Genetics and genetic testing:
Questions, answers and case scenarios

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Genetic testing technology has rapidly advanced and become more widely available in New Zealand. However, demand currently exceeds the ability to supply genetic testing services and an expected further increase in demand will put more pressure on a service already under-resourced. It is therefore expected that GPs will have an increasingly important role in meeting future demand in the area of genetic testing in New Zealand.

As part of a report commissioned by the National Health Committee (NHC), the authors conducted a national survey of GPs to find out about their current practice and training needs. The survey included three clinical scenarios with questions about managing patients in each and also included questions about access to genetic services. GPs responding to the survey felt they lacked experience and knowledge of genetic testing, had received little formal training and many were unsure of how to contact genetic services locally. GPs recognised the importance of their role in genetic testing and many wanted further information and training.*

This paper provides a practical guide to the understanding and management of two genetic case scenarios that GPs may be presented with. The first scenario was included in the survey, and the second was presented at the recent RNZCGP conference. Have a go at answering the questions to each scenario provided in the boxes below and compare this with your colleagues' answers (first scenario only) and with the information provided by the clinical geneticist.

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Case 1: Cystic fibrosis

Jane's sister died of cystic fibrosis. Jane does not have cystic fibrosis. Jane and her partner David are now thinking of having children. They would like to find out about the potential risk for their children of developing the disease.

1.1 What is the risk Jane is a carrier?

1.2 What information would be relevant to ask Jane about? What step would you take next?

1.3 If a genetic test is indicated who should be tested?

1.4 If Jane has a genetic test and the result for cystic fibrosis is negative and she doesn't know about her deceased sister's mutation status, what would the risk be for her child?

1.5 If both Jane and David have a genetic test and the result for cystic fibrosis is negative and she doesn't know about her deceased sister's mutation status, what would the risk be for her child?

* The full report including a copy of the survey is available on the NHC web site: www.nhc.govt.nz

Cystic fibrosis: background information

Cystic fibrosis (CF) is a genetic disease caused by a mutation in a gene that produces the protein CFTR (Cystic Fibrosis Transmembrane Regulator), which is responsible for the movement of chloride ions through cell membranes. Abnormal CFTR affects the mucus and sweat glands in patients who are diagnosed with CF, leading to respiratory and digestive problems. Over 600 different mutations causing CF have been identified, giving rise to disease with varying severity of symptoms.

Inheritance pattern

CF is inherited though autosomal recessive inheritance. In other words, for an individual to have CF, both of their parents must be carriers of CF, i.e. the parents each have one abnormal CF gene and one normal CF gene, but do not show symptoms of the disease because the normal CF gene is dominant. The chance a child of two carrier parents will inherit CF genes from both parents and therefore inherit the disorder is 25%. The chance that a child will inherit only one abnormal CF gene and become a carrier is 50% and the chance that the child will be unaffected is 25%. Because the recessive CF gene is inherited through the autosomal (non-sex-linked) chromosomes, male and female offspring are affected equally.

1.1 Jane's risk

In this scenario the chance that a healthy, unaffected sibling such as Jane being a carrier is 2/3 (66%), because the affected category of individuals is removed from the calculation (Jane does not have CF) (Figure 1).

GP survey: responses

Most GPs (45.7%) thought her risk was 50% and many were not sure (26.8%); 8.6% of GPs correctly identified Jane's risk as being 66%.

1.2 Relevant information to ask Jane

In this case it would be relevant for the GP to ask Jane about specific mutation(s) in the family, Jane and David's ancestry, other history of CF and whether there was a history of male infertility in their families. A history of male infertility is a relevant issue as congenital bilateral absence of vas deferens is often associated with a mild cystic fibrosis mutation.

There are variable rates and types of mutations in different ethnic groups, which affect carrier frequency and residual risk after testing. The laboratory cannot detect all mutations in CF but may be able to look for specific mutations, that are not part of the laboratory's usual screen, in certain racial groups. Therefore the ancestry of the patient would be relevant. Other history of CF in their families is also important, especially the partner's family. It would not be relevant to ask Jane about history of asthma in their families.

GP survey: responses

Most GPs correctly identified family history and Jane and David's ancestry as very important.

1.3 Who should be tested?

If the mutation in Jane's sister was not known, then testing the parents would be the best way to find out what the mutation was. If both mutations were known then testing the parents would not be necessary as they are obligate carriers. If the mutations were known Jane could be tested first and then David would only be tested if Jane were positive. Although most couples prefer to be tested in a one-stage not a two-stage process, there are cost implications as the second test may not be necessary.

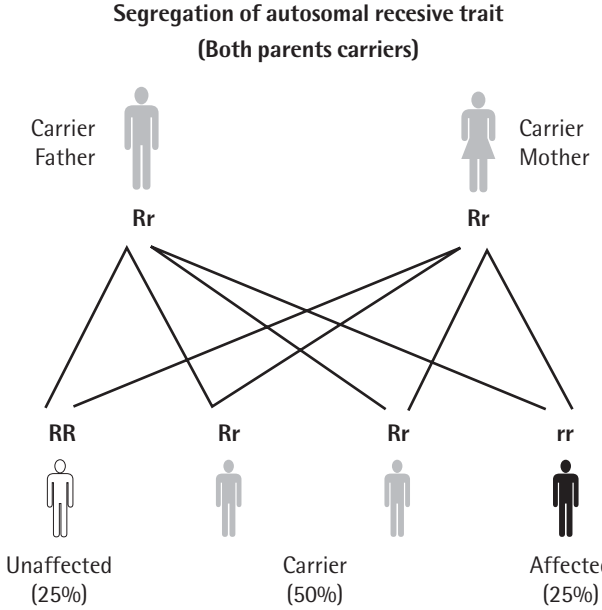
GP survey: responses

Most of the responding GPs thought both Jane and David should be tested in this scenario.

1.4–1.5 What do negative test results mean?

If Jane has a genetic test and the result for CF is negative and she doesn't know about her deceased sister's mutation status, the risk for her child would be lower but still significant as her sister may have had at least one unknown mutation. If both Jane and David have a genetic test and the result for CF is negative and Jane doesn't know about her deceased sister's mutation status, and her partner is European New Zealand, the residual risk (risk after testing) that he is a carrier is 1/200.

Figure 1. Autosomal recessive inheritance in cystic fibrosis



GP survey: responses

Approximately half (44.4%) of the GPs thought the risk to the child was low, and many were not sure (35.4%). A small number (1.2%) correctly identified the risk as significant if Jane was tested and the result was negative; 30.5% of GPs correctly identified the risk to the child as low if both parents were tested and the result were negative, and 41.2% thought there was no risk. Many were not sure (25.5%).

Case 2: Myotonic dystrophy

Johnny is three months old. He was born at term, had feeding difficulties and seemed 'floppy' compared with April's other two children. He had clubbed feet. He has a half brother, Sam, through his mother, aged 16 years, who is well and 'very bright'. He has a full sister, Jenny, aged 5, who is well. Mum, aged 40 years, April Brown, is well but the doctor taking the history notices April has a slightly expressionless face. Her second husband, Fred Brown, an accountant, is well and not related to her. He was adopted out and knows nothing of his birth family. April had a full sister, Jill, who died suddenly during an operation for a burst appendix aged 32 years. April also has a brother, Peter, who developed a stepping gait, history of 'fainting' and cataracts in his late 30s. He is unemployed and was born in 1958. He has two children: Mike, aged 14 years, who is struggling at school, and Sophie who is at University reading English and who is 12 weeks pregnant. Her father, aged 80 years, Harold Mann, developed cataracts aged 54 years and now is having investigations for swallowing problems but is otherwise very fit. His wife, Sue is well.

2.1 What is the pattern of inheritance?

2.2 What do you notice about the age of onset in the family?

2.3 Comment on the expression and penetrance in this family if most of the problems have the same cause?

The paediatric team, after taking an unusually full family history, suspected a specific diagnosis in Johnny. The family are referred and fully investigated at the local genetics outreach clinic and after some time the results at last come back, confirming their diagnosis: Johnny has myotonic dystrophy. He has 2036 CTG repeats. Mum has 200 repeats. April and Fred are given information after seeing the genetics team, and a letter summarising the consultation. They have been asked to pass on this information to Peter, Harold and Sue.

2.4 Who else should be offered testing?

2.5 What would be a possible explanation for April's sister's death?

2.6 If Peter decides to have a test, what type of test would it be?

2.7 If Sam decides to have a test, what type of test would it be?

2.8 If Jenny's parents request a test for Jenny, what type of test would it be?

2.9 Sophie is pregnant. What should you do?

Myotonic dystrophy: background information

Myotonic dystrophy is an inherited disorder of muscle function that can affect several different body systems. The condition can vary in severity from a very mild presentation in which adults do not even realise they are affected, to a severe presentation of extreme muscle weakness in infancy. Box 1 lists a number of health concerns that can be associated with myotonic dystrophy. Most people with myotonic dystrophy do not experience all of these problems.

2.1 Inheritance pattern

Myotonic dystrophy is inherited through autosomal dominant inheritance (Figure 2), where only one abnormal gene from one parent is required to cause the disease as the abnormal gene dominates the outcome of the gene pair. Therefore each child of an affected parent has a 50% chance of inheriting the disease. The inheritance of myotonic dystrophy is also not affected by the sex of the parent or child.

2.2–2.3 Age of onset/expression and penetrance

In this scenario the condition is appearing at an earlier age and with increasing severity as the disease is passed down from one generation to the next. This is a common feature of myotonic dystrophy known as 'anticipation'. The severity of the symptoms associated with myotonic dystrophy not only varies widely between people, but also between members of the same family. The symptoms can occur at any age, but usually develop during the 20s or 30s. However congenital myotonic dystrophy, the severest form of the disease, can occur at birth and can often be the point at which the disease is detected within a family.

Myotonic dystrophy is caused by a mutation or genetic change in the Myotonic Dystrophy Protein Kinase (DMPK) gene called a CTG repeat expansion. In myotonic dystrophy, the CTG pattern of DNA is repeated too many times in one copy of the

gene and disrupts the normal function of the protein made by the gene. Between five and 37 CTG repeats in both copies of the DMPK gene is considered normal, however if an individual has a higher number of repeats, their children are at risk of inheriting myotonic dystrophy. The penetrance of myotonic dystrophy is very high, so that almost everyone with a CTG repeat expansion of 50 or higher will develop symptoms of the disease at some stage in their life. Usually individuals with 50–150 will develop mild symptoms, and more severe symptoms are found in individuals with higher numbers of repeats. Congenital myotonic dystrophy is associated with around 1000 or more CTG repeats.

2.4 Who should be offered testing?

In this scenario Harold should be offered testing because the results of April's genetic test means that one of her parents have myotonic dystrophy. Harold's symptoms of cataracts and swallowing problems suggest he has the disease. Confirming a diagnosis is important for Harold's own health and to identify who else is at risk. Peter should also be offered testing as he also has symptoms (stepping gait and cataracts) that are seen in this condition.

2.5 Explanation for April's sister's death

Myotonic dystrophy can cause problems with recovery after an anaesthetic (because of underlying muscle weakness which may not have been previously detected). Therefore one explanation for April's sister death is that she had myotonic dystrophy.

2.6–2.8 Types of genetic tests

Diagnostic testing is used to help confirm a condition in a patient who already has symptoms. For example, a neurologist may request a diagnostic Huntington disease genetic test in a patient with dementia and choreiform movements. Predictive or predisposition tests differ from diagnostic tests in that they are carried out on individuals who are at an increased risk of a genetic disorder because of their family history, but who do not yet show any of the signs of the illness themselves.

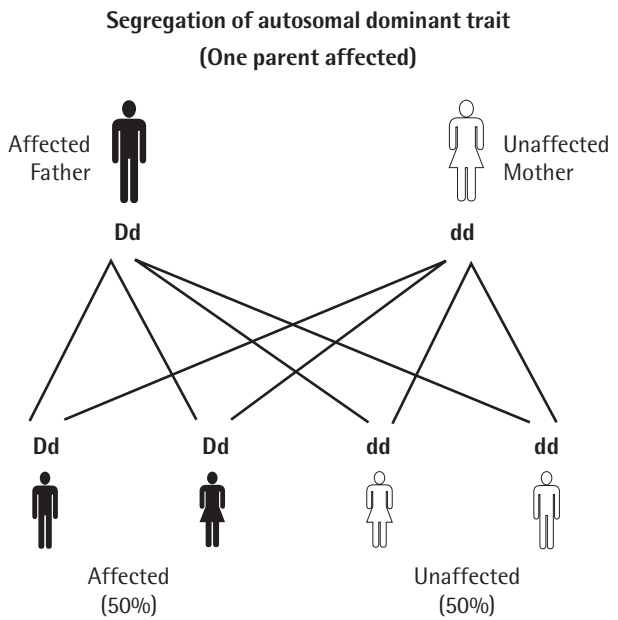
Predictive and predisposition testing are often used interchangeably. However predictive testing is used to find out whether or not patients have the gene mutation that will inevitably cause the disorder. Predisposition testing is used to detect a gene mutation, which indicates risk of getting a particular disease where those with an increased risk will not necessarily get the disease. Carrier testing is used to find out whether an individual carries a mutation in one copy of a recessive gene, with the other copy being normal. Carriers are usually asymptomatic. The term is used in both sex-linked (caused by genes on the X chromosome) and autosomal recessive disorders.

In this scenario, if Peter decides to have a test, the test would be a diagnostic test to confirm myotonic dystrophy. If Jenny's parents request a test for either Jenny or Sam, the tests would both be predictive tests to find out if they have inherited the CTG repeat expansion. However, where children are asymptomatic for adult-onset disorders (as is the case for Jenny and Sam) then predictive testing would not be appropriate until they are at or above the age of consent (16 years in New Zealand).

2.9 Sophie is pregnant. What should her doctor do?

In this scenario the GP should refer Sophie to genetic services. Genetic testing for Sophie to determine her mutation status (she is at 50% risk based on her father's presentation) would be very important. If she has a mutation expansion this may increase risks to her own health in pregnancy (increased risk of miscarriage and premature delivery). During pregnancy it is also possible to determine if the foetus has inherited the repeat expansion for myotonic dystrophy. This has the potential to provide additional information for Sophie regarding the risks to her foetus and the best options for managing the remainder of the pregnancy, delivery and neonatal care of her baby. However there are many ethical decisions involved and genetic services are in the best position to provide genetic counselling for patients such as Sophie.

Figure 2. Autosomal dominant inheritance of myotonic dystrophy



Box 1. Myotonic dystrophy health concerns

Muscle weakness

Weakness is very variable and can range from mild to severe. It particularly involves the face and eyelids, jaw, neck, forearms and hands, lower legs, and feet. It can affect speech and give lack of facial expression.

Myotonia

Myotonia is difficulty in relaxing a muscle after it has been contracted, e.g. after gripping something it may be difficult to let go.

Heart problems

Abnormal rhythm of the heart might require treatment. This can even affect those without symptoms. Regular ECGs (heart tracings) of affected individuals are advised to detect problems at an early stage.

Chest and breathing problems

Chest infections may result from weakness of breathing muscles, including the diaphragm, or from food entering lungs as a result of choking. At-risk or affected individuals are strongly advised not to smoke, which can make breathing problems worse. Inadequate breathing during the night might lead to disturbed sleep, snoring, difficulty waking, morning headaches and daytime sleepiness. Driving safety may be an issue for people who suffer from sleepiness.

Anaesthetics and other medications

Myotonic dystrophy can cause problems with recovery after an operation when certain anaesthetic drugs are used.

Digestive problems

These are common as the muscle throughout the digestive system may be affected. This may lead to swallowing problems (which can also be a cause of food entering the lungs), pains in the bowels with constipation and diarrhoea and occasionally enlargement of the large bowel. Gallstones, which can cause painful spasms after eating fatty food, can be a problem.

Eye problems

Cataracts can cause blurring and dimming of vision. This may be the only problem caused by myotonic dystrophy, particularly in the first affected generation of a family. Droopy eyelids can be a problem with reading and watching television.

Other problems may include:

Male infertility; diabetes; the muscle in the womb can be involved and lead to difficulties in pregnancy; the brain can be affected causing thinking and learning difficulty, especially when onset is in childhood.

Special difficulties in affected children

Muscle involvement can be more severe, especially when myotonic dystrophy is present at birth. Sometimes severely affected babies may live only a short time. Speech, educational and behavioural problems can occur.

Genetic services

Genetic services in New Zealand are based in Wellington and Auckland, with clinics held in many other centres. Referrals to genetic services are received for diagnosis of a variety of genetic conditions, to confirm or explain a genetic diagnosis, to discuss and arrange genetic testing, to discuss implications of a family history of genetic conditions and implications of a strong family history of cancer.

A medical geneticist provides diagnosis and initial management of individuals with genetic conditions. Information and support for individuals and families diagnosed with, or at-risk for, a genetic condition is provided by genetic counsellors (or associates). Services offered are outlined in Box 2. For information about how to contact Genetic Services see Box 3.

Box 2. Services offered by Genetic Services

- Up-to-date information
- Tracking and confirming family history
- Diagnosis of the condition
- Assessment of risk
- Mutation testing in high risk families
- Management recommendations
- Identifying other at-risk family members
- Understanding and support
- Referrals for ongoing care.

Box 3. How to contact Genetic Services

Northern Regional Genetic Services – Auckland DHB
Building 18, Auckland Hospital
Tel: 09-307 4949 extension 5530
or 0800 476 123
http://www.adhb.co.nz/akhealth/ClinSup.html#Clinical

Central & Southern Regional Genetic Services – Capital Coast DHB
Wellington Hospital
Private Bag 7902, Wellington South
Tel: 04-385 5999 or 0508 364 436
Email genetic.services@ccdhb.org.nz
http://www.ccdhb.org.nz/SS/gs/index.htm