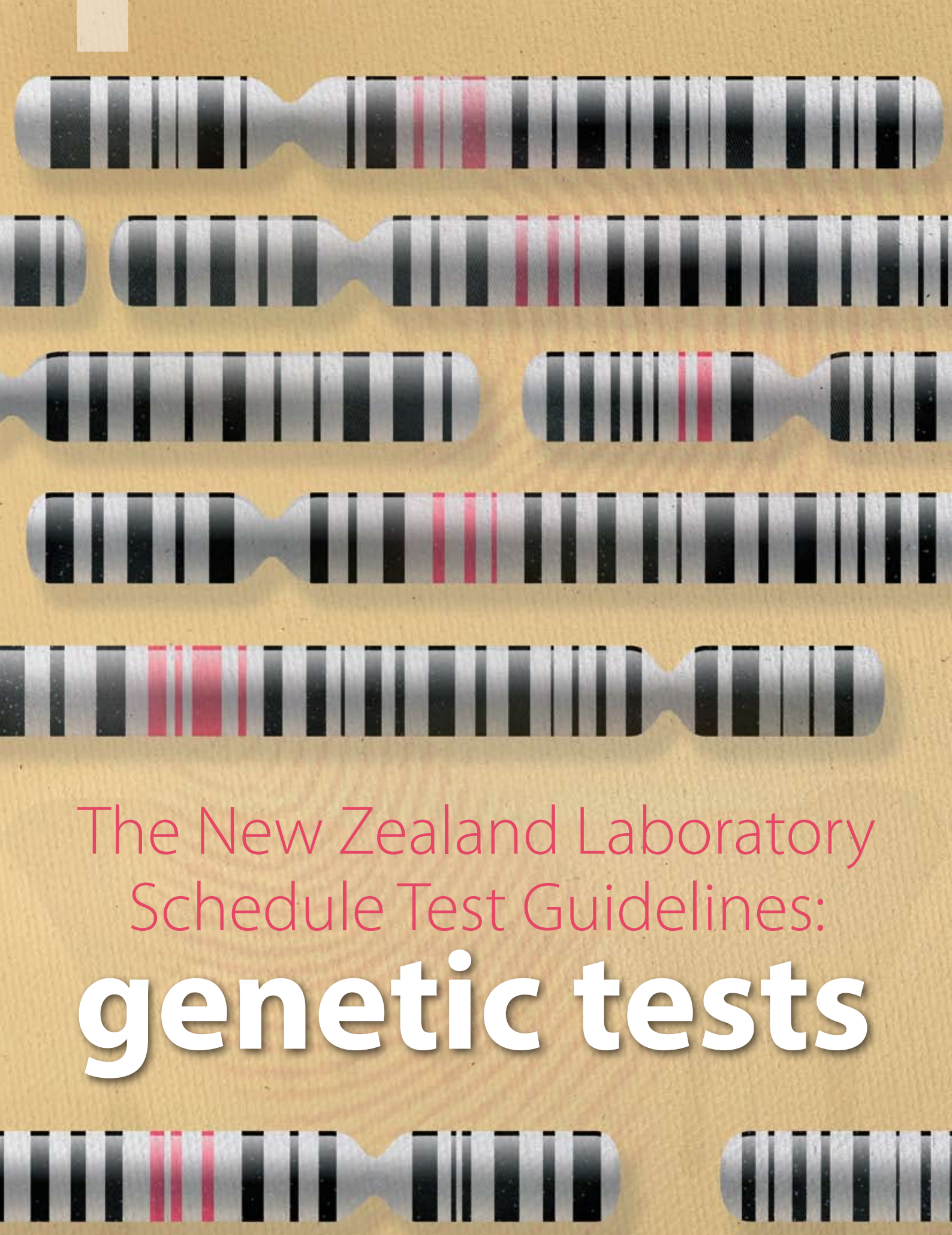


The New Zealand Laboratory Schedule Test Guidelines: genetic tests

The New Zealand Laboratory Schedule provides clinicians with consistent guidance when considering requesting laboratory tests. It will ensure the uniform availability of tests across District Health Boards (DHBs) in the future. Tests are divided into Tier 1, which all referrers can order, and Tier 2, meaning that the test must be ordered in conjunction with another health professional with a particular area of expertise. In addition, clinical guidance is provided on the use of some tests. In this article, with the assistance of Dr Joanne Dixon (leader of the Laboratory Schedule genetics subgroup), we focus on the genetic tests in the Schedule.

The role of primary care in genetic testing

Genetic testing can provide patients with information that may affect them for the rest of their lives, and potentially those of their family/whānau for generations to come. Given the potential significance of genetic testing it is important that requests for tests are appropriate and that patients are given sufficient information to make informed decisions before testing occurs. Equally, it is important that clinicians are able to provide this advice, to interpret the results of genetic tests correctly, and to support patients who are affected by genetic disorders.

Most general practitioners request only a few genetic tests. However, primary care does have a role in identifying patients who may benefit from genetic testing. For example:

- Testing to confirm a diagnosis, e.g. in a patient with abnormal iron metabolism suggestive of hereditary haemochromatosis
- Detecting the presence of a gene associated with a familial cancer syndrome, e.g. Lynch syndrome (hereditary non-polyposis colorectal cancer) in a person with a strong family history of colorectal cancer
- In rare cases, genetic testing may be useful to exclude a diagnosis, e.g. to avoid the necessity of performing small bowel biopsy in a young patient with suspected coeliac disease when the results of serology are equivocal

The New Zealand Laboratory Schedule

The Guidelines for genetic testing were developed by the Genetics Subgroup, led by Dr Joanne Dixon. The group included genetic diagnostic laboratory directors (LabPlus, Canterbury Health Laboratories and Wellington Regional Genetics laboratory) and clinicians.

The information about genetic tests in the Laboratory Schedule is divided into:

- Commonly requested genetic tests
- Genetic biochemistry
- Genetic haematology
- Genetic immunology
- Cyto-molecular genetics
- Genetic oncology

The majority of genetic tests listed on the New Zealand Laboratory Schedule are Tier 2. This means that as local DHBs choose to adopt the Schedule general practitioners will need authorisation from a clinician with relevant genetic experience before a request for testing is accepted.

There are several genetic tests available on the Schedule as Tier 1 tests, e.g. genotyping for hereditary haemochromatosis and testing for the absence of HLA-B27 when excluding ankylosing spondylitis, which can be requested by general practitioners without specialist authorisation. However, many genetic tests are for rare disorders and are only available through international laboratories via Genetic Health Services New Zealand (GHSNZ) clinicians. It is therefore generally recommended that all patients be discussed with a relevant clinician when considering the need for genetic testing. This also ensures that testing is appropriate and that patients have access to genetic counselling.

 For further information on the New Zealand Laboratory Schedule see: **www.dhbsharedservices.health.nz/Site/Laboratory/Laboratory-Schedule-Review-Project.aspx**

 For further information about GHSNZ, see: "Genetic Health Services New Zealand: what you need to know", Page 11.

Guidance on selected genetic tests

Genetic testing can provide clinical information of varying degrees of usefulness depending on the type of test that is requested, and the personal and family history of the patient. The different types of genetic testing that general practitioners need to have a broad knowledge of can be divided into:

1. **Diagnostic testing** to confirm a diagnosis, e.g. hereditary haemochromatosis in patients with elevated transferrin saturation.

2. **Pre-symptomatic testing** for a patient with a family history of a disorder that is caused by a single gene with full penetrance, i.e. all people with the gene will eventually display symptoms, e.g. Huntington disease.[1]

3. **Predictive testing** to determine whether a patient has a significantly increased lifetime risk of developing a condition due to the presence of a single gene, e.g. the **BR**east **CA**ncer gene (BRCA) for breast and ovarian cancer in females.[1]

4. **Carrier testing** to determine if a patient has a recessive gene for a condition, e.g. cystic fibrosis.

5. **Susceptibility testing** to determine if a combination of genetic variations results in a patient having an increased lifetime risk of developing a condition, e.g. diabetes or schizophrenia. However, these types of tests have limited clinical application as the relevant conditions often have multi-factorial causes.[1]

Specific examples of conditions encountered in primary care where genetic testing may be appropriate are provided below.

Hereditary haemochromatosis – an example of diagnostic testing

Hereditary haemochromatosis is predominantly found in people of European ancestry. This disorder causes an increase in iron absorption from the intestine due to a defect in hepcidin, the hormone which regulates iron homeostasis.[2] Iron deposits accumulate in the liver, pancreas, heart, joints, skin and gonads, which can cause serious damage if a person is untreated.

It is estimated that as many as one in ten people of European ancestry carry one copy of the gene for hereditary haemochromatosis, but the condition is rare among people of African or Asian ancestry.[3] Genetic testing for hereditary haemochromatosis is therefore unlikely to be clinically useful in people who do not have European ancestry.

Genotyping for hereditary haemochromatosis is available as a Tier 1 test where local guidelines permit. However, it is recommended that the patient is discussed with a gastroenterologist, haematologist or internal medicine specialist, or alternatively with GHSNZ.

The early symptoms of hereditary haemochromatosis are non-specific, including lethargy, arthralgia and abdominal pain.[2] Late complications include diabetes and peripheral arthritis. **Testing for hereditary haemochromotosis should only be considered in patients who have biochemical evidence of abnormal iron metabolism**, i.e. elevated fasting transferrin saturation of 45% or higher or elevated fasting serum ferritin concentration >300 ng/mL in males or >200 ng/mL in females, once more common causes of altered iron metabolism have been excluded.[4, 5] Elevated ferritin may be associated with inflammation due to infection, autoimmune conditions, cancer, excessive alcohol use and/or fatty liver, which can also cause transferrin levels to be raised.[2]

N.B. Fasting serum ferritin provides a more accurate marker of the total amount of iron stored in the body. Consuming some foods, e.g. iron-fortified breakfast cereals, can influence serum ferritin levels.

GHSNZ recommends that genetic testing of asymptomatic family members of an affected individual should only be undertaken following the recommendation of a clinician with relevant genetic experience or after discussion with a genetic counsellor.

There are two principle mutations in the HFE gene that can cause hereditary haemochromatosis: C282Y and H63D. Most people with haemochromatosis will be homozygous with the genotype HFE C282Y/C282Y, meaning they have two copies of the most common mutation for the condition; approximately one in 200 people in New Zealand have this genotype.[6] However, not all people with this genotype will develop haemochromatosis; the clinical penetrance is estimated to be 60 – 70%.[7] It has been estimated that in the United Kingdom a general practitioner with 1000 patients can expect to have approximately two patients with clinical hereditary haemochromatosis.[8]

A small number of people who are heterozygous carriers for the HFE gene (i.e. one copy of a mutant gene) will have elevated serum iron markers, and some will develop iron overload, but this does not result in significant iron deposition. Genetic testing of patients with suspected hereditary haemochromatosis ensures that this small proportion of patients do not undergo the intensive management that is required for patients with haemochromatosis and significant iron deposition (see below).

Approximately 5% of people with haemochromatosis carry the genotype HFE C282Y/H63D.[2] This is a compound heterozygous genotype where a person has copies of two different disease-causing mutations. Patients with a compound heterozygous genotype require management and treatment similar to that of patients with hereditary haemochromatosis who have a homozygous (HFE C282Y/C282Y) genotype.

Patients with hereditary haemochromatosis are treated by phlebotomy with blood removed once or twice per week to achieve a target ferritin level of < 50 micrograms/L, followed by maintenance treatment to keep ferritin levels between 50 – 100 micrograms/L.[2] Patients who commence phlebotomy treatment before they develop liver cirrhosis are likely to have a normal life expectancy.[2] Patients with haemochromatosis have an increased risk of osteoporosis and periodic DEXA scans are recommended.[2]

bpac[nz] will be publishing a more detailed article on the diagnosis and management of hereditary haemochromatosis in 2015.

Huntington disease – an example of presymptomatic testing

Huntington disease is a progressive neurodegenerative disorder that is ultimately fatal. It is inherited in an autosomal dominant pattern (only one copy of the abnormal gene needs to be present for the disease to be expressed), therefore there is a 50% chance that a person with an affected parent will develop the condition. The genetic test for the gene (HTT) that causes Huntington disease is more than 99% sensitive, because a single mutation accounts for the vast majority of cases.[9] People with Huntington disease have an expanded CAG repeat in the HTT gene which causes an abnormally long polyglutamine section in the huntingtin protein (N.B this is the correct spelling of the protein).[10] This results in an abnormal conformation of the mutant protein that is thought to cause selective neuronal toxicity within the striatum.[10] The prevalence of Huntington disease in Australia is reported to be 6 – 12 cases per 100 000 people.[11] There is limited data on the prevalence of Huntington disease in New Zealand.

Diagnostic testing for the Huntington disease mutation is classified as Tier 2 and should be requested by a neurologist, geriatrician or internal medicine specialist through GHSNZ. Pre-symptomatic testing in families with a history of Huntington disease is arranged by GHSNZ, and is not available for patients aged under 18 years. A positive Huntington test result is a life-changing event that requires careful management and support from both genetic counsellors and clinicians. Affected people may choose not to conceive, or they may wish to pursue prenatal testing for Huntington disease. People with children may feel anxious that they could have passed the disease-causing gene on. A positive test may influence a person's financial and career decisions and may affect relationships with their partner or siblings. For these reasons, many people who have a family history of Huntington disease prefer the uncertainty of not being tested.[12]

The mean onset of Huntington disease is age 40 years, with death occurring within 15 – 20 years of onset.[10] Patients who have developed Huntington disease can be identified by a progressive deterioration of motor control and cognitive function. Chorea is often seen early and is characterised by involuntary writhing movements. Later bradykinesia, incoordination and rigidity are more severely disabling.[10] There is currently no known cure for Huntington disease.

Inherited cancer syndromes – examples of predictive testing

There are many genes in which a mutation can allow the growth and replication of normal cells to escape usual control systems. In some situations these mutated genes can be passed on to an affected person's children. These include tumour suppressor genes, e.g. the BRCA mutation, oncogenes and mismatch repair genes. However, familial cancer syndromes are relatively rare. Patients who have been diagnosed with cancer, with a significant family history of cancer, may be referred for genetic testing by the clinician who is managing their treatment or by a general practitioner. General practitioners act as "gate-keepers" for asymptomatic people who are concerned that they may be affected by a familial cancer syndrome. A general practitioner with 1000 patients can expect to have 15 – 17 patients with a hereditary predisposition to cancer.[12]

If a person has a strong history of cancer in their family, especially if family members developed cancer before the age of 50 years, then it is reasonable to consider referring the patient to GHSNZ for counselling to determine their risk. It may be useful to discuss the patient with a relevant clinician, such as an oncologist or gastroenterologist, before considering a referral. Referral of families to GHSNZ for genetic assessment should include a three generation family tree which identifies family members who have been affected by cancer. If a familial mutation has not been previously identified, genetic testing must begin with DNA from an affected family member, in order to reduce false negative results.

Familial colorectal cancer

Autosomal dominant inheritance is estimated to account for 5 – 10% of cases of colorectal cancer.[13] Lynch syndrome (hereditary non-polyposis) is the most common hereditary colorectal cancer syndrome. A sample of 500 patients treated consecutively for colorectal cancer found that 3.6% had Lynch syndrome, of which 44% were diagnosed before age 50 years.[14] Each of these patients had at least three relatives with Lynch syndrome. Females with Lynch syndrome also have an increased risk of developing endometrial and endometrioid ovarian cancers.

Familial adenomatous polyposis (FAP) is caused by a mutation in a tumour suppressor gene and accounts for less than 1% of colorectal cancers. One in 5000 to 7000 people have FAP.[15]

If a patient has a personal or family history of colorectal cancer that is suggestive of a familial cancer syndrome then referral to the New Zealand Familial Gastrointestinal Cancer Service (see below) is recommended. Patients with an appropriate tumour histology and family history will then be referred to GHSNZ for mutation screening as required.

For further information visit: **www.nzfgcs.co.nz**

For further information see: "Surveillance of people at increased risk of colorectal cancer", (BPJ 44, May 2012).

Familial breast cancer and ovarian cancer

The predominant genetic abnormality that increases the risk of females developing breast and/or ovarian cancer is the presence of BRCA1 or BRCA2. It is thought that these mutated genes are present in approximately 5% of patients with breast cancer and 15% of patients with high-grade epithelial ovarian cancer.[16] Additional factors in a patient's family history that may indicate an increased risk for the development of cancer include: [17]

- Bilateral breast cancer
- Male breast cancer
- High-grade epithelial ovarian cancer*
- Jewish ancestry
- Sarcoma in a relative younger than age 45 years
- Glioma or childhood adrenal cortical carcinomas

* N.B. Borderline mucinous ovarian cancer is not associated with BRCA gene mutations

Women who are positive for a BRCA1 or BRCA2 mutation can be offered more frequent breast screening, as well as beginning screening at a younger age, e.g. having a mammogram every year, beginning at age 25 to 35 years. Hormonal therapy, e.g. tamoxifen, as well as prophylactic mastectomy, may be considered by some women as risk-reducing treatment options. Bilateral salpingo-oophorectomy (removal of the ovaries and fallopian tubes) is strongly recommended for patients who are BRCA mutation carriers, as increased frequency of monitoring has not been shown to result in improved long-term survival or earlier detection.

Examples of carrier testing that may be encountered in primary care

Every person is an asymptomatic carrier of a number of recessive genes that could potentially be passed on to their biological children. If their partner is also a carrier for the same autosomal condition there will be a one in four chance for each of their children having the genotype associated with the condition.

Thalassaemia (haemoglobinopathies) testing

The thalassaemias are the most common single gene disorders worldwide.[12] They are autosomal recessive blood disorders characterised by the abnormal production of one or more of the four protein chains (alpha or beta) that make up haemoglobin. Every person has four copies of the alpha globin gene and two copies of the beta globin gene.[18] Alpha thalassaemias are usually due to deletions of alpha globin genes, and beta thalassaemias are usually due to mutations in the beta globin genes.

Worldwide, approximately one in 20 people carry a gene for thalassaemia and it is thought that this provides protection against malaria.[18] The prevalence of genes causing alpha thalassaemia is increased among Māori and Pacific peoples,

as well as people of Chinese, South East Asian, Southern European, Middle Eastern, Indian subcontinent and African ancestry.[18] Deletion of a single gene (silent alpha thalassaemia) results in a mild decrease in mean cell volume. People with silent alpha thalassaemia are not generally anaemic. Deletion of two genes (alpha thalassaemia trait) causes a more marked microcytosis and hypochromia, but any anaemia is usually mild. People with deletion of three genes (haemoglobin H disease) are almost always anaemic with severe microcytosis and may require intermittent blood transfusions. Deletion of all four alpha globin genes (alpha thalassaemia major) results in fetal hydrops and is generally incompatible with survival.

There is an increased number of carriers for beta thalassaemia among people of Middle-Eastern, Southern-European, Indian subcontinent, Central and South-Asia and African ancestry.[18] People with a single mutated gene generally have mild anaemia with marked hypochromic microcytosis. Mutation of both genes (beta thalassaemia major) results in a severe transfusion-dependent anaemia. Because beta globin synthesis only starts around the time of birth, this will usually become apparent during the first year of life.

Haemoglobin electrophoresis has traditionally been used as the initial investigation for patients suspected of carrying a gene for thalassaemia.[19] Following electrophoresis, patients who have clinical signs consistent with thalassaemia or have a family history of thalassaemia should be referred to GHSNZ for genetic counselling before genetic testing is considered.

Patients who are carriers for thalassaemia do not require treatment.[12] Where both parents are carriers of a potential thalassaemia-causing gene, genetic testing during pregnancy may be appropriate and can be discussed with a haematologist or with GHSNZ.

For further information see: "Anaemia on full blood count: investigating beyond the pale" (BT Sept, 2013).

Cystic fibrosis testing

Cystic fibrosis is the most common autosomal recessive paediatric disease, although adults are increasingly affected as survival rates improve.[12] Approximately 1 in 20 – 25 people carry a mutation in a gene on chromosome 7 (CFTR) that can cause cystic fibrosis; approximately 1 in 2500 people of European ancestry develop the condition.[12] The mutation causes an abnormality in a membrane ion channel, resulting in impaired chloride and sodium transport across the epithelium and thick, viscous secretions. Cystic fibrosis mainly affects the lungs, but also involves other organs such as the pancreas, liver and intestines.[12]

Screening for immunoreactive trypsin (IRT) occurs routinely at birth as part of the Newborn Metabolic Screening Programme (formerly known as the heel prick or Guthrie test), and a test for mutations in CFTR is performed in infants with IRT above a threshold level. This is reported to detect 95% of infants born with cystic fibrosis.[20] Infants who have only one copy of the altered CFTR gene (heterozygotes) may also have a positive cystic fibrosis screening test. Analysis of the salt content of the infant's sweat is then used to confirm a diagnosis of cystic fibrosis.[20]

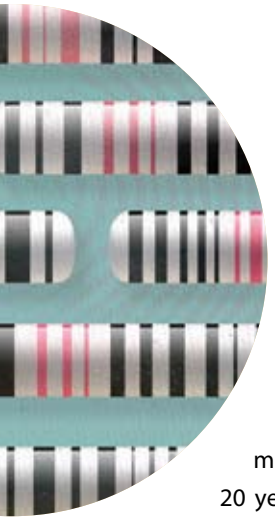
CF carrier testing is appropriate for patients with a family history of cystic fibrosis. If both prospective parents are genetic carriers it is recommended that they discuss their reproductive options with a genetic counsellor at GHSNZ. Prenatal testing for cystic fibrosis during pregnancy is available for couples who are both carriers for cystic fibrosis. Pre-implantation genetic testing may also be available to screen embryos for cystic fibrosis.

The clinical features of cystic fibrosis are malaise, failure to thrive, chronic respiratory problems, malabsorption, pale bulky stools, jaundice, pancreatic dysfunction and some males may be infertile due to a congenital absence of the vas deferens.[12] A sweat test may be considered for patients who have clinical features of cystic fibrosis, regardless of whether or not newborn screening was performed.[20]

In general, treatment of cystic fibrosis involves maintaining adequate nutrition and preventing and limiting the impact of chest infections.[12] Patients with cystic fibrosis often use bronchodilators followed by hypertonic saline solution via nebuliser.[12] Pancreatic enzyme supplements may also be used in some patients.[21] Physiotherapy is beneficial in clearing the patient's airways.[12]

Muscular dystrophy (myotonic dystrophy)

Duchenne muscular dystrophy and a rarer less severe variant, Becker muscular dystrophy, are X-linked recessive conditions and are therefore more common in males.[12] Duchenne muscular dystrophy affects approximately one in 3500 males and Becker muscular dystrophy affects approximately one in 30 000 males.[22] The mutation that causes the condition occurs in the gene coding for the protein dystrophin, which connects muscle fibres to the extracellular matrix; this is the largest gene on the X chromosome.



Both forms of muscular dystrophy are characterised by increasing weakness of proximal muscles as muscle tissue is progressively replaced by connective tissue.[12] Duchenne muscular dystrophy is generally diagnosed between the ages of two to five years and is progressive from this point.[12] Respiratory problems are the main cause of death for people with Duchenne muscular dystrophy, and this often occurs by age 20 years.[12] People with Becker muscular dystrophy have a similar, but much later and slower, onset of symptoms. A very small number of females who are carriers for muscular dystrophy will display muscle weakness.[22]

Genetic counselling should be offered to female patients of reproductive age who have a family history of muscular dystrophy; this can be arranged by GHSNZ. A focus of genetic counselling in this situation will be to determine the likelihood that the female is a carrier of a faulty dystrophin gene. The patient's family tree is used in the following way:[22]

- If a female has an affected son and an affected brother, uncle or cousin, then it is certain that she has passed on the faulty gene to her son
- If a female has an affected son, but no other affected relatives then she may be a genetic carrier, but there is also the possibility that the mutation may have occurred for the first time when the son was conceived
- A female who has two affected sons and no other relevant family history is most likely a genetic carrier

A constantly elevated serum creatine kinase (CK) level is consistent with a person being a genetic carrier for muscular dystrophy, however, approximately one third of genetic carriers do not have an elevated level.[22] Measuring serum creatine kinase levels is therefore of limited clinical value in this situation. If a female is confirmed as a carrier for muscular dystrophy then genetic counselling offers her the opportunity to discuss her personal risks and that of other family members. Pre-implantation genetic testing may also be available to screen embryos for muscular dystrophy.

Women who are genetic carriers for muscular dystrophy can experience changes in cardiac function and may benefit from referral to a cardiologist for assessment of cardiac function.[22]

There is no treatment for muscular dystrophy although corticosteroids can delay disease progression.[12]

Genetic testing is rarely useful to exclude or support a diagnosis

There are several genetic tests available to general practitioners in the Laboratory Schedule that relate to conditions with non-specific symptoms. These have limited clinical usefulness in the context of primary care; it is recommended that these tests only be requested in specific situations following consultation with GHSNZ.

Genetic testing for coeliac disease is rarely indicated

Coeliac disease is a systemic immune disease associated with gastrointestinal dysfunction and highly variable non-gastrointestinal features. The prevalence of coeliac disease in New Zealand adults is estimated to be approximately 1%.[23] There is a strong genetic component to coeliac disease with more than half of affected people having at least one other affected family member.[4] Most people who have coeliac disease have coeliac-associated antibodies and specific pairs of variations in two human leukocyte antigen (HLA) genes, HLA DQA1 and HLA DQB1.

Genetic testing for patients with suspected coeliac disease is available as a Tier 1 test under the immunology section of the Laboratory Schedule, however, the genetic section of the Schedule recommends that test requests be restricted to paediatricians, immunologists and gastroenterologists, i.e. Tier 2. This is because tissue transglutaminase antibodies (TGA) are the preferred test when investigating patients with suspected coeliac disease. Following a positive antibody test the diagnosis is generally confirmed with duodenal biopsy. In the rare situations when the results of serological tests are equivocal, and a duodenal biopsy is relatively contraindicated, e.g. in a young child, it may be appropriate to test for genetic variation, as exclusion of at-risk genotypes may mean that it is unnecessary to perform this procedure. However, as only 3% of patients with one or both of HLA DQA1 and HLA DQB1 will develop gluten intolerance,[24] the presence of these alleles is not diagnostic for coeliac disease, but their absence essentially excludes a diagnosis of coeliac disease.

Testing asymptomatic family members for genetic markers of coeliac disease is not indicated.

For further information see: "Investigating the Gut: Coeliac disease" (BT Mar, 2010).

Ankylosing spondylitis

Ankylosing spondylitis is an uncommon cause of back pain typically seen in patients aged in their mid-20s.[4] The condition

is more frequent in males and is caused by a mixture of genetic and environmental factors; most of which have yet to be confirmed.[4]

The prevalence of ankylosing spondylitis is higher in North America (0.32%) and Europe (0.24%) than in Asia (0.17%), and is lowest in Latin America (0.1%) and Africa (0.074%).[25]

The clinical features of ankylosing spondylitis as well as spinal abnormalities on radiology are used to diagnose patients with ankylosing spondylitis. The presence of HLA B27* confers susceptibility to ankylosing spondylitis, however, testing for the presence of HLA B27 has limited clinical value. This is because approximately 8 – 10% of people with Caucasian ancestry are HLA B27 positive and more than 90% of these people will never develop the condition.[26] A negative test result for HLA B27 can be useful as approximately 90% of people with ankylosing spondylitis (some estimates are as high as 98%) are HLA B27 positive and a negative result makes a diagnosis much less likely.[26]

Family testing for variations in HLA B27 is not indicated in asymptomatic family members of an affected patient.

* The products of the human leukocyte antigen (HLA) genes play an important role in the immune system by binding proteins resulting from the breakdown of self-cells or foreign pathogens and presenting them to T cells.

Further reading about genetic testing

Testing in children - American Academy of Paediatrics: **http://pediatrics.aappublications.org/content/131/3/620.full.pdf+html**

Cardiac inherited diseases – Cardiac Inherited Diseases Group: **www.cidg.org/webcontent/cidg/Home/tabid/53/Default.aspx**

Gastrointestinal Cancers – NZ Familial Gastrointestinal Cancer Registry: **www.nzfgcr.co.nz/home**

Policy on pre-symptomatic testing in children and young adults (Human Genetics Society of Australasia: **www.hgsa.org.au/documents/item/244**

Policy on pre-symptomatic and predictive testing for genetic disorders (Human Genetics Society of Australasia): **http://www.hgsa.org.au/documents/item/272**

DNA storage requirements: **www.geneticheathservice.org.nz**

Genetic Information (Centre for Genetic Information, NSW Government): **www.genetics.edu.au**

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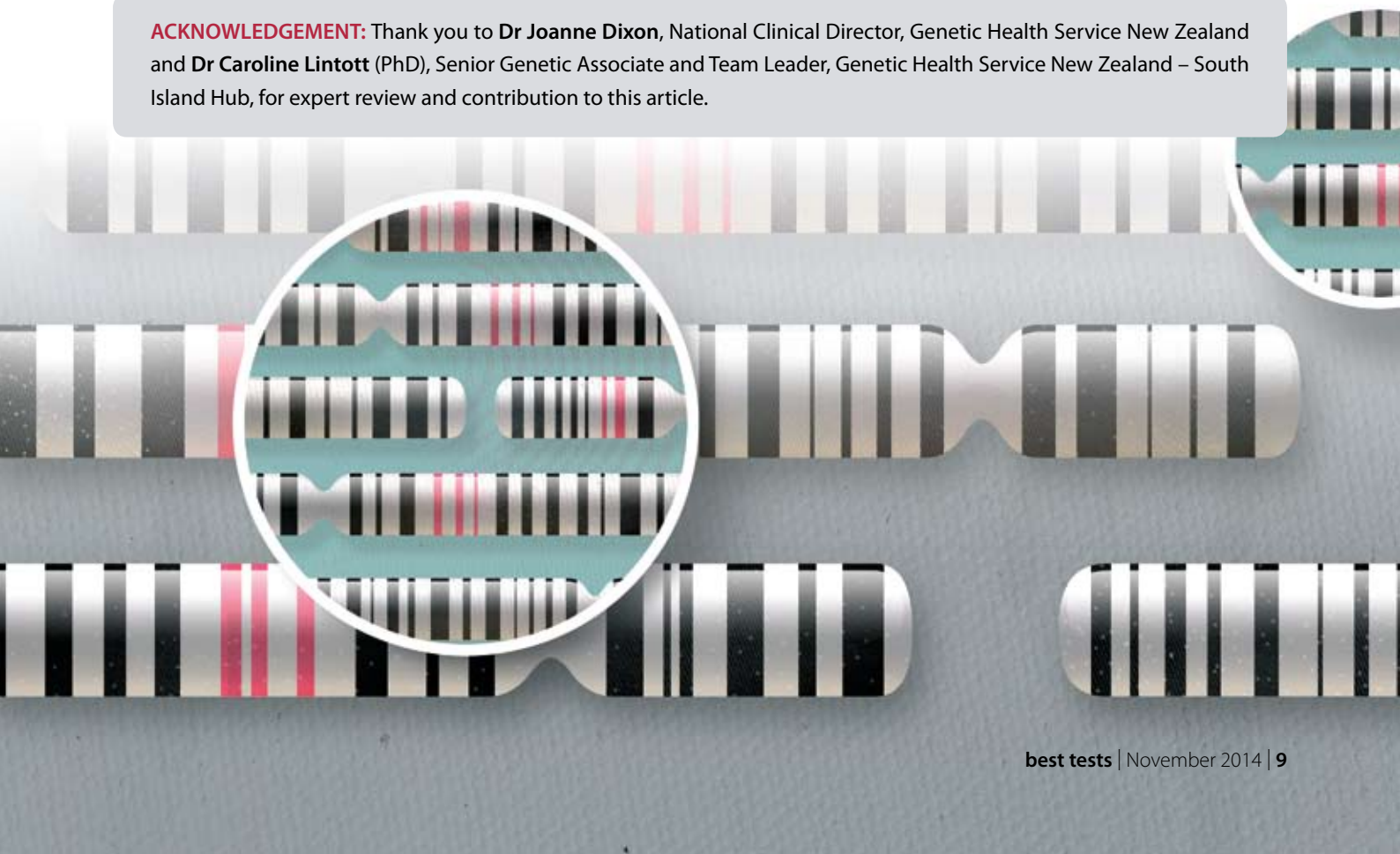

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