GENETIC TESTING AND RELATED ETHICAL ISSUES

As a result of the sequencing of the human genome it is now possible, and preferable in most instances, to scan an individual's DNA directly for actual mutated sequences. Genetic testing is generally performed on DNA, but RNA or other types of biological material can also be used.

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WHAT IS GENETIC TESTING AND HOW DOES IT WORK?

Scanning an individual's DNA is quick, cheap and easy. When DNA is to be used for genetic testing it is usually obtained from whole blood or from a mouth-wash sample. DNA can also be extracted from fresh or stored tissue collected during surgery, from cultured cells, hair roots, archived biopsy specimens and numerous other sources. Genetic testing using other materials includes chromosome analysis in Down syndrome, measurement of blood cholesterol to diagnose familial hypercholesterolaemia, haemoglobin electrophoresis for the diagnosis of carriers of beta-thalassaemia and abdominal ultrasound scans to detect kidney cysts in adult polycystic kidney disease.[1]

As with other diagnostic testing, clinical assessment of the affected individual, and documentation of the pedigree (family history), are the starting point for genetic testing. This defines which gene/s the laboratory should study. Identifying the mutation causing the disorder is straightforward if a single gene with one or a small number of mutations is identified as causing the disorder. For the vast majority of genetic disorders however there is often the possibility of many different mutations occurring in a host of genes in different families.

PRE-TEST AND POST-TEST COUNSELLING

Ideally all patients having genetic testing should have pre-test counselling by someone trained in genetics because of the complexity of this type of testing and the need to determine the most appropriate test(s) for that individual. A trained genetic counsellor or specialist who is registered with the HPCSA should ideally counsel patients and families. If this is not possible, another appropriately trained person, such as a genetic nurse, should inform them of their options and then refer them to a registered counsellor for post-test counselling at least.[2] Genetic counselling is labour-intensive and sometimes sessions can take a few hours. Genetic test results are regarded as highly confidential and should never be given to an individual over the telephone or sent in the post. Post-test counselling is also unpredictable in terms of time and course and is often very emotionally charged.

Trained genetic counsellors are in short supply and it is likely that the task of education and counselling could fall to primary care doctors and nurses. Few primary health care providers however have been trained in this area. Public health costs are already significant. An additional charge for genetic tests, counselling, follow-up clinical screening and frequent monitoring now needs to be factored in. Whatever the reason for requesting the testing, it is essential that the individual's informed consent is always obtained.

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CONSENT FOR GENETIC TESTING

According to the new South African National Health Bill, a person may not remove tissue, blood or gametes from the body of another living person for the purpose of genetic testing unless written consent has been obtained.[3] The regulations relating to the Bill deal primarily with genetic testing performed as a clinical service in a medical environment. Consent to genetic testing needs to be accompanied by appropriate genetic counselling that precedes the testing. It is advisable that written medical and scientific information also be provided to the individual at the time of obtaining signed consent. Most genetic testing should also be supported by post-test genetic counselling and genetic management, not only for the individual concerned, but also for the extended family, if so desired. When DNA testing is required for research, it is essential that relevant guidance be provided. Research settings can be very diverse and researchers need to consider issues such as a detailed information leaflet, a consent form that has been approved by a research ethics committee and also an appropriate process for the delivery of results.

In practice, the details of the consent process will vary according to the circumstances. For example, it would be very straightforward for someone who has just had a venous thrombosis to request a diagnostic genetic test such as for factor V Leiden.[1] On the other hand, consent required to perform presymptomatic testing for a late-onset genetic disorder, such as an inherited form of Alzheimer disease or Huntington disease, for which there is no prevention, treatment or cure, is very different. At major centres in South Africa there are currently highly structured predictive testing protocols for such conditions, based on international guidelines.[4]

WHO WILL AND WHO WILL NOT DEVELOP THE CONDITION?

More recently, genetic testing for the complex but more common diseases is the subject of much debate.[1] These include some forms of inherited blindness as well as the near-mendelian subgroup of diseases such as hypertension and diabetes. In most instances, these tests are targeted at perfectly healthy (presymptomatic) people who are identified as being at high risk because of a strong family history of the condition. The problem is that these test results can only give a **probability** for developing the disorder. Some individuals who carry a disease-associated mutation may never develop the condition, and unfortunately there is still no way of telling who will and who will not do so.

Genetic testing for sporadic forms of Alzheimer disease currently involves the identification of genetic markers that are associated with an increased risk of developing the disease, which is more a probability than a definitive prediction. This is therefore considered a susceptibility test rather than a predictive test. There is consequently a strong belief among genetic specialists that results should be delivered to family members according to a very carefully planned protocol and by trained genetic specialists, as outlined above.[4,5]

WHEN AND WHY TO REQUEST A GENETIC TEST

Genetic tests are used for several reasons, including:

- confirmational diagnosis (of a symptomatic individual)
- carrier screening (identifying unaffected individuals who carry one copy of a gene for a disease that requires two copies for the disease to be expressed, e.g. cystic fibrosis)
- prenatal diagnostic testing
- tests that are performed postnatally
- genetic screening tests
- voluntary presymptomatic, predictive and/or susceptibility tests
- preimplantation DNA tests carried out on a polar body of an ovum (so that an ovum without a mutation that is known to cause a serious genetic condition can be selected for *in vitro* fertilisation)
- preimplantation DNA tests following the removal of one or two blastomeres of a developing embryo (for the purpose of implantation of an embryo without a mutation — a blastomere is an undifferentiated embryonic cell, also called a 'blastocyte', which is derived from the blastocyst)
- forensic/identity testing.[3]

Genetic tests used to clarify a diagnosis can guide a doctor toward appropriate treatments, while others allow families the option of not having children with devastating diseases. Other more recent tests can now identify people at high risk for conditions that may be preventable. Aggressive monitoring for and removal of colon growths in those who have inherited a genetic mutation known to cause an inherited form of colon cancer has saved many lives.[6] Whatever the reason for the test, genetic testing has already dramatically improved lives. Screening tests however do not provide a diagnosis but rather an indication of an increased or decreased risk and need to be followed with a diagnostic test. Whatever the type of test being considered or offered, people contemplating genetic testing need

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information and guidance in order to make informed choices and cope with the psychological stresses that could follow such testing.

MONOGENIC V. THE MORE COMPLEX GENETIC DISEASES

Currently it is most unusual for a single mutation or even only a few different mutations in one gene to be responsible for the clinical presentation of a genetic condition in affected individuals. For a given genetic disorder, there are often different mutations in different families. A classic example of this is the CFTR gene that is associated with cystic fibrosis, where more than 1 000 different known mutations are dispersed along the CFTR gene. One mutation, known as delta F508, accounts for about 70% of the disease in families reported internationally. In SA it has been identified in 76% of white, 50% of coloured and not at all in black patients.[7] It is essential to be aware that a laboratory report that indicates that an individual does not have the delta F508 mutation does not actually exclude carrier status, but it does reduce the risk.

Then there are examples of situations in which a disorder is strongly associated with a single mutational mechanism such as haemophilia, sickle cell anaemia, Huntington disease, fragile X mental retardation and myotonic dystrophy. In these conditions, virtually everyone with the disorder has the identical type of mutation but the size of the disease-associated allele (alternative form of the gene) varies considerably in the latter 3 diseases. Slightly more complicated is the fact that about 60% of boys with Duchenne muscular dystrophy (DMD) will have a deletion (missing linear sequence of DNA) in the dystrophin gene. However, in the remaining 40% of affected boys, the disease-causing mutation could be a point mutation (different nucleotide, which is the basic chemical unit of DNA) or a rearrangement of the nucleotide sequence in the dystrophin gene. It is therefore important to be aware that some laboratories may use a testing protocol to detect deletions for DMD but may be unable to screen for other mutations when no deletion is found. In porphyria variegata, on the other hand, one specific mutation is present in over 90% of affected persons in South Africa, whereas elsewhere in the world porphyria variegata is very heterogeneous.[8]

From the above it is clear that population specificity of genetic mutations, and the fact that there are many different types of mutations in the same gene that cause genetic disorders, increases the complexity of genetic testing. The biggest challenge today, however, is the fact that there are multiple genes which are capable of causing a genetic disorder. For example, familial breast cancer can be caused by many mutations in BRCA1 or BRCA2 or a number of other breast cancer-causing genes. To date, over 1 000 different mutations have been identified in BRCA1 and BRCA2 and not all of them are associated with disease. Hereditary non-polyposis colorectal cancer has been found to be caused by mutations in at least five different genes and for the inherited retinal degenerative disorders there are over 150 different genes that have been found to be associated with inherited eye disease. In South Africa to date, 32 families with a history of genetic blindness have been identified as having mutations in 15 different genes.[9]

LABORATORIES TESTING FOR SPECIFIC GENETIC DISORDERS

The result of this genetic complexity is that many laboratories, rather than offering a single test for every disorder, only screen certain genes for mutations or only test for a small number of known common mutations. Today there are many methods of screening genes for mutations and each has its own strengths and weaknesses. It is important to be aware therefore that different laboratories use different methods and so selecting the right laboratory to perform the appropriate investigation is very important.

In the past most referrals for genetic disorders went to an academic human genetics department in a South African institution where diagnostic genetic testing was performed by experts involved in genetic research and service delivery. Today certain private laboratories (genetic and/or chemical pathology laboratories) are also recognised as specialising in certain genetic testing procedures. They too are currently used as referral centres for genetic testing, as long as there is a formalised structure in place for the delivery of results, appropriate for the type of test that is being performed. In the public sector, the National Health Laboratory Service (NHLS) is the preferred service provider although they do not test for every genetic condition. They do however have a good national and international referral network and so for the private sector, the NHLS would be a good starting point for referral for genetic testing in South Africa.

WHAT TESTS SHOULD BE OFFERED?

There is general unease that economic issues will drive aggressive marketing of genetic tests and determine which tests are available, irrespective of their

actual usefulness for health care. This has the potential to result in poor genetic management and could lead to unnecessary duplication of testing and therefore costs. There has been particular concern about the possibility of direct marketing of genetic tests to the public under the guise of so-called 'preventive genetic diagnosis' or 'genomic profiling'. Many believe that genetic testing is by no means ready for routine use at this time, so possibly only testing known to have clinical benefit should be offered to the general public.[5]

CONCLUSION

Genomic profiling undoubtedly has the potential to herald a revolution of personalised health care and disease prevention. However, scientific evidence to support such genomic profiling is inconsistent and data on the health outcome benefits based on such testing are being examined. Science is still in the early stages of unravelling gene-gene and gene-environment interactions and their health implications. Genomic medicine will continue to be hampered for some time by a lack of knowledge about the long-term clinical implications of this type of testing.

Limitations of genetic testing should be clearly described and explained to the public and enhanced controls and safeguards should be recommended around the provision of genetic testing directly to the public.

For future reference regarding what genetic tests are available, consult GeneTest-GeneClinics at **http://www.geneclinics.org**. This site includes a comprehensive list of available genetic tests, as well as further clinical information about many genetic conditions.

References available on request.

IN A NUTSHELL

Genetic testing using DNA is quick, cheap and easy.

Clinical assessment of the affected individual, and documentation of the pedigree (family history), should be the starting point for all diagnostic genetic testing as this will define which gene/s the laboratory should study.

Owing to the complexity of this type of testing, laboratories might have to screen many genes for mutations, or might only test a small number of known common mutations rather than offer a single test for each disorder.

It is therefore important to be aware that different laboratories use different methods and do different tests. Often different laboratories have to be used for different tests.

The National Health Laboratory Service (NHLS) is a good starting point for referrals, although they do not test for every genetic condition, but would have a good national and international referral network.

Genetic testing is by no means ready for prime time yet, so it is suggested that only testing known to have clinical benefit should be offered to the general public right now.

SINGLE SUTURE

MEDICAL STUDENTS CAUSE BLOOD PRESSURE TO INCREASE

A new study has shown that the presence of a medical student can increase blood pressure when measured in general practice. The researchers found that blood pressure was significantly higher in consultations where measurements were taken in the presence of a medical student or trainee than in consultations where no student was present.

'If confirmed, our findings imply that doctors should be cautious to initiate or adjust antihypertensive drug treatment when blood pressure readings are obtained in the presence of a trainee,' say the researchers in their report.

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