to be used for other purposes without consent, and disposal of samples when individuals are no longer employed by the organisation.

The ALRC/AHEC Report Essentially Yours concludes that genetic testing is inappropriate in the workplace unless there is:

- strong evidence of a clear connection between the working environment and the development of the disease

Commentary

Two examples that have been cited are sickle cell anaemia and work at high altitudes and certain HLA genetic types that indicate predisposition to berylliosis, a disorder that causes chronic lung disease and which can be prevented by avoiding exposure to beryllium.

- the disease may seriously endanger the health or safety of the employee
- the test is a scientifically reliable method of screening for the disease.

The number of known situations in which the work environment is harmful because of genetic susceptibility is very small. In contrast, there are a number of examples given where employers have inappropriately used genetic (and non-genetic) medical information to discriminate against employees. In all cases, there was little to no scientific basis for this type of response from the employers.

Examples

In Australia, a workers compensation claim was questioned because of a family's history of Huntington disease. The employee was pressured to have testing to prove the fall was not an early sign of the disease (Barlow-Stewart et al 2009). Another example of genetic discrimination in the workplace is the Burlington Northern Santa Fe Railroad in the USA which used genetic information to predict risk for carpal tunnel syndrome in employees who were asking for worker's compensation. The tests were conducted without the employees knowledge of the purpose of testing and were found to be scientifically flawed (Geppert and Roberts 2005). See **www.mindfully.org/GE/GE4/Railroad-Workers-Genetic-Defects8may02.htm**

7.6 Genetic testing in sport

Two main uses for genetic testing in sport are:

- *Talent search*—There is potential to use genetic information to predict more accurately the likelihood of success in elite athletes. However, like the multifactorial genetic diseases and normal traits, the contribution of genetics to sporting ability is complex and involves a mix of genetic and environmental factors, including the availability of training opportunities.
- *Risk assessment*—Genetic testing may help identify athletes at increased risk of a medical disease being precipitated by involvement in sport, or those who are at increased risk of injury that would arise directly from the sport. For example, athletes with a familial predisposition to cardiomyopathy or cardiac arrhythmia may be at increased risk of sudden cardiac death while stressed during competition. Boxers with certain APOE4 variants are at increased risk of neurological complications and permanent brain injury (McKee et al 2009).

The benefits or otherwise of screening have not eventuated. As more information is gathered about a variety of physiological parameters (e.g. muscle and joint functions) it might be possible on the basis of a genetic or genomic profile to identify those more likely to be at risk of injuries from rigorous training. These uncertainties complicate the use of the DNA testing in sport.

The Australian Sports Commission, in consultation with the relevant stakeholders, is developing a national policy on genetic research in sport as well as talent search and predisposition to sports-related illness or injury.

Resources

The HGSA has published a position statement on Genetic Testing and Sports Performance (HGSA 2007) available at **www.hgsa.com.au/index.cfm?pid=111468**

Ethical, legal and social issues

Talent search—The fact that there is not enough known about genes and sporting ability raises significant ethical issues for the organisations or DNA testing laboratories that promote or use this form of testing at present.

Risk assessment—The finding of a genetic abnormality that might increase the risk of injury or other medical consequence of sport can raise complex ethical, legal and social issues, including the potential to discriminate against a person (for reasons of safety for the individual or concern by a sporting organisation that it would be liable if an accident occurs), the potential to prevent harm and an individual's choice about what he or she wants to do. On the other hand, if evidence were provided that a genetic marker predicted injury or more serious medical consequences, the sporting organisation might be placed in a difficult medico-legal situation if it did not offer this test or the information about risk as part of the medical workup.

7.7 Genetic testing for research purposes

The development of tests in the research setting is an important route by which a new genetic test is discovered and then translated into clinical practice. However, the point at which a genetic test moves from being a research tool (to increase understanding of the disease) to being a resource for clinical services (to assist clinical decision making) can be problematic particularly as some new gene discoveries are widely disseminated in the media with the promise of important and immediate benefits to health before the findings are evaluated or reproduced by others (see Section 3.1). This is an important distinction because genetic tests used in clinical practice in Australia are not usually formally evaluated for their clinical validity or utility. This means a genetic test that is used as part of a research program is, even less likely to have undergone some form of evaluation.

Genetic research can raise similar ethical issues as have been discussed in relation to genetic testing for medical purposes. The *National Statement* is the key document for ethical guidance in relation to research and includes a chapter on human genetics (Chapter 3.5).

Resources

The HGSA has published a position statement on Genetic Testing and Sports Performance (HGSA 2007) available at **www.hgsa.com.au/index.cfm?pid=111468**

Part D: Current and emerging technologies

This chapter considers some technologies that have recently started to be used in the context of medical genetic testing, or technologies that are emerging and are expected to play an important role in new approaches to genetic testing.

8.1 Microarrays and related technologies

A microarray consists of a highly miniaturised assay that is replicated thousands of times on a small chip. The resulting chip may be only 1 centimetre square yet be able to assay for the presence of tens of thousands of different genetic variants. Microarrays are a relatively new technology which may be useful tools in analysis of cancer tissue (identifying profiles of mutations that carry prognostic or therapeutic significance), analysis of multiple genes that cause the one medical disease, or analysing multiple genes implicated in the metabolism of or response to a specific medication.

Although the possibility for using them is vast, there is a paucity of information regarding the use of DNA microarrays to give clinically-relevant data. Considerable research is being conducted worldwide on the use of microarrays for multiple gene expression analysis, copy number variation, DNA methylation analysis and highly specific regulatory miRNA analysis.

Such multiplexed assays, with their novel and complex interpretation algorithms may present significant analytical and clinical validity problems compared to single gene detection assays. However most of these are now being overcome. Consequently their use has moved into the clinical arena, for example in the investigation of unexplained developmental delay in children. In these patients genome-wide microarray with targeted assessment focussed on known syndromes and subtelomeric regions is resulting in significantly increased diagnostic yield. This is leading to benefits in clarification of recurrence risk, better access to services, avoiding unnecessary further testing, and appropriate guiding of medical referrals.

Ethical, legal and social issues

Microarray-based genetic tests present a number of complex issues. To demonstrate clinical efficacy expensive long term prospective clinical trials will be needed. These take time and in the context of a disease like breast cancer, there is considerable pressure from media (and perhaps consumer groups) who will expect the perceived benefits of new discoveries to be implemented sooner rather than later.

Since microarray-based genetic technologies for these potentially beneficial tests are likely to be expensive (and so far only one—comparative genomic hybridisation, is funded through the MBS), there will be issues in relation to access and equity: those who can afford these tests will be able to purchase them while others will be excluded.

The shift from conventional cytogenetic karyotyping to high resolution whole genome array comparative genomic hybridisation (array CGH), also known as molecular karyotyping, is resulting in more unanticipated incidental findings, particularly in children with developmental delay and congenital abnormalities. These may be of potential health or reproductive significance, either for the person being tested or for other family members, and may vary from copy number variations (see next section) known to be benign or of unknown significance to those known to be pathogenic including segmental loss of heterozygosity.

The potential for microarray tests to reveal findings unrelated to the clinical presentation has significant implications for the informed consent process and both pre and post test genetic counselling.

8.2 Copy number variation

The investigation of genomic structural variation in disease initially focussed on visible chromosomal changes, starting in 1959 with the identification of an additional small acrocentric chromosome in Down syndrome. Other visible chromosome changes resulting from deletions of parts of chromosomes were also described, such as Cri-du-chat syndrome with a partial deletion of the short arm of chromosome 5- characterised by a monotonic cat-like cry and some dysmorphic features. Then, in the 1990s, with the advent of the ability to analyse short DNA sequences, single gene mutations were identifiable in which only one base pair may differ from the normal gene.

More recently, however, the use of array-based CGH scanning has led to the realisation that whole sections of the genome may be replicated (often more than once) or deleted, and that whilst some of these changes may lead to disease states such as Charcot-Marie-Tooth neuropathy, others may be classed as contributing to normal genetic variation both within and between populations. Insertions and inversions may also be found.

A CNV may be described as a DNA segment, of at least 1 kb in size, for which copy number differences have been observed in comparison to a reference genome sequence. These quantitative variants can be genomic copy number gains (insertions or duplications) or they can be losses (deletions or null genotypes) (Scherer et al 2007). This broad definition makes no reference to the clinical impact of a given genomic imbalance.

Determination as to whether a CNV is pathogenic or benign in nature may require consideration of the following risk criteria (Lee et al 2007):

Major risk criteria	Potentially pathogenic	Potentially benign
1a. CNV inherited from a healthy parent		×
1b. CNV inherited from an affected parent	×	
2a. CNV similar to one in a healthy genetic relative		×
2b. CNV similar to one in an affected genetic relative	×	
3a. CNV overlaps an imbalance in a CNV database for healthy individuals		×
3b. CNV overlaps an imbalance in a CNV database for affected Individuals (e.g. DECIPHER*)	×	
4. CNV contains disease-causing genes	×	
5a. CNV is gene rich	×	
5b. CNV is gene poor		×

Minor risk criteria	Potentially pathogenic	Potentially benign
1a. CNV is a deletion	×	
1b. CNV is a homozygous deletion	×	
2a. CNV is a duplication		×
2b. CNV is a gain of more than one copy	×	
3. CNV is greater than 3 Mb in size	×	
4. CNV is devoid of known regulatory elements		×

*DECIPHER – Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (www.Sanger.ac.uk/PostGenomics/decipher/)

8.3 Quantitative real-time polymerase chain reaction (Q-PCR)

Measuring the relative amount of DNA that is produced by end point PCR amplification measured on post PCR agarose gels is both time-consuming and inaccurate.

Quantitative real time polymerase chain reaction (Q-PCR) is a method that continuously measures the amount of DNA during the whole of the PCR cycle and thus allows accurate measurement of fluorescent emission, relative to the starting amount of DNA. This is best performed during the early exponential phase when the reaction is at its highest efficiency, and the amount of DNA is doubling with each cycle.

The use of messenger RNA converted to complementary DNA by reverse transcription may also be used in real time PCR (known as RQ-PCR), thus allowing quantification of messenger RNA much more accurately than other methods such as northern blot analysis. Combining Q-PCR with the numerous detection chemistries (primers and probes) has enabled its utilisation in many clinical applications such as gene expression analysis, estimation of CNV, assessment of minimal residual disease (e.g. BCR-ABL in chronic myeloid leukaemia), SNP analysis, mitochondrial DNA studies, DNA methylation studies, microsatellite instability, chimerism studies following haemopoeitic progenitor cell transplantation, and rapid detection of fetal aneuploidy following amniocentesis. However newer techniques such as digital PCR may soon allow non-invasive prenatal diagnosos (NIPD) of aneuploidies rapidly and economically.

8.4 Point-of-care genetic testing

Normally point-of-care testing (PoCT) is considered to be most useful in situations where a rapid turnaround of a test result is required in order to manage the clinical condition of the patient urgently or where immediate institution or change of therapy is required (e.g. glucose testing using hand held glucose meters by diabetic patients in their own homes).

The use of PoCT in genetic testing has long been problematic from a technical perspective because of the need for thermal cycling (commonly called PCR – polymerase chain reaction) to deliver amplification of the target DNA, and the inability to develop an instrument that is portable and fast enough to allow the production of accurate results while the patient is being seen by the health professional. The ability to detect and characterise genetic markers without PCR has been a goal of the diagnostic manufacturing industry for some years now, as the potential for growth are considered to be enormous especially in the fields of human pharmacogenetics, infectious disease testing, bioterrorism and natural pandemics.

Recent developments include rapid iso-thermal amplification techniques and methods utilising DNA as a molecular nanowire by inserting a metalised backbone. This becomes highly conductive following hybridisation and then measuring change in conductivity rather than light detection have dramatically improved sensitivity to the point where DNA PoCT devices are easily achievable.

In the near future, patients about to be prescribed Warfarin, may be tested for their *CYP2C19* and *VKORC1* gene variants before initial dosing without leaving the health professional's surgery.

The European Community is currently funding a project known as CD-MEDICS (Coeliac Disease Management Monitoring and Diagnosis using Biosensors and an Integrated Chip System) to devise a PoCT device to measure the HLA-DQ2 & 8 genes to provide information on the genetic predisposition of the individual, and serum IgA and IgG antibodies associated with gluten in the diet. This microarray device will then automatically communicate with hospital information systems to provide the health professional with appropriate feedback. The device will form an efficient way to identify at-risk individuals, may negate the need for invasive diagnosis, and will allow monitoring of patients who have the disease in order to ensure that they are complying with a gluten free diet.

The Department of Health and Ageing has recommended that a Working Party develop non-statutory guidelines for PoCT. It is likely that any commercial PoCT test not being used by an accredited laboratory will require a mandatory Technical File Review by TGA before release in Australia.

One of the major problems with PoCT in genetics is that the rapid advancement of PoCT technology will inevitably move from genetic diagnosis of single gene diseases to more complex evaluations in which the results cannot be readily either validated or understood by the health professional.

As PoCT becomes more common, it will be need to be accompanied by the delivery of good genetic information to the point of care, so that primary care providers are able to accurately assess and relay test results.

8.5 Epigenetics

DNA can exhibit specific chemical or physical changes which do not alter the genetic sequence of nucleotides, but do alter the way in which this genetic sequence is accessed and utilised by the cell. These specific chemical changes are referred to as epigenetic changes. Epigenetic mechanisms result in potentially heritable changes in gene expression that are not encoded within a DNA sequence, and which may also be reversed, to manage such functions as genetic imprinting and X chromosome inactivation, chromatin organisation, repetitive element silencing, and normal specific methylation and histone modification. Epigenetic errors can result in abnormalities through imprinting defects, hypermethylation, hypomethylation, mutations involving cytosine in methylated CpG or mutations resulting in changes to specific chromatin structure. Methylation patterns are known to fluctuate in response to diet and exposure to environmental toxins. Sensitivity to diet or toxins may vary due to genetic polymorphisms in genes that impact upon methyl metabolism such as the *MTHFR* gene. Depending on when these acquired fluctuations occur they may be passed on to the next, and possibly subsequent, generations.

Another way by which the function of genes can be altered epigenetically is via ncRNA. Although it was initially thought that humans had about 100,000 genes, it became apparent as the Human Genome Project progressed that the actual number was considerably less. Today, it is estimated that humans have about 20,000 genes which is remarkably similar to other vertebrates and even plants. Therefore, the complexity of the human phenotype has to be explained by other mechanisms beyond the traditional protein-coding genes. Attention has now shifted to non-protein coding intronic and intergenic sequences in genomes where there is an increase in complexity commensurate with the developmental complexity of the organism (Mattick 2009). ncRNA and their potentially different effects on gene expression are therefore additional mechanisms for epigenetic changes.

Epigenetic errors have been detected in relation to imprinting and paediatric diseases, cancer, neurological diseases, systemic lupus erythematosus (a form of autoimmune disease), cardiovascular diseases, reproductive diseases and diseases associated with ageing. The individual diseases can vary from single genes or multiple genes to outcomes affecting the whole genome.

These modifiers of transcriptional control offer new approaches to molecular diagnosis and treatment. Detection of aberrant methylation in specific CpG islands can potentially be used:

- to detect cancer in biopsy specimens
- to detect degraded cancer cells in body fluids
- to monitor clinical response to therapy or for prognosis
- as a cancer risk marker in normal tissue.

Investigation of genomic methylation in stem cells may provide better insight into transplantation.

The use of histone deacetylase inhibitors (HDAC) and DNA methyl transferase (Dnmt) may provide opportunities for therapeutic gene silencing. Dnmt inhibitors are already being used in the treatment of myelodysplastic syndromes, and the anti-epileptic drug valproic acid, found to be a HDAC inhibitor, have recently being undergoing Phase II trials in refractory solid tumours (Candelaria et al 2007).

Ethical, legal and social issues

Ethical, legal and social issues in epigenetics remain largely unexplored. There is the potential for epigenetic changes to influence individuals as well as future generations but unlike the more traditional Mendelian type genetics, the epigenetic changes are considered to be reversible and interacting with the environment. The growing evidence that many aspects of human behaviour and environmental exposure have the potential to impact upon the methylation patterns of the individual and also their offspring and future generations impart some responsibility not only on that individual but may confer multi-generational liabilities on others (Rothstein et al 2009).

Commentary

Of interest is that the House of Lords Report on Genomic Medicine does not consider epigenetics in any great detail (**www.publications.parliament.uk/pa/ld200809/ldselect/ldsctech/107/10702.htm**). The report states that advances in epigenetics are not likely to have any significant impact on healthcare in the next several years due to the lack of understanding about the cause and effect of epigenetic changes on disease prevalence, and lack of specific therapies that target epigenetic processes.

8.6 Whole genome DNA sequencing

Determining the whole genome sequences of many organisms including humans is essentially a research application with many goals – understanding how genes work, understanding evolution, identifying genes or DNA sequences useful for novel therapies or as markers for organisms.

The first human genome sequence completed in 2003 is estimated to have cost about US$3B. Today, it is possible to request a whole genome DNA sequence through DTC genetic testing companies in the US or Japan for about US$70,000. The ultimate goal being pursued is a cost of US$1,000 for a whole DNA sequence and this seems likely in the near future. As the cost continues to fall, it will be increasingly available through DTC genetic testing as well as traditional genetic testing laboratories.

DNA sequencing is considered the 'gold standard' and so quality assurance is difficult as there is nothing to compare except for other sequences. In addition to the actual hardware to produce a DNA sequence, it is essential to have software to analyse the results. Software programs allow DNA sequences to be interrogated and identify places in the sequence where there are changes from the listed 'control' sequence or where there are likely to be abnormal changes in the DNA sequence. Therefore, the quality assurance aspects of genetic testing will be an even greater challenge than the more straightforward DNA mutation tests that generally focus on a single mutation.

Ethical, legal and social issues

Whole genome sequencing poses interesting challenges:

- They will produce a large amount of data most of which will have little meaning today. However, as the bioinformatics tools are better able to interrogate the sequence data and as our understanding of genes and gene function grows, data obtained will be reinterrogated and additional information about genetic predisposition to disease found. Some of this may be unwanted. Similarly, while individuals who request a whole genome sequence may not be concerned about these implications, they should be aware that the information will be shared by their children and other genetic relatives and this has an impact on their privacy, including their right not to know.

Examples

Dr James Watson when having his whole genome sequence made available for all to access specifically requested that sequence information on the APOE4 gene variant (see Section 7.6) be excluded because of potential implications for his son.

- The costs for whole genome sequencing are falling rapidly and as of late 2009, there are reports of US companies offering these (without the bioinformatics interpretation) for <US$5,000. The goal of the $1,000 whole genome sequence would seem feasible in the near future. This is relatively cheap as it would only need to be obtained once in an individual's lifetime and could be reinterpreted as required eg. pharmacogenetic information as new drugs are prescribed. It is unlikely that individualised DNA tests targeting individual genes would then be cost effective except for those involving somatic cells. Presumably low costs will make the whole genome sequence more attractive than targeted mutation testing as is undertaken today.
- What if an individual did not want a whole genome sequence because of privacy concerns? This will limit access to pharmacogenetic information in the scenario just mentioned.
- As whole genome sequences become an integral part of clinical management, they will need to be kept in electronic form because of their size, hence the relevance of eHealth and Electronic Health Records to capture the most information from genomic medicine.

Commentary

An Individual Electronic Health Record (IEHR) is a secure, electronic record of a person's medical history, stored and shared in a network of connected systems. The IEHR will bring key health information from a number of different systems together and present it in a single view. Information in the IEHR will be able to be accessed by the person and their authorised healthcare providers. In the future, as the IEHR becomes more widely available, people will be able to access their own health information anytime and from anywhere in Australia. More than 80% of Australians are in favour of electronic health records and are increasingly aware of the safety and quality benefits that e-health can deliver. For further information see **www.nehta.gov.au**

- Finally, while whole genome sequencing is becoming very cheap, it is still subject to many errors across the whole genome. So information obtained would need to be verified.

Resources

A recent review in the American Journal of Human Genetics describes the technological advances that have allowed whole genome sequencing to progress to where it is. This review also highlights a number of potential ethical legal and social issues that will need to be addressed (Tucker et al 2009).

Appendices

Appendix A: Acronyms and abbreviations

ACCE	Analytic validity, clinical utility, clinical validity and ELSI (ethical, legal and social issues). Four standard criteria recommended as a means of evaluating genetic tests.
AHEC	Australian Health Ethics Committee
ALRC	Australian Law Reform Commission
ARTG	Australian Register of Therapeutic Goods
ASHG	American Society for Human Genetics
CNV	Copy Number Variation
DoHA	(Commonwealth) Department of Health and Ageing
DNA	Deoxyribonucleic acid
DTC	Direct to consumer
ELSI	Ethical, legal and social issues
FDA	(US) Food and Drug Administration
HGC	(UK) Human Genetics Commission
HGSA	Human Genetics Society of Australasia
HREC	Human Research Ethics Committee
IVD	In vitro diagnostic device (a genetic test is considered an IVD)
IEHR	Individual Electronic Health Record
IFSA	Insurance and Financial Services Association
IPPs	Information Privacy Principles (see also NPPs)
miRNA	MicroRNA
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee (the Commonwealth committee that evaluates all medical devices, pathology tests before they are allowed to go on the MBS)
NATA	National Association of Testing Authorities (Australia)
ncRNA	Non-protein-coding RNA
NEHTA	National eHealth Transition Authority (Australia)
NPPs	National Privacy Principles (see also IPPs)
NPAAC	National Pathology Accreditation Advisory Committee
OH&S	Occupational health and safety
OMIM	Online Mendelian inheritance in man (a free and reputable internet based catalogue of genetic diseases see **www.ncbi.nlm.nih.gov/sites/entrez?db=omim**)
PCR	Polymerase chain reaction
Q-PCR	Quantitative polymerase chain reaction

PoCT	Point of Care Testing
RACP	Royal Australasian College of Physicians
RCPA	Royal College of Pathologists of Australasia
RNA	Ribonucleic acid
SNPs	Single Nucleotide Polymorphisms
TGA	Therapeutic Goods Administration

Appendix B: Glossary

ACCE – analytic validity, clinical validity, clinical utility and ELSI

Analytic validity: defines the tests 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: ability to detect or predict the presence or absence of the disease (phenotype) – its sensitivity, specificity, positive and negative predictive values.

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

Ethical, Legal and Social Issues

Ancestry genetic testing (also called kinship and genealogy testing)

This can be used for many purposes: (1) By an individual to try to identify ancestral origins or population origins for the person and his or her family. (2) Ancestry genetic testing (also called ancestry estimation) can be used in the research environment to infer biogeographical originals or admixtures of populations (from the American Society of Human Genetics 2008).

Anticipation

The tendency for some autosomal dominant diseases to manifest at an earlier age and/or to increase in severity with each succeeding generation.

Cascade testing

Testing of genetic relatives for a mutation that has been identified in the first affected family member.

Charcot-Marie-Tooth neuropathy

Charcot-Marie-Tooth neuropathy is a heterogeneous inherited disorder characterized by loss of muscle tissue and touch sensation, predominantly in the feet and legs but also in the hands and arms in the advanced stages of disease. Presently incurable, this disease is one of the most common inherited neurological disorders, with 37 in 100,000 affected.

Chromatin

Chromatin is the complex combination of DNA, RNA, and protein that makes up chromosomes. Its structure and organisation changes at different stages of the cell cycle, depending on the access required to DNA.

CpG: These are frequently found at the beginning of a gene and are involved in the turning on and off of genes. They contain a high density of hypomethylated cytosine residues (C) associated with guanine (G).

Coeliac disease

Coeliac disease is an autoimmune disorder of the small intestine that occurs in genetically predisposed people of all ages from middle infancy onward. A growing portion of diagnoses are being made in asymptomatic persons as a result of increased screening. Coeliac disease is caused by a reaction to gliadin, a prolamin (gluten protein) found in wheat.

Copy number variation

A DNA segment, of at least one kilobase in size, for which copy number differences have been observed in comparison to a reference genome sequence. Without further annotation, the term CNV carries no implication of relative frequency or of phenotypic effect. The following are useful qualifiers when discussing clinical significance: Pathogenic CNV, benign CNV, CNV of unknown clinical significance.

Cri-du-chat syndrome

Cri-du-chat syndrome also known as chromosome 5p deletion syndrome, 5p minus syndrome or Lejeune's syndrome, is a rare genetic disorder caused by a missing part of chromosome 5. Cri du chat syndrome results from a partial deletion of the short arm of chromosome 5, also called '5p monosomy'. Approximately 90% of cases result from a sporadic, or randomly-occurring deletion. The remaining 10-15% are due to unequal segregation of a parental balanced translocation where the 5p monosomy is often accompanied by a trisomic portion of the genome.

Cystic Fibrosis (CF)

CF is caused by a mutation in the gene cystic fibrosis transmembrane conductance regulator (CFTR). The product of this gene is a chloride ion channel important in creating sweat, digestive juices and mucus. Although most people without CF have two working copies (alleles) of the CFTR gene, only one is needed to prevent CF. CF develops when neither allele can produce a functional CFTR protein. Therefore, CF is considered an autosomal recessive disease.

Dermatogenetics

The study of the impact of variations in gene sequence on skin and hair growth, development and disease.

Down Syndrome

Down Syndrome is a chromosomal disorder caused by the presence of all or part of an extra chromosome 21. Often Down syndrome is associated with some impairment of cognitive ability and physical growth as well as facial appearance.

Electronic health record

An individual's medical record in electronic format, which integrates all elements of the individual's health history including consultations, medications and investigations.

Epigenetics

The study of heritable changes in gene function that occur without a change in the DNA sequence. They refer to modifications in gene expression that are controlled by heritable but potentially reversible changes due to: (1) DNA methylation patterns formed by the presence of methyl molecules (-CH3) attached to CpG dinucleotides along the entire length of the DNA double helix and (2) Various covalent modifications to the histone proteins around which the DNA helix is wound.

Familial adenomatous polyposis (FAP)

FAP is an inherited condition in which numerous polyps form mainly in the epithelium of the large intestine. While these polyps start out benign, malignant transformation into colon cancer occurs when not treated.

Gene silencing

The epigenetic process of gene regulation describing the 'switching off' of a gene by a mechanism other than genetic modification. That is, a gene which would be expressed (turned on) under normal circumstances is switched off by machinery in the cell.

Genetic material

Any source of DNA or RNA that can be tested to obtain genetic information. This includes cells, whether as single cells or as part of tissues, and extracted DNA and RNA.

Genetic test

A genetic test may be performed using DNA, RNA or protein (the 'gene product'), or involve measurement of a substance that indirectly reflects gene function or by analysing chromosomes. A genetic test reveals genetic information.

Genomics

The genome is the complete genetic material in an organism. Hence, genomics is the study of the structure of the genome including its DNA sequence. In contrast to genetics, which predominantly focuses on one gene – one disease, genomic-based technologies allow many (even hundreds or thousands) genes or gene markers to be assessed simultaneously. This has expanded the potential for studying complex multifactorial diseases such as diabetes. Related to genomics are the other 'omics' including transcriptomics (study of all the mRNA species), proteomics (study of all the protein species), metabolomics (study of the global metabolic profile in any cell, tissue or organism), phenomics (overall phenotypic characteristics of an organism based on the interaction of the complete genome with the environment) and the other 'omics'.

Germline variant/mutation

A change in the DNA sequence that may be neutral, of unknown significance, or associated with a genetic disease. It is found in the germ cells (ova or sperm) and so transmitted to the offspring. A germline DNA variant that was present in the ovum or sperm from which the individual developed is present in all the individual's cells and may provide information about future health. May have been inherited from one or both parents (but not always, as a variant can be the result of a change that occurred in the ovum or sperm from which the individual developed). All changes in the DNA sequence are called variants. Those causing disease are usually referred to as mutations. In contrast, a somatic cell variant/mutation is only found in somatic cells and so not transmissible to future generations.

See also Variant

Haemophilia

Haemophilia is a group of hereditary genetic disorders that impair the body's ability to control blood clotting or coagulation, which is used to stop bleeding when a blood vessel is broken. Haemophilia A is a recessive X-linked genetic disorder involving a lack of functional clotting Factor VIII and represents 90% of haemophilia cases. Haemophilia B is a recessive X-linked genetic disorder involving a lack of functional clotting Factor IX. It is similar to but less common than haemophilia A. Haemophilia C is an autosomal genetic disorder involving a lack of functional clotting Factor XI.

Huntington Disease (HD)

HD is an incurable neurodegenerative genetic disease that affects muscle coordination and some cognitive functions, typically becoming noticeable in middle age. HD has autosomal dominant inheritance with each offspring of an affected individual having a 50% chance of inheriting the mutant allele and therefore being affected with the disease.

Hybridisation

The process of combining complementary, single-stranded nucleic acids into a single molecule. Nucleotides will bind to their complement under normal conditions, so two perfectly complementary strands will bind to each other readily (called annealing). However, due to the different molecular geometries of the nucleotides, a single inconsistency between the two strands will make binding between them more energetically unfavourable. Measuring the effects of base incompatibility by quantifying the rate at which two strands anneal can provide information as to the similarity in base sequence between the two strands being annealed. Southern and Northern blotting are two examples of nucleic acid hybridisation.

Insurance

Community rated insurance: Everyone pays the same premium regardless of the individual's personal or family health history. Health insurance in Australia is community rated. Therefore, a genetic test result has no implication for health insurance.

Risk rated insurance: In contrast, life insurance products are risk rated and so a genetic test result (like any other form of health information) could be used to influence whether life insurance is available or whether it comes with a loaded premium. Life insurance products include cover for death, trauma, disability and income protection.

In vitro diagnostic device (IVD)

The TGA defines an IVD as:

> "Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system whether used alone or in combination (with other diagnostic goods for in vitro use), intended by the manufacturer to be used in vitro for the examination of specimens derived from the human body, solely or principally for the purpose of giving information about a physiological or pathological state, a congenital abnormality or to determine safety and compatibility with a potential recipient or to monitor therapeutic measures".

Leber's optic atrophy

A rare inherited condition of the eye that is characterised by the relatively slow, painless, progressive loss of vision, typically with onset in 20-30 year old males. This is due to a mutation of the mitochondrial genome and hence is passed exclusively through the mother.

Lifestyle genetic test

In the context of DTC genetic testing, these quasi-medical genetic tests purport to measure DNA changes that will allow decisions on lifestyle such as what one eats to live a healthier and longer life, or what types of creams will result in younger looking skin. In some cases, the lifestyle choices are specifically directed to different types of health such as cardiovascular health, skeletal health and so on.

Linkage analysis

Linkage analysis is used to determine the genetic location of a disease gene when there are no other 'signposts' available The goal being to identify a piece of DNA of known location that is inherited by all family members affected by the genetic disease, and is not inherited by any of the unaffected family members.

Mendelian diseases

The disease is primarily due to an inherited mutation in a single gene.

Methylation

Methylation can occur either through DNA methylation or protein methylation, and acts epigenetically to repress or activate gene expression.

Microarrays

Tools that allow the analysis / measurement of the expression of genes including their interactions and responses to disease and other challenges.

Multifactorial diseases

Results from varying contributions of gene mutations, complex interactions between inherited mutated genes, spontaneous gene mutations occurring during life, environment, lifestyle and chance.

Mutation in DNA

See Variant

Nutrigenetics

The impact of variations in gene sequence on an individual's responses to nutrients or food bioactives. Therefore, *nutrigenomics* would mean the effects of nutrients or food bioactives on gene expression.

Omics: see Genomics

Penetrance

Describes the proportion of individuals carrying a particular variation of a gene (the genotype) that also express an associated trait (the phenotype). For example, known mutations in the gene responsible for Huntington disease have 95% penetrance, because 95% of those with the dominant allele for Huntington disease develop the disease and 5% do not.

Personalised medicine

The US President's Council of Advisors on Science and Technology in its Sept 2008 report *Priorities for Personalized Medicine* defines personalised medicine as: "The ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not".

Pharmacogenomics

The study of variations of DNA and RNA characteristics as related to drug response i.e. the focus is the study of multiple genes and/or their function.

Pharmacogenetics

The study of variations in DNA sequence as related to drug response i.e. the focus is a single gene and its DNA sequence change.

Point-of-care genetic testing

Diagnostic genetic testing that is performed by or on the behalf of the treating health professional near to or at the site of the patient care, at the time of and for use during consultation.

Polymerase chain reaction

A technique for copying and amplifying the complementary strands of a target DNA molecule. It is an in vitro method that greatly amplifies, or makes millions of copies of, DNA sequences that otherwise could not be detected or studied.

Polymorphism

The presence, in a proportion of people in a population, of multiple sequence variations at a particular point in a gene.

Positional cloning

Identifying the location of the putative gene on a specific chromosome, and then testing genes in that region for mutations.

Post-transcriptional regulation

The control of protein synthesis by genes after synthesis of RNA has begun.

Post-translational regulation

Refers to the control of the levels of active protein produced, either by means of reversible events (post-translational modifications, such as phosphorylation or sequestration) or by means of irreversible events (proteolysis).

Predictive genetics (predictive and presymptomatic genetic testing)

Predictive testing: is undertaken to determine if a person who generally has no signs or symptoms of a specific disease at the time of testing, has the specific genetic mutations that increase the likelihood that he/she may/will develop the disease in the future. Predictive testing in diseases such as familial cancer can only be done when the family-specific genetic mutation is known.

Presymptomatic testing: is undertaken to determine if a person will develop the disease if they live long enough but symptoms of the disease have not yet manifested, e.g. Huntington disease testing. While this distinction may have benefit, for practical purposes it is not necessary to capture both uses. Predictive genetic testing is the more popularly used term and so this will be continued in this Information Paper. In the USA the preferred term is *susceptibility* testing and this has some merit.

Pre-disease: Predictive genetics has produced a new concept of disease – 'pre disease' because now it becomes possible to identify DNA variants in inherited genetic diseases long before there are signs of symptoms of disease having developed.

Privacy Principles (IPP and NPP)

The *Privacy Act 1988* (Cwlth) contains two sets of privacy principles that are directed to personal privacy: The Information Privacy Principles (IPPs) which apply predominantly to public sector agencies and the National Privacy Principles (NPPs) which apply to private sector organisations.

Repetitive element silencing

This describes a process of epigenetic gene regulation, where repeat sequences of DNA are switched off and unable to be transcribed.

Single Nucleotide Polymorphisms (SNPs) (pronounced Snips):

See Variant

Somatic cell variant/mutation

This was not present in the ovum or sperm from which the individual developed. Somatic cell variants arise in a single cell at some time after conception (that is, during prenatal or postnatal growth and development) and are limited in its distribution in the cells of the body. Somatic cell variants will not be present in the individual's parents and will not be passed on to children (unless it occurs in an ovum or sperm cell of the individual during their life).

See also Variant

Therapeutic good

The TGA defines a therapeutic good as:

> "A good that is represented in any way to be, or is likely to be taken to be, for therapeutic use (unless specifically excluded or included under Section 7 of the Act)".

Therapeutic use

Means use in or in connection with:

- preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury
- influencing, inhibiting or modifying a physiological process
- testing the susceptibility of persons to a disease or ailment
- influencing, controlling or preventing conception
- testing for pregnancy
- replacement or modification of parts of the anatomy.

Variant

Changes in the DNA sequence (usually single base changes) are called variants. Historically, a variant that is disease causing (pathogenic variant) is called a mutation. Some variants are difficult to characterise in terms of their ability to cause disease. Others are found commonly in the population and have been shown to have no obvious disease causing potential. These are often called polymorphisms or if a single nucleotide base is involved they are referred to as SNPs (single nucleotide polymorphisms).

Whole genome sequencing

Refers to methods that allow the whole DNA sequence of an organism to be identified. In the human this will require the sequencing of about 3 billion 'bases' (A, T, C and G).

Appendix C: NATA and NPAAC standards

NATA Accreditation Standards

ISO17025 (1999)

Provides general requirements for the competence of testing and calibration laboratories. This standard is currently used in the accreditation assessment of parentage testing laboratories.

AS ISO15189 (2003)

A standard for medical testing laboratories. It is based on ISO17025 (1999) and ISO9000 (2000). It takes into account the special constraints imposed by the medical environment and the essential contribution of the medical laboratory service to patient care. Allows laboratories to demonstrate technical competence, as well as providing a mechanism allowing harmonisation of clinical laboratory practice internationally.

In Australia, AS ISO15189 (AS 4633) is a NATA requirement for *medical testing* laboratories from 1 July 2005 (NPAAC Tier 5 document).

Each country has its own distinctive approach to regulation of genetic testing and so it is difficult to make meaningful comparisons. The ISO standards provide the only international benchmarks.

NPAAC Standards

The following general NPAAC Standards are applied to all medical laboratories

Tier 2

- Requirements for the Supervision of Pathology Laboratories 2007
- Requirements for Pathology Laboratories 2007

Tier 3

- Requirements for Quality Management in Medical Laboratories 2007
- Requirements for the Estimation of Measurement of Uncertainty 2007
- Requirements for the Packaging and Transport of Pathology Specimens and Associated Materials 2007
- Standards for Pathology Laboratory Participation in External Proficiency Testing Programs 2007
- Requirements for the Retention of Laboratory Records and Diagnostic Material 2007
- Requirements for Information Communication 2007
- Guidelines for Approved Pathology Collection Centres 2006

Requirements for the Development and Use of In-house In Vitro Diagnostic Devices (IVDs) (2007 Edition)

This Standard is designed to assure the safety of in-house IVDs in line with the TGA risk categories. It does this by introducing strong requirements for the design, production, verification and validation of in-house IVDs. As many molecular genetic tests are currently developed in-house, this Standard is applied extensively in laboratories providing molecular genetic tests.

In addition the following specific NPAAC Tier 4 Standards are applicable to human genetic testing laboratories:

Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis (2006 Edition)

Provides consensus standards and guidelines for using nucleic acid analysis. It is directed at:

- laboratories that are either using nucleic acid detection techniques in medical diagnosis, or intending to establish a testing program using these techniques
- accreditation authorities such as NATA so that laboratories using nucleic acid detection techniques may be assessed for compliance.

This Standard was reviewed in the latter half of 2008.

Classification of Human Genetic Testing (2007 Edition)

This document is a supplementary guide to *Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis (2006)* and provides additional information about the classification of genetic tests particularly in relation to the level of pre-test counselling and consent required.

Appendix D: The Australian genetic testing survey

The *Australian Genetic Testing Survey* reviewed the provision of genetic testing in 2006. Professionals working in 56 laboratories were identified as providing molecular genetic testing for clinical purposes during that year that was not rebated by Medicare. Of these, 93% provided data for the Survey. Additional data about Medicare-rebated tests were obtained from Medicare.

The following points are from the summary of the report (RCPA 2008):

- Approximately 60% of the laboratories operated in the public sector, 20% were private sector laboratories, and 20% could be categorised as research/academic laboratories.
- Apart from the five types of molecular genetic tests rebated by Medicare, 437 types of tests were offered by Australian laboratories, of which 75% were offered by only one or two laboratories.
- Of the molecular genetic assays performed in Australia that year, 25% (41,497 assays) had been rebated by Medicare. The remaining 75% (119,354 assays) had been funded from other sources (principally State/Territory government grants).
- For the majority of types of tests provided (75%), there were less than 100 assays during the year.
- Of all the tests performed:
  - 40% were for medical screening purposes (i.e. pre-transfusion testing or neonatal screening)
  - 28% were for diagnostic testing of affected patients
  - 8% were for genetic variants in cancer tissue
  - 5% were for predictive testing in unaffected genetic relatives
  - less than 1% were to predict patients' response to specific medications i.e. pharmacogenetic testing
  - in the remainder (18%) the reason for testing could not be identified.
- There was great diversity in the number of types of test offered by different laboratories. There was also a 10,000-fold difference in the total assay volumes reported by different laboratories.
- Most of the tests were provided by specialist laboratories. Only 10% of the laboratories offered 40 or more types of tests, while 27% reported doing more than 1,000 assays.
- Most types of tests were provided by laboratories in only one State or Territory. Only 56 types of tests (13%) were provided by laboratories in four or more regions.
- Twenty-eight laboratories (54%) reported that all the types of test provided were within the scope of the laboratory's accreditation. Six (11%) reported that none of the types of test they provided were accredited. Eighteen (35%) reported that they provided a mixture of accredited and non-accredited tests.
- During 2007, the same number of types of test was nominally provided as in 2006, but this overestimates the real level of test diversity available during the year. The challenge lies in determining whether a lack of testing in one year represented low demand for a rare test, or lack of provision of the test.

Assay volumes—During 2007, the volume of all Medicare-rebated testing increased by 7% compared with 2006. But Medicare-rebated molecular genetic testing increased by 90%. In addition to the Medicare tests, a further 117,342 molecular genetic tests were provided by laboratories using non-Medicare funding. This was a reduction in assay volume of 2,012 (1.7%) compared with 2006. In 2007, the molecular genetic tests rebated by Medicare accounted for 40% of the molecular genetic tests provided overall, an increase of 14% since 2006.

Appendix E: FDA approved pharmacogenetic/ pharmacogenomic tests

The following tests have been approved by the FDA for use in optimising dosage when prescribing drugs. This information has been included on drug labelling for use by health professionals. **www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm**

Test / gene(s)	Drugs / therapies involved	Comment
TPMT	TPMT is the gene that metabolises the thiopurine class of drugs including azathioprine, 6 mercaptopurine and 6 thioguanine.	These drugs are used in treatment of leukaemia, rheumatoid arthritis, inflammatory bowel disease and prevention of graft rejection. The TPMT enzyme has trimodal activity with high, intermediate and low metabolising potential. Poor metabolisers (~1 in 300 individuals) are more prone to complications predominantly neutropenia (low white blood cell counts) if given conventional doses of the thiopurine drugs. High metabolisers are more likely to reject organ transplants because the effective drug dose is reduced. DNA tests can distinguish the low and high metabolisers and so individualise drug dosage.
AmpliChip™	Proprietary kit for CYP2D6 and CYP2C19 genes required to metabolise a range of drugs for treating depression and psychosis. Tamoxifen used in prevention of breast cancer recurrence after treatment requires conversion by the above to become active.	Approximately 25% of prescription drugs are metabolised by products of the CYP2D6 and CYP2C19 genes. Different forms of the above genes (genotypes) have a significant impact on drug metabolism e.g. 7-10% of Caucasians are poor CYP2D6 metabolisers, and the percentage of rapid CYP2D6 metabolisers varies considerably in different ethnic groups. CYP2D6 is also required to convert tamoxifen into its active metabolite leading to the suggestion that poor metabolisers avoid tamoxifen and are instead given aromatase inhibitors.
UGT1A1*28	A genetic variant of the gene UGT1A1 that metabolises the drug irinotecan used in treatment of metastatic colorectal cancer.	20-35% of patients treated with irinotecan experience severe diarrhoea and neutropenia. Up to 5% can die from this drug. The UGT1A1*28 variant has been shown to be associated with higher risk of complications from irinotecan.
MammaPrint™	Genomic based DNA profile of about 70 genes claimed to provide information on how to determine the optimal long term care following treatment of early breast cancer.	The pharmacogenomic-based strategies (involving the measurement of multiple genes using microarrays) introduces new technology in DNA diagnostics. Sometimes called 'gene expression signatures' the rationale behind this type of personalised medicine is to assay the expression of many genes and from this identify the class of risk which guides subsequent treatment. The MammaPrint ™ test measures the expression of 70 genes which allows prediction into high and low risk of relapse for breast cancer. High risk profile would encourage a more aggressive form of adjuvant therapy after primary treatment of the breast cancer. Low risk of relapse might encourage a more wait and see approach.
Warfarin	Warfarin is used as an anticoagulant for many clinical indications. Two genes (VKORC1) and CYP2C9 are considered to explain up to 50% of the variance in warfarin dose. Other risk factors include age, sex, smoking, liver disease and concomitant medications.	A narrow therapeutic index and high variability in drug response make warfarin a good candidate for pharmacogenetics. Poor metabolising variants associated with VKORC1 and CYP2C9 can lead to bleeding complications associated with warfarin treatment. This is a particular risk in the first few months after starting warfarin.

The following tests have been approved by the FDA for use in deciding whether to prescribe certain drugs.

Gene	Disease	Application
KRAS	Metastatic colon cancer	Mutations in this gene taken from the patient's tumour tissue correlate with failure to respond to a new class of drugs that are EGFR inhibitors. These drugs are expensive and should not be used if KRAS mutations are found.
HER2	Breast cancer	Herceptin is a novel form of therapy that targets certain types of breast cancer. It is expensive and is associated with side effects. It has now been shown that unless the breast cancer has amplification of the HER2 gene, it will not respond to this class of drug. HER2 gene amplification can be detected by a type of DNA test called FISH.
HLA-B*5701	HIV-AIDS	Potentially fatal hypersensitivity reaction to Abacavir, an anti-HIV drug, occurs in those with a certain HLA marker (about 5% of patients). Alternative drugs should be used in patients whose genotype is HLA B*5701. This is one of the small number of DNA tests that are funded through Medicare.

Appendix F: Register of medical genetic tests by the UK Genetic Testing Network (GTN)

The UK has a formal process for evaluating the clinical usefulness and other aspects of germline DNA medical genetic tests, using a modification of the ACCE method. Tests satisfying the ACCE criteria are listed as having clinical relevance, effectively giving a 'tick of approval'. The GTN does not fund the tests. The GTN list of medical genetic tests can be found at **http://www.ukgtn.nhs.uk/gtn/Home**

In Australia the formal and national approach to evaluation would come through the MSAC (Medical Services Advisory Committee) route. However, formal evaluation by MSAC is both expensive and time consuming because of the association with payment through the MBS (Medical Benefits Schedule) and includes a comprehensive cost effectiveness assessment.

In Australia, there is no central government sponsored listing of DNA tests in medical genetics. Lists of tests are provided by the Human Genetics Society of Australasia (**http://www.hgsa.com.au/index.cfm?pid=111496**) and the Royal College of Pathologists of Australasia (**http://genetictesting.rcpa.edu.au/**). These lists are meant to inform health professionals about tests that are available and in what laboratories. They do not evaluate DNA tests. The RCPA listing does provide a comprehensive and informative summary of each test including clinical and laboratory aspects.

APPENDIX G: Bibliography and resources

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Web links

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National Health and Medical Research Council (NHMRC): www.nhmrc.gov.au

NHMRC eGenetics www.nhmrc.gov.au/your_health/egenetics/practitioners/gems.htm

NHMRC Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer (2005) www.nhmrc.gov.au/publications/synopses/cp106/_files/sumguidecp106.pdf

NHMRC National Statement on Ethical Conduct in Human Research (2007) www.nhmrc.gov.au/PUBLICATIONS/synopses/e72syn.htm

Genetics in Family Medicine: The Australian Handbook for General practitioners (2007) www.nhmrc.gov.au/your_health/egenetics/practitioners/gems.htm

Australian Law Reform Commission (ALRC): www.alrc.gov.au

Essentially Yours: The Protection of Human Genetic Information in Australia (2003) www.austlii.edu.au/au/other/alrc/publications/reports/96/index.html

National Pathology Accreditation Advisory Council (NPAAC): www.health.gov.au/npaac

Requirements for Information Communication (2007) www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-InfoComm.htm

Laboratory accreditation standards and guidelines for nucleic acid detection techniques (2006) www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-nad.htm

Classification of Human Genetic Testing – (2007 Edition) www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-HumanGenTest.htm

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National Association of Testing Authorities (NATA): www.nata.asn.au

Requirements for standard ISO 15189 www.nata.asn.au/index.cfm?objectid=DBCABA6C-B07C-AD52-0EB6E2E877F61885&productId=6B15E04D-9D6B-8F05-05109B7174B506C7

How to become accredited www.nata.asn.au/go/accreditation/how-to-become-accredited

Therapeutic Goods Administration (TGA): www.tga.gov.au

The Regulation of Nutrigenetic Tests in Australia: Guidance Document (2007) www.tga.gov.au/devices/ivd-nutrigenetic.htm

Australian Register of Therapeutic Goods www.tga.gov.au/docs/html/artg.htm

Forthcoming (new) regulatory framework for IVDs www.tga.gov.au/ivd/forthcoming.htm

Department of Health and Ageing (DOHA): www.health.gov.au

Medicare Benefits Schedule www9.health.gov.au/mbs/search.cfm?cat1=147&cat2=156&cat3=&adv

Report on a Review of the Level of Public Health Risk and Adequacy of Controls over Non-Medicare Pathology Services www.healthyactive.gov.au/internet/main/Publishing.nsf/Content/health-pathology-PhillipsFoxReview.htm

Medical Services Advisory Committee (MSAC) www.msac.gov.au/

Royal Australasian College of Physicians (RACP): www.racp.edu.au

Specialist clinical geneticists www.racp.edu.au/amtrain/spec/s_cgen1.htm and www.racp.edu.au/training/paed2003/advanced/vocational/genetics.htm

Royal College of Pathologists of Australasia (RCPA): www.rcpa.edu.au

RCPA Manual www.rcpa.edu.au//careers.htm, rcpamanual.edu.au/

Medical specialists www.rcpa.edu.au/Pathology/Disciplines/GeneticPathology.htm

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Guidelines for reporting molecular genetic tests to medical practitioners (2009) www.rcpa.edu.au/static/File/Asset%20library/public%20documents/Policy%20Manual/Guidelines/Guidelines%20for%20reporting%20molecular%20genetic%20tests%20to%20medical%20practitioners.pdf

Human Genetics Society of Australasia (HGSA): www.hgsa.com.au

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Presymptomatic and predictive testing in children and young people (2008) www.hgsa.com.au/images/UserFiles/Attachments/Pre-symptomaticandPredictiveTestinginChildrenandYoungPeople.pdf

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Training and professional certification in genetic counselling www.hgsa.com.au/Index.cfm?pid=111440

Other

Discussion paper on non consensual genetic testing by the Standing Committee of Attorneys-General (2008) www.ag.gov.au/www/agd/agd.nsf/Page/Modelcriminalcode_Non-Consensual GeneticTestingDiscussionPaper

Lab Tests OnlineAU: www.labtestsonline.org.au

Insurance industry standard 11 – Genetic Testing Policy (2005) www.ifsa.com.au/public/content/ViewCategory.aspx?id=618#S11

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Privacy Legislation

www.privacy.gov.au/law, www.comlaw.gov.au/ComLaw/Legislation/Act1.nsf/all/search/592A1E3B62096FD6CA2571ED0012E038

The Association of genetic support of Australasia www.agsa-geneticsupport.org.au/home Centre for Genetics Education NSW Health www.genetics.edu.au/

Machado Joseph Disease Foundation www.mjd.org.au

Multicultural Disability Advocacy Association of NSW www.mdaa.org.au/faqs/interpreters.html

National E-Health Transition Authority www.nehta.gov.au/

International Indian Treaty Council www.treatycouncil.org

National Breast and Ovarian Cancer Centre (NBCC): www.nbocc.org.au

Guidelines for Health Professionals (2006) Advice about familial aspects of breast ovarian cancer. www.nbcc.org.au/bestpractice/resources/BOG182_adviceaboutfamiliala.pdf

Cancer Australia www.canceraustralia.gov.au/about-cancer/cancer-information/cancer-in-australia.aspx

International

UK Human Genetics Commission (HGC): www.hgc.gov.uk

Genes Direct: Ensuring the effective oversight of genetic tests supplied directly to the public (2003) www.hgc.gov.uk/Client/document.asp?DocId=34&CAtegoryId=10

More Genes Direct: A report on developments in the availability, marketing and regulation of genetic tests supplied directly to the public (2007) www.hgc.gov.uk/UploadDocs/DocPub/Document/More%20Genes%20Direct%20-%20final.pdf

Hogarth S, Melzer D, and Zimmern R (2005) www.hgc.gov.uk/client/document.asp?DocId=97&CAtegoryId=8

Common Framework of Principles (currently draft principles and consultation document) www.hgc.gov.au/Client/Content.asp?ContentId-816)

US National Institutes of Health (NIH): www.nih.gov/

Genetics Home Reference 'What is direct to consumer Genetic Testing? http://ghr.nlm.nih.gov/handbook/testing/directtoconsumer

Online Mendelian Inheritance in Man (OMIM): www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM&itool=toolbar

Understanding Gene Testing www.accessexcellence.org/AE/AEPC/NIH/index.php

GeneTests GeneReviews www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests

National Human Genome Research Institute: Catalog of Published Genome-Wide Association Studies www.genome.gov/gwastudies/

US Food and Drug Administration (FDA) www.fda.gov

Guidance for Industry: E15 definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories (2008) www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073162.pdf

Table of valid genomic biomarkers in the context of approved drug labels: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

UK National Health Service (NHS) www.nhs.uk/Pages/HomePage.aspx

Genetics Education www.geneticseducation.nhs.uk/

Ethical, legal and social implications (ELSI) of genetic information www.library.nhs.uk/GENETICCONDITIONS/ViewResource.aspx?resID=59911

US Department of Health and Human Services Resource packet for health professionals www.hhs.gov/familyhistory/respachealth.html

Family Health History https://familyhistory.hhs.gov/fhh-web/home.action

Other

Centers for Disease Control (CDC) www.cdc.gov/genomics/gtesting/ACCE/

Human genome project information www.ornl.gov/sci/techresources/Human_Genome/home.shtml

Your genes your choices explaining the issues raised by genetic research http://ehrweb.aaas.org/ehr/books/index.html

Genetic Alliance Policy: Promotion of Genetic Testing Services to Consumers www.geneticalliance.org/ws_display.asp?filter=policy.tmarket

National Human Genome Research Institute, Frequently Asked Questions about Genetic Testing www.genome.gov/19516567

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The Pharmacogenomics knowledge base www.pharmgkb.org/index.jsp

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National Coalition for Health Professional Education in Genetics www.nchpeg.org/

Genetics and Your Practice www.marchofdimes.com/gyponline/index.bm2

DECIPHER CNV database: www.Sanger.ac.uk/PostGenomics/decipher/

Genetics and public policy centre www.dnapolicy.org/resources/DTCcompanieslist.pdf