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The clinical geneticist and the "new genetics"

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ABSTRACT

- The "new genetics" will provide new genetic tests that can be used for diagnosis, prognosis, treatment selection, carrier and predictive testing in affected families, and potentially for susceptibility testing for later-onset multifactorial disease and population screening.
- Doctors will increasingly need to consider the family implications of a genetic diagnosis — to identify family members at risk of the disorder or of having affected children and to consider how these individuals might be advised of their situation.
- Clinical geneticists can be a valuable resource for doctors who need advice about whether genetic testing is available, which tests to pursue, how to access testing services, and how to interpret and act on test results.
- Clinical geneticists also provide genetic counselling, a process which gives people understandable information about the genetic disorder in the family, and makes the information useful for decision-making given the person's unique circumstances and beliefs.
- The Internet will increasingly be a key source of information about genetic disorders for patients, their families and healthcare professionals.

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THE HUMAN GENOME PROJECT and genetic research in general have increased understanding of the genetic contribution to health and disease, and new information will accrue rapidly for the foreseeable future. This will result in increased possibilities for genetic testing for diagnosis, management and assessment of genetic susceptibility in individuals and families. Medical practitioners will need to embrace new knowledge that is relevant to their areas of practice so as to make it accessible to their patients. This will involve thinking in terms of the genetic basis of disease and disease susceptibility, considering the availability of genetic testing when appropriate, and considering the family implications of genetic disorders. Clinical geneticists can assist medical practitioners.

What is a clinical geneticist?

Clinical geneticists have undergone specialty training in genetics after general professional training in internal medicine or paediatrics (and occasionally other disciplines, such as psychiatry, obstetrics and gynaecology, or ophthalmology).[1] The specialty training covers a broad range of areas, such as the genetics of adult and paediatric disorders, cancer, dysmorphology, reproduction and neurology. Training also includes basic theoretical genetics, counselling theory and practice, ethics, laboratory experience and research. Clinical geneticists work within clinical genetics centres in partnership with genetic counsellors and medical scientists to provide genetic services to the population of a defined geographical region. Services are delivered through a network of metropolitan and country outreach clinics. Australasian regional clinical genetics services are listed in Box 1.

What do clinical geneticists do?

Clinical geneticists see referred patients for diagnosis, management, genetic testing and genetic counselling. The disorders they investigate are not limited by age group, organ system or sex. Most patients are seen on only one or a few occasions.

The process of genetic counselling runs through the work of clinical geneticists and involves the provision of both information and counselling. Information is provided about the features and natural history of the disorder, its genetics, the risk of developing it or passing it on to children, and ways in which the disorder might be prevented or the outcome improved. Counselling involves making that information understandable and useful for decision-making in light of the person's expectations, beliefs, emotional state and family relationships. Implications for other family members are also considered.

Many ethical issues arise in the course of genetics practice as a consequence of the predictive nature of some genetic information, the fact that genetic information has significance for both the individual and his or her family, and the sensitive nature of genetic information. There is a need for:

- confidentiality;
- formal consent procedures in several settings;
- careful counselling to ensure that patients understand the consequences of any proposed genetic testing;
- consideration of possible stigma and discrimination in families and the community as a result of genetic testing;
- application of guidelines for predictive or carrier testing of children; and
- appropriate procedures for approaching family members identified as at risk of a genetic disorder.

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The main clinical components of the clinical geneticist's role are set out in Box 2 and reasons for referral to a clinical geneticist in Box 3.

The clinical geneticist and other healthcare professionals

While individually uncommon, Mendelian disorders collectively affect a significant proportion of the patients seen by general and specialist medical practices, and in this context

2: Clinical roles of the clinical geneticist*

The symptomatic individual

- Diagnosis and management of symptomatic individuals (eg, syndrome diagnosis of children with birth defects and management of children with inborn errors of metabolism and bone dysplasias), including health surveillance for specific genetic conditions (eg, neurofibromatosis, Marfan syndrome).
- Explanation of the features, natural history and genetics of the disorder, genetic test results, implications for other family members, and reproductive options.

The family

- Identification of affected but as yet asymptomatic family members by clinical methods (eg, Marfan syndrome, neurofibromatosis).
- Genetic risk assessment (eg, based on Mendelian inheritance patterns or empiric data).
- Informing family members who are at increased risk of their situation and the options available to them.
- Clarification of risk by genetic testing of family members (eg, carrier testing for fragile X mental retardation, cystic fibrosis, beta thalassaemia and haemochromatosis, or predictive testing for late-onset disorders such as Huntington disease, myotonic dystrophy or familial cancer).

Maintenance of genetic registers

- Provision of information about strategies for reducing the burden of the disorder for those at increased risk (eg, by surveillance with a view to early diagnosis or implementation of a prevention strategy).

The community

- Participation in population screening (eg, newborn screening, prenatal screening and adult population screening).
- Directing families to sources of high quality information.
- Assisting community support groups for genetic disorders.

Healthcare professionals

- A resource for other healthcare professionals with regard to the diagnosis of, information about and testing for genetic disorders.

Laboratories

- Liaison with laboratories performing genetic testing.

* Some of these functions are not unique to clinical geneticists.

doctors need to recognise and address the genetic and family issues. Yet, most doctors have had little undergraduate or postgraduate genetics education, and do not feel confident to deal with the detail of the genetic issues. Clinical geneticists and genetic counsellors can assist, but many doctors are unaware of clinical genetics as a medical specialty and the role a clinical geneticist can play in patient management, and have never referred a patient to a clinical genetics service. This situation is likely to change as the genetics component of medical curricula increases and as postgraduate educators focus on genetic topics of relevance in general practice and medical and surgical specialties.

Clinical geneticists and genetic testing

Clinical geneticists play an important role in the provision of genetic testing, interpretation of test results and explanation of test results to families and doctors. This is because of the

3: When to refer to or consult with a clinical geneticist

For diagnosis

- If unable to make a diagnosis in an individual or family with an unusual constellation of clinical features (eg, children with intellectual disability and dysmorphic features).
- When clinical geneticists have particular expertise (eg, Marfan syndrome, inborn errors of metabolism and bone dysplasias).
- To assess the significance of a family history of a disorder.

For management

- When clinical geneticists provide specialist management services (eg, children and adults with bone dysplasias or inborn errors of metabolism).

For genetic counselling following diagnosis of a genetic disorder or before genetic testing

- To explain the disorder and its genetics.
- To assess risk for future children, to discuss genetic testing that can clarify risk and to discuss reproductive options.
- To consider the emotional and social impact of the disorder.
- To assess risk for relatives, to discuss clinical assessment or genetic testing (diagnostic, carrier or predictive) to clarify the risk, and to discuss surveillance and prevention strategies, if they exist.
- To refer families to a genetic register, if appropriate.

In relation to genetic testing

- Help with interpretation of the results of genetic tests and their clinical significance.
- Advice about which test to use in a particular situation.
- Assistance with accessing tests that are available locally but require specialist assessment before testing (eg, Huntington disease predictive testing and testing for mutations in genes associated with familial cancer).
- Assistance with accessing tests that are not available locally.
- Before prenatal diagnosis that involves specialised molecular genetic testing techniques or where the test result may need specialist interpretation, and before pre-implantation genetic diagnosis.

novelty and complexity of genetic testing (Box 4), and the associated ethical issues.[5] For some tests, the role of the clinical geneticist will reduce as testing becomes more accessible and familiar, as technologies become standardised and robust, as interpretation of test results becomes easier, and as the clinical implications of test results become clearer. Complexity will increase, however, for testing that assesses disease susceptibility resulting from variation in multiple genes, especially as the test information must be combined with environmental and lifestyle information before it can be useful for management.

Until recently, it has not been necessary for GPs to know much about genetic testing. That situation is changing. For example, mutations in the genes that predispose to haemochromatosis and thrombophilia have now been identified, and progressively more people are being tested in the relevant clinical settings. GPs are being asked to deal with the relatives of people who test positive. This is not a trivial task given that, for haemochromatosis for example, about 10% of the population carry the *HFE* C282Y mutation that is associated with a high risk of haemochromatosis when homozygous. There is a good chance of finding the abnormality in close relatives, needing to explain the implications and to give advice on what to do. Most GPs are confident about ordering a complete blood profile and haemoglobin electrophoresis to detect carriers of beta thalassaemia and, faced with a couple who are both carriers, would know the risk to the couple's future children, that prenatal diagnosis is available, and how to access prenatal diagnostic services. Education and clear practice guidelines will provide GPs with equal confidence to deal with other common disorders such as haemochromatosis.

The medical and surgical specialties have had a different experience. For several, genetic disorders comprise a significant part of their practice, and this has been a stimulus to understanding the genetics of the disorders they diagnose and manage, and to using that knowledge personally — for example, haematologists for thalassaemia and haemophilia, respiratory physicians for cystic fibrosis, and gastroenterologists and surgeons for familial bowel cancer. Although knowledge about genetics in the specialties will continue to increase, the clinical geneticist will continue to contribute to the interpretation of test results, such as mutations in familial cancer genes, for some time to come.

Future possibilities

Further in the future, it will be possible to perform genetic testing that provides information about multiple genes in the one test, so-called "multiplex testing". For example, it may become possible and cost effective to obtain pharmacogenetic profiles (documentation of variation in the key genes involved in drug metabolism) on everyone early in life to assist doctors with choosing the most appropriate drug and dose based on the individual's likely metabolism of the drug (thus avoiding the consequences of under- and overdosing), and even to predict serious idiosyncratic side effects.

Similar tests are likely to provide information about the inherited and somatic genetic variation predisposing to a person's illness. For example, gene expression profiles from an individual's cancer tissue, which reflect both inherited and acquired genetic variation, can be of great utility for diagnosis, prognosis and management.[6] Such profiles can be obtained using array technology, which allows the expression of thousands of genes to be studied at the one time — having biopsied the tumour, you then biopsy its unique genome!

It may also become possible to use multiplex testing predictively to provide information about variation in multiple genes that contribute to susceptibility to the common multifactorial disorders of childhood and adult life. If such testing is performed early in life, it may be possible to offer susceptible individuals surveillance or prevention strategies that can improve their health in the long term.

Simultaneous testing of multiple genes may well be available as a clinical service soon, and pharmacogenetic profiling and multiplex genetic testing are likely to be on the Medicare Benefits Schedule within the professional lifetimes of many doctors currently in practice.

Clinical geneticists and the family

Once a genetic diagnosis has been made, it is essential to consider the implications for other family members, both living and future, and to contact those at risk to make them aware of their situation and the options open to them. This is already a major component of the work of clinical geneticists, but the new genetics will greatly expand this area of practice by delivering new tests that can be used for family studies.

The risk for family members can be clarified by "cascade genetic testing". Testing proceeds sequentially in a cascade, starting with the close relatives (parents, siblings and offspring, as appropriate) of the symptomatic individual who drew the family to attention, followed by testing the close relatives of those found in the first round to have inherited the mutant gene, and so on.

Cascade testing is labour-intensive and costly, and is sometimes best done using a genetic register to contact relatives. Clinical geneticists have traditionally been active participants in establishing and operating genetic registers, and have expertise in this area. Register staff ensure that genetic counselling and testing is offered to all family members at increased risk, and maintain contact with the family over time. Register staff usually do not provide genetic counselling and testing, which is arranged through an appropriate healthcare professional. Ethical guidelines for the establishment and operation of genetic registers require consent from registrants and strict confidentiality of register information.[7]

For recessive and X-linked disorders, the aim of cascade testing is usually to identify carriers at risk of having affected children. Once the mutation has been identified in the first affected family member, carrier studies can be offered to relatives and their partners as necessary. For example, cascade testing is frequently performed for cystic fibrosis, beta thalassaemia, fragile X syndrome, and Duchenne muscular dystrophy.

For dominant disorders, the aim of cascade testing is to determine whether at-risk family members have inherited the mutant gene and are likely to develop symptoms of the disorder. For a few disorders, such as Huntington disease and familial adenomatous polyposis, people who inherit the mutation are almost certain to develop the disorder. However, for most disorders, people who inherit the mutation may not develop the disorder, although they will have a substantial risk of doing so, as, for example, for mutations in the *BRCA1* and *BRCA2* familial breast/ovarian cancer susceptibility genes. Predictive testing is available for an increasing number of dominant disorders, such as Huntington disease,[8,9] myotonic dystrophy, several familial cancers and familial cardiomyopathy.

Clinical geneticists, members of some other medical specialties, genetic counsellors and medical social workers have acquired expertise in predictive testing, which requires a multidisciplinary approach and a lengthy counselling process. Predictive testing is less problematic for disorders, such as familial cancer, that are treatable, that impose less personal and social burden on the affected individual and their family, and for which preventive and surveillance strategies exist. Nonetheless, the counselling process needed to ensure informed consent for predictive testing requires specific expertise that is currently found mainly within clinical genetics services.

Most GPs and other specialists do not see family studies as a role to be taken on personally. There are good reasons why this is so: contacting family members in a systematic way takes time and persistence, and there are no mechanisms within current models of remuneration that support it. There are also complex issues about how to approach relatives in a way that is acceptable to both the person being contacted and the person whose situation triggered the need for contact, and how to do so in a way that is consistent with medical confidentiality and privacy legislation. In contrast, family studies are core activities for clinical geneticists; most are employed in the public sector and have resources for these studies.

4: Genetic tests and the role of the clinical geneticist

Feature making test interpretation difficult	Example	Contribution of the clinical geneticist
Disorder caused by mutations in more than one gene	Familial colon cancer: *MLH1, MSH2, MSH6, APC*	Advising which genes to test
Test method will not detect all mutations in the gene	Cystic fibrosis: 20% of *CFTR* mutations are not detected by routine screening	Calculating residual risk after a negative test and considering implications for the patient and other family members
Test method detects DNA sequence variations that are not pathogenic	Most genes	Providing reassurance that variation is not pathogenic and advising that the test result should not influence management
Test method detects DNA sequence variations of uncertain significance	Familial breast/ovarian cancer: *BRCA1* and *BRCA2* variants	Recognition of uncertainty and advice about implications for management of patient and other family members
Consequences of a pathogenic mutation uncertain because of incomplete penetrance	*HFE* C282Y homozygosity: 40%–70% chance of haemochromatosis	Advising about implications of test result and approach to surveillance for onset of the disorder
Complex genetic mechanism	Triplet repeat expansions in Huntington disease, fragile X syndrome and myotonic dystrophy	Interpreting test result
Unfamiliar testing method	Linkage method for excluding carrier status for Duchenne muscular dystrophy	Deciding which family members need to give a blood sample and interpreting the test result
Test not available locally	Many	Identifying a testing laboratory[2-4] and arranging testing

Clinical geneticists and population health

Presently, there are only a small number of population-based screening programs in existence. These include newborn screening (eg, for phenylketonuria, hypothyroidism and cystic fibrosis),[10] prenatal screening (eg, maternal serum screening for Down syndrome and spina bifida)[11] and carrier screening in specific ethnic groups (eg, beta thalassaemia and Tay–Sachs disease). Clinical geneticists are members of the teams that provide these programs.

The new genetics, by identifying the genetic contribution to an increasing number of disorders, will create opportunities to consider population screening for susceptibility to many disorders of childhood and adult life, or risk of having children with serious genetic disorders. There is no whole-of-population genetic screening (other than newborn screening) being carried out at present in Australia, although screening for haemochromatosis and for carriers of cystic fibrosis and fragile X mental retardation are considered possibilities. There are considerable complexities and costs involved in population screening, and it is essential that each screening program be evaluated critically before implementation.[12] Together with public health practitioners and others, clinical geneticists can contribute to these assessments, and it is likely that GPs will be key participants if population screening is implemented. GPs will provide information before testing and, once the test result is known, will provide information and advice to people with abnormal screening results. This includes advising close relatives who have not yet been screened.

Clinical geneticists and access to information

The new genetics is fortunately being paralleled by the "new informatics". Families and healthcare professionals, including clinical geneticists, who are hungry for information are increasingly able to access a smorgasbord of information about genetics, genetic disorders and genetic testing through the Internet. This is an invaluable resource for the practice of medicine. The Internet can lead to high quality websites, and to community-based support groups[13] that take care to ensure their information is accurate and offer support and information about the experience of being affected, having an affected family member, or being at risk. However, not all information on the Internet is relevant or of high quality, and families who rely on the information they find run the risk that it may be incorrect, not relevant to them, or would require medical advice to be used appropriately in their unique circumstances.

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