The evolving role of general practice in genetic testing

Genetic information was first used clinically over 100 years ago when a practicing physician, Sir Archibald Garrod, found that a single gene was responsible for alkaptonuria; a rare disorder resulting in dark urine due to an inability to metabolise certain amino acids. Since then there has been an explosion in the number of genetic tests that are available. Many commercial laboratories now list hundreds of tests, by disease or gene, and clinicians and patients are able to incorporate the results they provide into decisions about managing their health. For this decision making to be meaningful clinicians need to understand the limitations and complications of genetic testing, including that:

- Multiple genes can cause the same disease phenotype, i.e. genetic heterogeneity, as is likely to be the case in multi-factorial conditions such as cardiovascular disease or bipolar disorder;
- There may be multiple mutations within each gene for any given disease. Therefore the possibility exists for false negatives following genetic testing, e.g. there are approximately 1300 mutations within the same gene that can cause cystic fibrosis, and laboratories routinely test for only the 29 most common mutations.
Multiple diseases may be associated with one gene, or even one mutation, causing problems in the interpretation of test results, e.g. attention deficit hyperactivity disorder and autism have been found to be linked through studies of single nucleotide polymorphisms.

There are many family-specific mutations for most genetic disorders, e.g. familial cancer syndromes, that have yet to be discovered.

There is intra-familial and inter-familial variability in disease presentation, e.g. the wide ranges in age of symptom onset for patients with a gene for Huntington disease.

Non-penetrance, i.e. a mutation being present but no disease is evident, can mean that some patients will be asymptomatic despite their genotype, e.g. some patients who are homozygous for an autosomal recessive mutation that can cause hereditary haemochromatosis will not develop the condition.


The link between general practice and GHSNZ

Genetic testing can be used for a range of clinical purposes, from pre-conception planning to predicting the occurrence of late-onset neurological conditions. As some patients can expect to be adversely affected by genetic variation expert counselling may also be provided, before and after the test is performed. This allows patients to make informed decisions, to better accept the result once it is known, to adjust their life accordingly and to make effective use of the health system both during and after this process.

General practitioners may have ongoing contact with patients undergoing genetic testing. Therefore a broad understanding of genetic testing is required to:

- Guide pre-test discussions with the patient to decide whether or not a genetic test might be appropriate
- Outline the testing process and its implications to the patient
- Collect the appropriate medical information from the patient prior to any referral, e.g. a family history, to improve triaging of requests

Support and manage patients who have received a positive test result

Coordinate multidisciplinary care that a patient with a progressive condition may require

Improving coordination between genetic services and primary care

Genetic Health Service New Zealand (GHSNZ) was launched as a national service in May 2012. GHSNZ has clinics throughout New Zealand staffed by clinical geneticists and genetic associates, as part of the public health system. Clinical geneticists are doctors with training in medical genetics. Genetic associates are health professionals with post-graduate qualifications in medical genetics and genetic counselling.

There are three regional services:

- **The Northern Hub is based in Auckland** and has clinics in Whangarei, Hamilton, Tauranga, Rotorua and Gisborne.
  Ph: 0800 476 123

- **The Central Hub is based in Wellington** and covers the lower half of the North Island and Nelson. Clinics are also available in New Plymouth, Whanganui, Hastings, Palmerston North, Porirua and Lower Hutt.
  Ph: 0508 364 436

- **The South Island Hub is based in Christchurch** and covers the remainder of the South Island. Clinics are also available in Blenheim, Greymouth, Timaru, Dunedin, Queenstown and Invercargill.
  Ph: 0508 364 436

GHSNZ has the specialised knowledge required to select the most appropriate test for a patient and to establish whether clinical phenotypes are the result of genetic variation. To ensure genetic testing is appropriate it is recommended that general practitioners contact the GHSNZ telephone enquiry service (telephone numbers above). For appropriate patients, pre-symptomatic, predictive and carrier testing for a variety of genetic conditions as well as diagnostic assessments ranging from fetal abnormalities to adult-onset disorders are available from GHSNZ. Patients and their family/whānau are also able to discuss the results of genetic tests with GHSNZ staff to allow them to understand the implications of test results.
What information do general practitioners need to make better use of genetic testing?

We asked Dr Caroline Lintott, Senior Genetic Associate and Team Leader of the GHSNZ South Island Hub, to provide comment on how health professionals in primary care can improve outcomes for patients in New Zealand affected by genetic disorders.

What services does Genetic Health Services New Zealand (GHSNZ) offer to patients?

There are a range of funded services that GHSNZ offers to patients depending on their stage of life and the specific genetic condition in question. Services frequently accessed by patients include:

- Genetic diagnosis and counselling, as well as pre-conception or pre-natal tests for genetic conditions and information about reproductive options including pre-implantation genetic diagnosis
- Diagnostic assessment for:
  - Pregnancies in which there is a concern about fetal abnormalities
  - Infants or children with dysmorphic features or developmental delay
  - Adults with late-onset genetic disorders
- Pre-symptomatic/predictive genetic testing to confirm carrier status, which requires a referral to GHSNZ prior to testing
- Funded genetic testing, as appropriate, for patients seen through GHSNZ
- Assessment of a personal or family history of cancer, and mutation screening in specific familial cancer syndrome genes when appropriate

What referral criteria are available for general practitioners?

Referral criteria for general practitioners are not provided by GHSNZ, however, local DHBs do have referral criteria for some conditions, e.g. HealthPathways in the Canterbury DHB region. The referrals that GHSNZ receives for infants or children who require diagnostic assessment are usually initiated by paediatricians.

For patients who may require assessment for familial cancer syndromes Dr Lintott points out:

“Referrals for Familial Breast Ovarian Cancer syndrome assessments require that a patient meets at least ‘moderately increased risk’ criteria (e.g. one first degree relative diagnosed with breast cancer before age 50 years, or two second degree relatives on the same side of the family, at least one diagnosed before age 50 years), or high risk features such as male breast cancer, epithelial ovarian cancer, bilateral breast cancer with first diagnosis under age 50 years, or individuals or families with a history of both breast and ovarian cancer. Referrals for patients who come into the ‘at-risk, or slightly above average risk’ groups for breast cancer will be declined as pressure on our waiting lists means we can no longer offer consultations for patients at general population risk.”

In general, GHSNZ requests that referrals to its genetic clinics be arranged by faxing, posting or emailing a request to the Auckland, Wellington or Christchurch centre. Contact details are available on their website (Page 16). Detailed medical information will usually be required about the patient.

For further information see: “Inherited cancer syndromes – examples of predictive testing (Tier 2)”, Page 5.

How is GHSNZ being currently used and how can it be used better?

As GHSNZ is a tertiary service, most of its paediatric and adult referrals for clinical genetic services come from hospital clinicians. However, Dr Lintott reports that about half of the referrals they receive for familial cancer assessment come from general practitioners. She also notes that there are hundreds of different mutations in genes causing familial cancer syndromes and searching for a mutation usually has to start in an affected family member, to reduce the risk of false-negative result. For example, there are more than 2000 different mutations in BRCA1 and BRCA2 genes, therefore searching for mutations in BRCA genes should begin in a family member with breast or high-grade epithelial ovarian cancer. As the main point of contact with the patient, general practitioners can assist GHSNZ by collecting information about the patient’s personal and family history when making a referral. A family history going back three generations is particularly useful when referring patients with a family history of cancer to GHSNZ (see: “Taking a family history”, Page 15).
The importance of genetic counselling when patients undergo genetic testing

The aim of genetic counselling is to help affected or at-risk individuals to understand the nature of a genetic disorder, its inheritance, risks and management options. Therefore counselling is provided before testing so that people understand the information that a genetic test will and will not provide, as well as the processes involved, and the risks and benefits of genetic testing for themselves and their family/whānau.

A positive genetic test can have implications for a family/whānau for many generations to come. It is important that patients consider this and discussion with other family members is encouraged. Genetic counsellors also obtain written consent from patients before genetic testing arranged by GHSNZ.

What is the role of general practitioners if patients test positive for a genetic variation?

Dr Lintott explains that the role of GHSNZ is to provide general surveillance and management recommendations to general practitioners when the result of the genetic test is provided. As with other conditions, it is then up to the general practitioner to coordinate the multidisciplinary care which may be required. For example, young patients with cystic fibrosis require physiotherapy to improve lung function.

The care requirements of patients with progressive conditions will also evolve with time. For example, patients with progressive conditions, such as muscular dystrophy, require access to occupational therapists as their mobility becomes increasingly restricted. Patients with later onset diseases such as Huntington disease are likely to need treatment from a psychiatrist or a geriatrician later in life.

The varying certainty of genetic tests results

As a genetic associate Dr Lintott will often consult with patients where there is considerable uncertainty surrounding the clinical meaning of some genetic tests.

“Approximately 10% of all individuals undergoing genetic testing with full sequencing of the genes associated with Familial Breast Ovarian Cancer syndrome (BRCA1 and BRCA2) will not have a clearly pathogenic mutation detected, but will have a variant of uncertain (or unknown) significance (VUS). VUS may cause substantial challenges in genetic counselling, particularly in terms of cancer risk estimates and risk management. Predictive testing for a variant is therefore not available for other family members as the clinical significance of the variant is unknown.

If no mutation is detected on full sequencing of the BRCA1 and BRCA2 genes in a patient where a pathogenic mutation has not been previously identified in the family, the result is not ‘negative’; but ‘uninformative’ as there remains a small chance that a BRCA mutation is present but which cannot be identified with the current technology. Currently it is only possible to screen about 95% of these large complex genes. A result is only ‘negative’ if a patient is being tested for a known mutation previously identified in the family.”

In situations where patients undergo pre-symptomatic testing for late-onset neurological conditions, such as Huntington disease, genetic testing will indicate definitively whether or not the patient will develop the condition in the future. However, testing does not provide specific information as to age of onset, nor how the disease may affect them as this can be highly variable.

The role for genetic testing in tailoring treatment of patients

Tailoring pharmacological treatments to patients according to the results of genetic tests is referred to as pharmacogenomics. Generally this involves testing for genetic variation in genes that code for metabolic pathways, transporter systems or drug targets. If genetic variations are detected that alter the function of proteins or enzymes then this can be very useful in predicting how individual patients respond to treatment such as chemotherapies.

For example, one of the many HLA-B alleles (HLA-B*58:01) is known to be strongly associated with severe cutaneous adverse reactions in patients taking allopurinol. In the future, genotyping of patients groups with a high prevalence of HLA-B*58:01, e.g. people of Taiwan Han-Chinese ethnicity, before beginning treatment with allopurinol may be used to predict safe starting doses.

It is unusual for pharmacogenomic-related test requests to arise from primary care. The requests that GHSNZ receives for genetic testing to assist with treatment choices are generally arranged by the specialist who is managing the patient’s treatment.
Taking a family history

Providing a family history, going back three generations, with patient referrals is generally helpful for staff at GHSNZ. However, it depends on the condition the patient is being referred for as to whether this is necessary. Any family history should include first- and second-degree relatives (see below) on both sides of the family. Information about how and when any family diagnoses were made is useful, as the advice that is given to the patient is only accurate if the diagnoses provided in the family history are correct. Age at diagnosis is particularly valuable when creating a history for a potential familial cancer syndrome.

Degrees of family separation

- A first-degree relative refers to a patient’s: mother, father, daughter, son, sister or brother
- A second-degree relative refers to a patient’s: grandmother, grandfather, aunt, uncle, niece, nephew, half-sister or half-brother
- A third-degree relative refers to a patient’s first cousin

Before taking a family history it is useful to ask the patient to speak with other family members about any health-related family history, including infertility, miscarriage, still births or birth defects, as well as any significant disease, e.g. cancer or kidney disease, at a young age. Asking the patient to bring information such as death certificates of grandparents may also be helpful.

The history should begin with the patient and their partner’s date of birth recorded. The couple’s children should then be listed with their date of births, from oldest to youngest. Any brothers and sisters of the patient should then be recorded, again, from oldest to youngest. The date of death of family members should be recorded as well as the date of diagnosis of any conditions, along with relevant information, such as cancer type. The nieces and nephews of the patient should then be recorded systematically, and then the grandparents of the patient.

Before finishing the family history, ask if there is any other health-related information known about family members that may be of relevance.

Finally, ask the patient if they are happy for the information that has been recorded to be shared with other health professionals to assist with interpretation.
Further information about genetic testing

The following websites are recommended by GHSNZ for health professionals wanting more information on genetic testing and/or the clinical situations where genetic testing may be useful.

- [www.genetichealthservice.org.nz](http://www.genetichealthservice.org.nz)
  The GHSNZ website provides information for patients and health professionals, including information about privacy and confidentiality, as well as contact details for making referrals

- [www.genetics.edu.au](http://www.genetics.edu.au)
  The Centre for Genetics Education (Australia) contains extensive information about a range of genetic disorders and genomic techniques

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References


Have you signed up yet?

Clinicians are encouraged to sign up for a free “My bpac” account in order to personalise the content you see on the bpac™ website, save favourite articles, access personalised report data (for prescribers) and complete CME quizzes. Over time we will be releasing new interactive features of “My bpac”.

You may actually already have a “My bpac” account; most General Practitioners were signed-up to our old website, and we have carried over these accounts. If you have forgotten your user name and password (and you are a General Practitioner), your user name is most likely your MCNZ number, and you can use the “reset password” option on the website to receive a new password. Or you can just create a new account.

To sign up, visit [www.bpac.org.nz](http://www.bpac.org.nz) and click on the “My bpac” tab.
Advising patients interested in direct-to-consumer genetic testing

Direct-to-consumer genetic testing generally involves patients purchasing tests online; prices are reported to vary from $100 to $1000. This is a rapidly expanding area of commercial interest. It has been estimated that by 2018 the global direct-to-consumer genetic testing market will be worth more than NZ$300 million. However, whether this market will be able to provide health-related information in the future is currently uncertain. In late 2013, the U.S. Federal Drug Administration (FDA) contacted the major supplier of direct-to-consumer genetic testing and ordered them to “immediately discontinue marketing” their testing kit and personal genome services. This was due to concerns about how information provided by testing kits might be interpreted by consumers. In order to comply with the FDA request direct-to-consumer genetic testing companies in the United States must not provide consumers with genetic interpretations that relate to health.

The quality of any information provided by direct-to-consumer genetic testing can vary enormously. Therefore health professionals can recommend caution to patients who are considering purchasing private testing, focusing instead upon the specific health concerns the patient has, and providing evidence-based advice. For example, a patient who is concerned about colorectal cancer can be advised to eat a healthy diet, e.g. that includes fish as a source of protein, nuts, seeds and olives as sources of fats, and legumes and fruits for carbohydrates. However, if a patient has purchased a genetic test, and asks for assistance in interpreting the results, the information the test provides should not be dismissed.

The majority of people who purchase direct-to-consumer genetic tests do not have a known family history of a specific disease; the test is purchased out of simple curiosity. Results from tests requested for these purposes are unlikely to be clinically useful as there are many factors affecting phenotypes such as cardiovascular disease or diabetes. Any decision to further investigate the patient’s health should be evidence-based.

A second reason that people purchase direct-to-consumer genetic testing is to discover information about their ancestry. These tests use maternal mitochondrial DNA and Y chromosome DNA to provide continental and regional information about ancestors. These tests can even tell consumers what percentage of their DNA is shared with Neanderthal. However, this sort of ancestry testing has no clinical use.

Some people may purchase direct-to-consumer genetic testing to request pre-symptomatic testing for susceptibility genes with a high predictive value, e.g. BRCA1 and BRCA2, or to determine carrier status of autosomal recessive conditions such as cystic fibrosis. Patients who present to general practice with results of genetic testing that suggest the presence of a known genetically inherited disorder should be referred to GHSNZ for counselling. When discussing test results that are negative for a specific condition, it is important to point out to patients the possibility of a false negative result where only a few mutations have been tested.

Before purchasing direct-to-consumer testing, consumers should be aware that there are currently no commercially available genetic tests that have been approved by the FDA and therefore their accuracy and reliability is not known. In New Zealand, people who have undergone genetic testing are also required to disclose this information if they purchase new health or life insurance policies. Furthermore, a lack of regulatory control concerning the use of genetic information collected by commercial entities means that it is uncertain what happens to this information if companies go bankrupt.

It is important to advise patients that are considering purchasing genetic testing that they will also, in effect, be testing their family members. It is possible that family relationships can be harmed if genetic information is not accompanied by appropriate counselling. The results of genetic testing can also have lasting effects on generations to come. Consultation with other family members before purchasing direct-to-consumer genetic testing should be strongly advised.