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NZ Laboratory Schedule & Test Guidelines: Genetic tests

Genetic Health Services New Zealand

Exposure to body fluids

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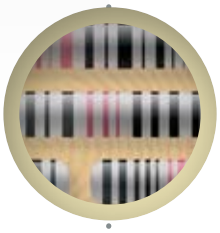


2 The New Zealand Laboratory Schedule and Test Guidelines: genetic tests

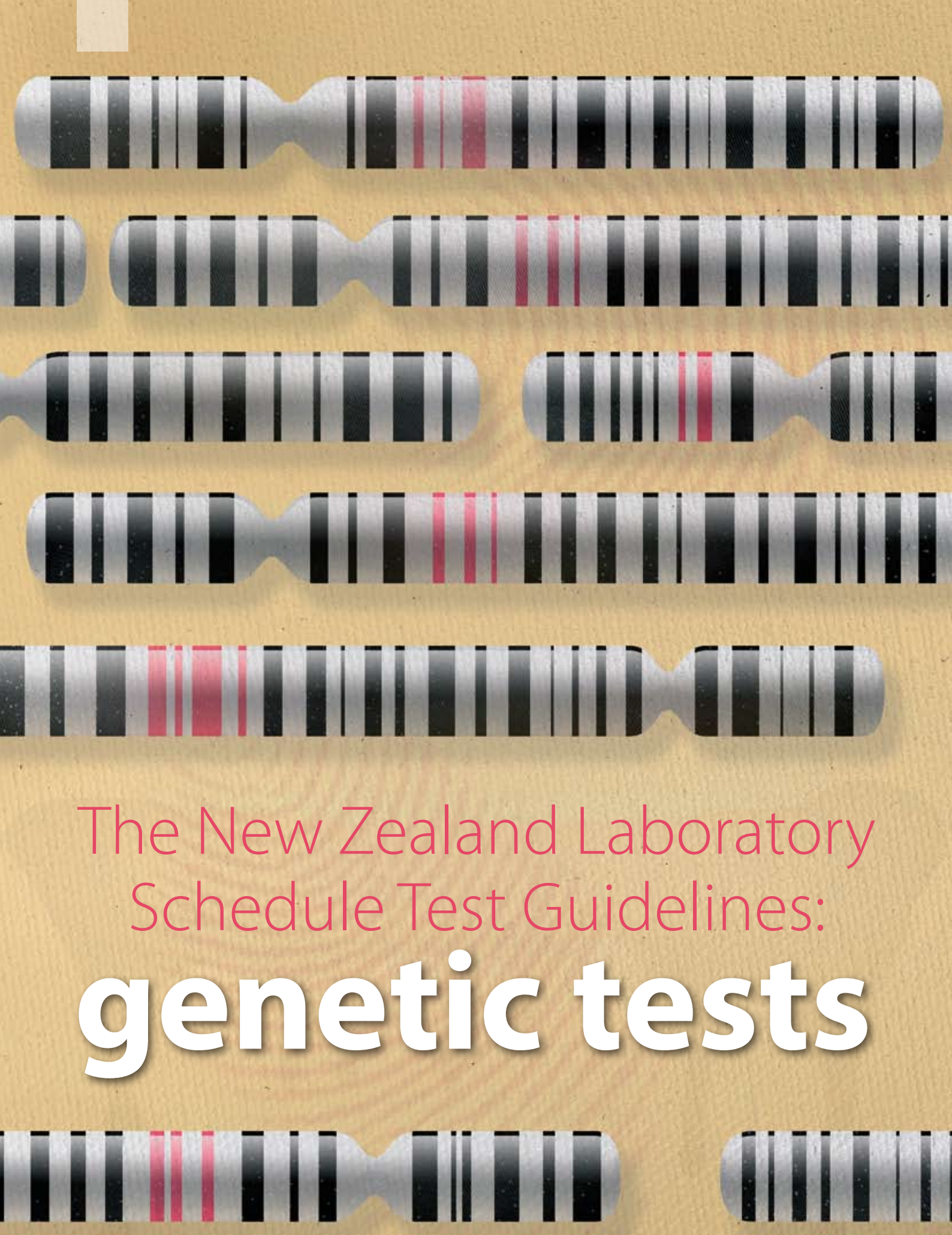
The New Zealand Laboratory Schedule provides clinicians with consistent guidance when considering requesting laboratory tests. It will ensure the uniform availability of tests across District Health Boards (DHBs) in the future. Tests are divided into Tier 1, which all referrers can order, and Tier 2, 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 genetic subgroup), we focus on the genetic tests in the Schedule.

11 Genetic Health Services New Zealand (GHSNZ): What you need to know

Genetic Health Services New Zealand (GHSNZ) provides expert genetic advice, counselling and diagnostic services to patients and health professionals throughout the country. Many patients are referred to GHSNZ by a secondary care service. However, general practitioners can assist in this process by ensuring that patients who may require genetic testing receive appropriate referral, as well as discussing possible implications and limitations of genetic testing with the patient, and coordinating multidisciplinary care. In order to optimise the use of genetic testing in New Zealand we asked Dr Caroline Lintott, Senior Genetic Associate and Team Leader at GHSNZ, to provide input on how this can be done.

18 Exposure to body fluids: keeping the primary healthcare team safe

Providing a safe working environment involves both minimising the risk of transmission of infectious pathogens and dealing with exposures after they have occurred. Exposure to body fluids is one of the major occupational hazards faced by healthcare workers. Effective use of standard precautions, including hand hygiene and personal protective equipment, is the best way to protect healthcare workers from infectious pathogens. However, even strict adherence to standard precautions will only minimise the infection risk and dealing effectively with any potential exposures, e.g. needlestick injuries, if they occur is vital in protecting healthcare workers.



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]

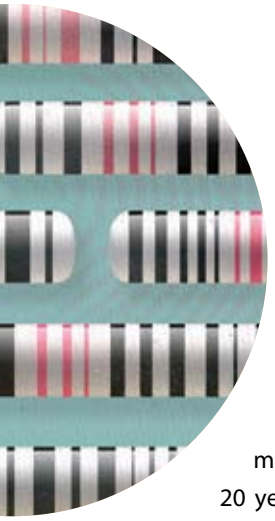
CF carrier testing is appropriate for patients with a family history of cystic fibrosis. If both prospective parents are genetic carriers it is recommended that they discuss their reproductive options with a genetic counsellor at GHSNZ. Prenatal testing for cystic fibrosis during pregnancy is available 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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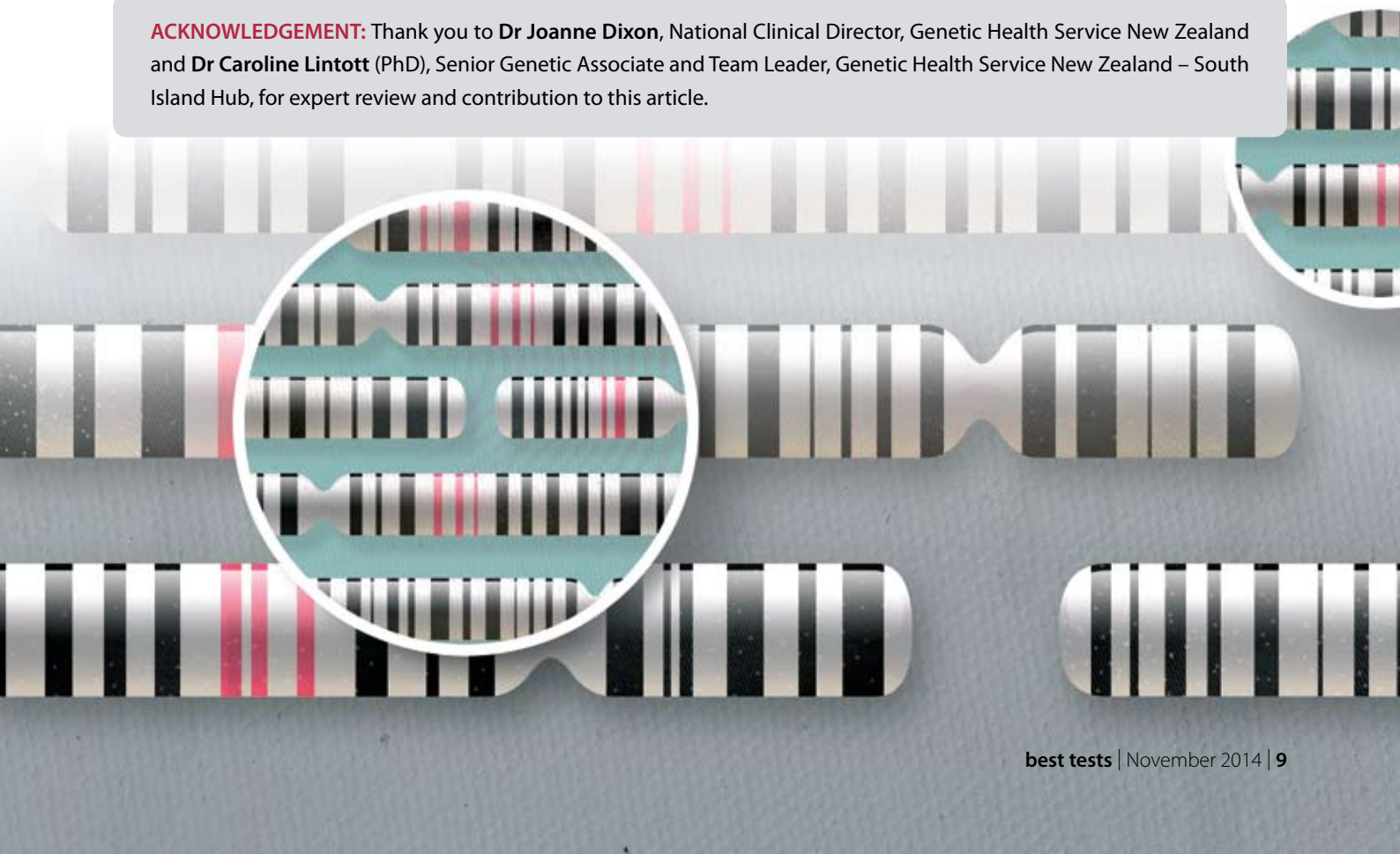

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Genetic Health Services New Zealand (GHSNZ): What you need to know

Genetic Health Services New Zealand (GHSNZ) provides expert genetic advice, counselling and diagnostic services to patients and health professionals throughout the country. Many patients are referred to GHSNZ by a secondary care service. However, general practitioners can assist in this process by ensuring that patients who may require genetic testing receive appropriate referral, as well as discussing possible implications and limitations of genetic testing with the patient, and coordinating multidisciplinary care. In order to optimise the use of genetic testing in New Zealand we asked Dr Caroline Lintott, Senior Genetic Associate and Team Leader at GHSNZ, to provide input on how this can be done.

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.[1] 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[2]
- 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

For further information on investigating specific genetic disorders see: "The New Zealand laboratory Schedule Tests and Guidelines: Genetic tests", Page 2.

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 appropriawte, 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.[3] 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 testingw

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.geneticheathservice.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**

  The Centre for Genetics Education (Australia) contains extensive information about a range of genetic disorders and genomic techniques

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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.[4] 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.[4] 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.[5] 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.

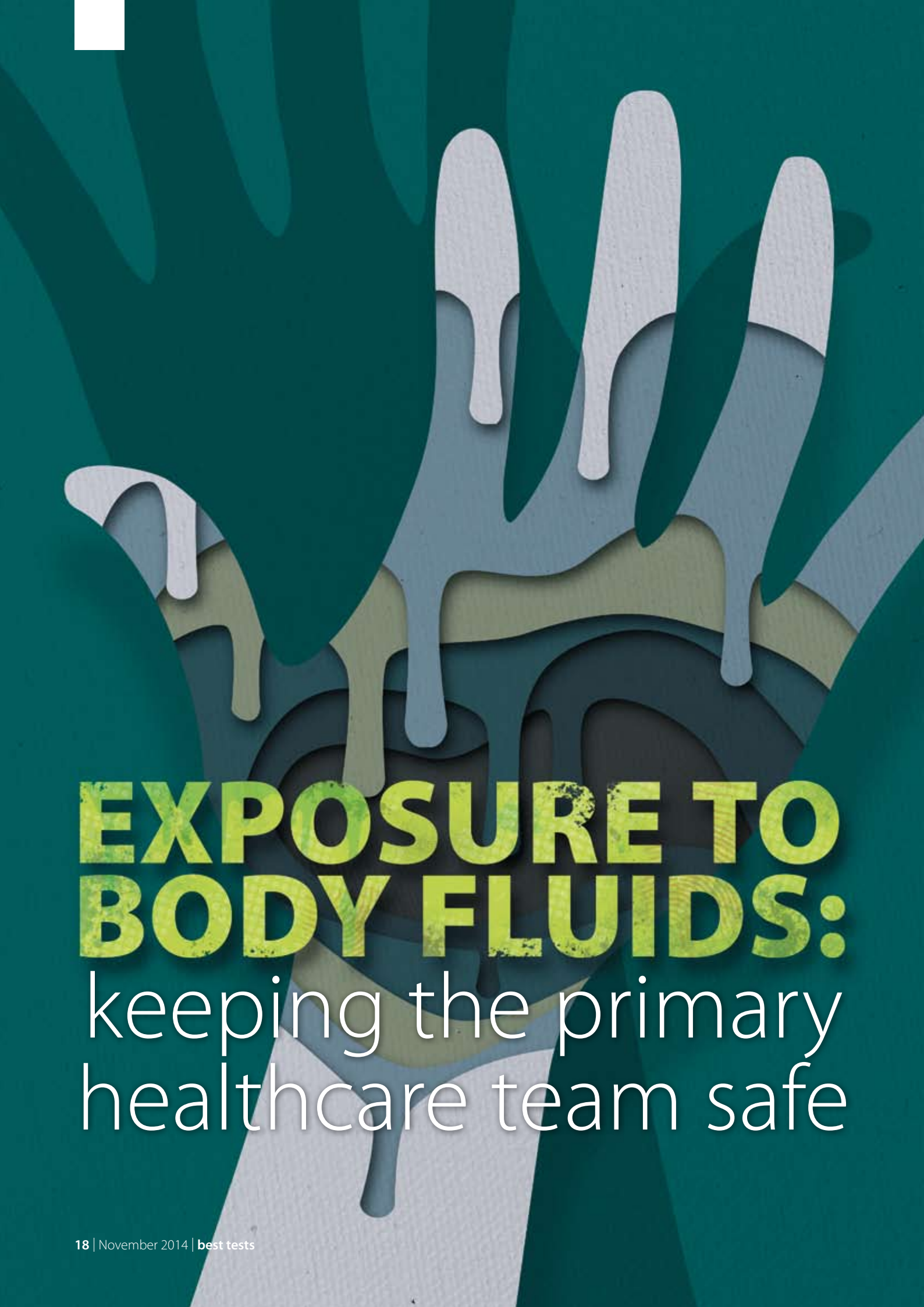
The majority of people who purchase direct-to-consumer genetic tests do not have a known family history of a specific disease; the test is purchased out of simple curiosity. Results from tests requested for these purposes are unlikely to be clinically useful as there are many factors affecting phenotypes 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.[4] 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.[4]

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.



EXPOSURE TO BODY FLUIDS: keeping the primary healthcare team safe

Providing a safe working environment involves both minimising the risk of transmission of infectious pathogens and dealing with exposures after they have occurred. Exposure to body fluids is one of the major occupational hazards faced by healthcare workers. Effective use of standard precautions, including hand hygiene and personal protective equipment, is the best way to protect healthcare workers from these infectious pathogens. However, even strict adherence to standard precautions will only minimise the infection risk and dealing effectively with any potential exposures, e.g. needlestick injuries, if they occur is vital in protecting healthcare workers.

Prevention is better than cure: keeping the practice environment safe

Healthcare workers are likely to be exposed to a number of potentially infectious body fluids on a daily basis. All body fluids should be assumed to contain transmissible infectious pathogens. Reducing transmission of these pathogens, and dealing with exposures if they occur, is vital in protecting healthcare workers and complying with the Health and Safety in Employment Act 1992. A practice-wide staff health policy should be in place to achieve the safest working environment possible. This should include maintaining appropriate levels of vaccination, training and education in infection control and prevention procedures for all clinical and non-clinical workers. The most important principles for achieving a safe working environment are based on standard precautions, which are regarded as the minimum requirements for infection control and prevention. A number of easy-to-implement procedures can substantially reduce the rates of infectious disease transmission in general practice; promotion of effective hand hygiene is a good starting point.

Good hand hygiene procedures are the first step in preventing transmission

Hand hygiene is regarded as the single most important activity for preventing the spread of infection in the healthcare setting.[2] The Hand Hygiene New Zealand (HHNZ) programme, which is run by the Health Quality and Safety Commission of New Zealand, recommends following the World Health Organisation's "Five moments for hand hygiene".[2] These recommendations, although intended for people working in a hospital setting, provide a useful guide for when hand hygiene should be considered in the general practice setting.

Standard precautions – the backbone of good infection control and prevention

Standard precautions are a set of procedures which can be followed to achieve a minimum level of infection control and prevention. They help prevent the risk of transmission of infectious pathogens and protect both healthcare workers and patients.

Some of the basic standard precautions include:[1]

- Hand hygiene
- Use of personal protective equipment
- Promotion of respiratory hygiene and cough etiquette
- Use of aseptic technique
- Appropriate sharps/waste management
- General cleaning of the practice environment
- Dealing with spills
- Appropriate reprocessing of reusable medical equipment

The five moments for hand hygiene are:[3]

- Before patient contact
- Before performing a procedure
- After a performing a procedure or a potential exposure to body fluids
- After patient contact
- After contact with patient surroundings. In a primary care setting this may be relevant when clinicians see patients in rest homes or perform home visits.

Alcohol-based hand rubs are recommended when hands are not visibly soiled

Alcohol-based hand rubs should almost always be preferred over hand washing with soap and water for hand hygiene in general practice, except when the hands are visibly soiled.[2] This is because alcohol-based hand rubs:[2]

- Have been shown to be more effective than soap and water against the majority of pathogens encountered in a healthcare setting (with the exception of *Clostridium difficile*). In a randomised study it was found that reductions in bacterial contamination were significantly higher after using an alcohol-based hand rub (83%) than after washing hands with an antibacterial soap containing chlorhexidine gluconate (58%).[4]
- Cause less irritation to the skin as they contain moisturising agents, are less associated with contact dermatitis and are less drying on the hands than soap and water.[3]
- Can be quickly and conveniently used at the point of care, e.g. placed on the clinician's desk, and carried on home visits.

It is recommended that hands are rubbed with the alcohol solution for 20 – 30 seconds.[5] HHNZ recommends using products that have ethanol concentrations of at least 70% or isopropyl alcohol concentrations of at least 60%.[3] Some alcohol-based hand rub preparations also include chlorhexidine to provide a more prolonged antibacterial effect after the alcohol dries; however, in primary care, the plain alcohol preparations are preferable as they result in less skin irritation. Alcohol remains the essential component of these formulations as it has the more potent antibacterial activity.[3]

Soap and water should be used when hands are visibly soiled

Hand washing with soap and water should be performed when hands are visibly soiled with blood or other body fluids, or after using the toilet.[6] The duration of the entire hand washing procedure should be 40 – 60 seconds.[7] For optimal effect it is important to ensure that hands are completely dry after hand washing. Hand washing with soap and water is also recommended following known or suspected exposure to *C. difficile* infection (or as a standard precaution after contact with a patient with diarrhoea or vomiting), as it has been shown to be more effective in removing *C. difficile* spores than alcohol-based hand rubs.[8, 9] Plain or antimicrobial soaps, e.g. containing chlorhexidine or triclosan, can be used for routine hand washing; antimicrobial soaps are not necessary for everyday use.[10]

A poster on hand washing for the clinic is available from:
www.handhygiene.org.nz/images/stories/HHNZDOWNLOADS/promotionalMaterialsNEW/pdfs/How%20to%20handwash%20poster.pdf

Personal protective equipment should be used according to risk

The decision to use personal protective equipment, such as gloves, gowns, protective glasses and masks, should be based on a risk assessment of the probability of transmission of infectious pathogens. There are certain circumstances when additional precautions may be necessary (see: "What to do during a highly infectious pandemic", Page 23).

Gloves are not a substitute for hand hygiene

Pathogens can gain access to the hands via small defects in gloves or by contamination when removing gloves.[2] In general, gloves should be used when there is a risk of exposure to the patient's blood or body fluids or when there is contact with non-intact skin or mucous membranes. It is recommended that hand hygiene is performed before and after using gloves.[2] Gloves should ideally be put on last and removed first when used in combination with other protective equipment. Used gloves should be discarded in a yellow biohazard bag and not in a general purpose rubbish bin.

It is particularly important for clinical staff to wear gloves if they have broken skin on their hands and direct physical contact with a patient is likely.

N.B. Latex allergy can pose a problem for both clinicians and patients. An allergy to latex should be documented in the patient's notes and alternative latex-free gloves available for use.

Masks may sometimes be required

Although masks are not routinely used in general practice, there are a number of circumstances when it is important to consider their use to protect both practice staff and patients from airborne pathogens (see: "What to do during a highly infectious pandemic", Page 23). An example is when a patient presents with respiratory symptoms, e.g. coughing and sneezing, and there is an increased likelihood of airborne/droplet transmission. This is particularly important during outbreaks of respiratory-transmitted infections, e.g. measles and influenza. If this situation occurs, it may be appropriate to ask the patient to wear a mask and have them wait in a vacant area of the practice rather than in the waiting room. Reception staff should be aware of these procedures as they usually have first contact with the patient. Where possible, the patient should be asked to maintain at least a one metre gap between other patients and healthcare workers, although this is not always practical.[10]

Body fluid spills need to be dealt with quickly and effectively

When spills occur, all blood or body fluids (with the exception of sweat) need to be treated as potentially infectious and promptly dealt with by staff members wearing personal protective equipment appropriate to the situation, e.g. gloves, disposable aprons and masks. The exact management of the spill will depend on the type and volume of the body fluid spilt, the possible pathogens present and the type of surface or area where the spill has occurred, e.g. all blood spills on hard/vinyl surfaces should be disinfected using a diluted sodium hypochlorite solution. Ideally, practices will have fully-equipped spill kits available, i.e. containing protective equipment, waste bags and detergents, and have procedures in place to manage spills appropriately. In some circumstances, e.g. large spills or spills on carpeted areas, it may be necessary to use a commercial cleaning company. Ensure that the area containing the spill is isolated.

An example of specific procedures for dealing with body fluid spillages is available from: **www.cdhb.health.nz/Hospitals-Services/Health-Professionals/CDHB-Policies/Documents/4810-Volume-10-Decontamination-of-the-Environment.pdf**

Safely dispose of medical waste and sharps

Collection and disposal of all medical waste should follow the New Zealand Standards for Management of Healthcare Waste (NZS 4304: 2002). All sharps including needles, scalpel blades, glass ampoules or any other objects with sharp points capable of causing penetrating injuries should be placed in a yellow sharps bin which is periodically collected and disposed of by an authorised medical waste service.[1] The bin should not be overfilled, as this increases the risk of an injury when disposing of a sharp. Ensuring that sharps are handled in a safe manner can also reduce the risk of injuries occurring, e.g. not recapping needles and not passing sharps from person to person.

Other hazardous clinical medical waste should be placed in yellow biohazard bags for disposal, including waste that contains blood or pus present in a large enough volume to be squeezed from absorbent material, and tissue not being sent for histology.[10] Disposable equipment that has been used to examine a patient, e.g. spatulas and ear covers for otoscopes, should also be disposed of in yellow biohazard bags. Hair and nail clippings that are not contaminated can be placed in general purpose rubbish bags. Urine and faeces can be tipped down the toilet.

Keep the practice environment as hygienic as possible

All environmental surfaces in the practice need to be included in a regular cleaning schedule – surfaces that are used frequently and are likely to be contaminated need to be cleaned more often, e.g. door handles, reception counters and consultation desks. Linen also needs to be changed and washed on a regular basis, especially when it becomes visibly soiled or after contact with a patient with an infectious disease.

It is important to consider that some pathogens can remain viable on fomites (any inanimate object or substance capable of carrying infectious organisms) for prolonged periods. For example, the hepatitis B virus is comparatively stable in the environment and can remain viable on surfaces for several days.[11] A 2014 study that investigated the duration of hepatitis C viability on fomites reported that the virus remains viable for up to six weeks at room temperature, which is much longer than previously thought.[12]

Give disinfectants time to work

Disinfectants, e.g. hypochlorite and quaternary ammonium compounds, are antimicrobial agents that reduce the levels of infective pathogens on surfaces, although they do not necessarily kill all pathogens and have been shown to fail where prior cleaning has been non-existent or ineffective.[10] Disinfectants need to be accurately diluted and usually require a contact time of five to 15 minutes to kill micro-organisms.[13] When surfaces are wiped with disinfectants and dried immediately, the disinfectant does not have time to act and is simply being used as a cleaning agent.[13]

It is recommended that frequently touched surfaces are disinfected at least daily as well as when visibly soiled or after likely pathogen contamination.[10] It is unrealistic to clean some frequently touched items after each use, e.g. pens, phones, computer keyboards and mouse. However, these items can be sources of indirect contact transmission and should be cleaned with alcohol wipes (or discarded where applicable) in situations where the risk of infection is increased, e.g. after contact with a patient who may have a highly infectious or significant infection such as influenza or methicillin-resistant *Staphylococcus aureus* (MRSA).

Alcohol-based wipes are recommended to clean stethoscopes and should ideally be used after the stethoscope has been in direct contact with a patient.[14] Bacterial contamination on stethoscopes has been shown to be substantial following a single physical examination, with rates comparable with those observed on the clinician's dominant non-gloved hand after patient contact.[14] Products containing chlorhexidine, phenol, hypochlorite or quaternary ammonium compounds should not be used to clean medical devices as they can cause surface oxidation and denaturing of rubber seals.[15]

Ensure healthcare workers are up to date with vaccinations

Maintaining a high rate of immunity within general practice staff helps to reduce personal disease risk for healthcare workers and has the flow on effect of reducing transmission to patients, especially those at increased risk of developing complications following infections. The National Immunisation Advisory Centre has released a set of guidelines on vaccinations for clinical, non-clinical and cleaning staff in primary care, including hepatitis A and B, influenza, measles mumps and rubella (MMR), tetanus/diphtheria/pertussis and varicella, as well as advice on poliomyelitis and tuberculosis.[19] These guidelines provide important recommendations about the vaccinations required for primary healthcare workers depending on their role and therefore risk of infection.

For additional information see:
www.immune.org.nz/sites/default/files/resources/NonprogrammeOccupationalPhc20121009V01Final.pdf

Toys in waiting rooms: teddy may have to go

Children toys, particularly "soft" toys, pose an infection risk for staff and patients as they can carry high levels of bacterial contamination. A New Zealand study that investigated bacterial contamination of children's toys in the waiting room of six general practices found that "hard" toys had lower levels of bacterial contamination, did not re-contaminate as quickly and were easier to clean than soft toys.[16] The study reported that hard toys had lower rates of coliform contamination than soft toys (14% vs. 90%), and there were less instances of moderate-to-high bacterial contamination in hard toys compared to soft toys (27% vs. 90%).[16]

In the study it was found that hard toys were effectively cleaned after soaking in a hypochlorite solution (2.5 g/L) for one hour.[16] To effectively reduce bacterial counts and eliminate coliforms in the soft toys, they required a 30-minute soak in a hypochlorite solution followed by machine washing and drying.[16] Frequent washing of toys is recommended as bacterial counts have been shown to return to pre-wash levels within a week for both soft and hard toys – with soft toys undergoing more rapid re-colonisation.[16] Consideration should be given to removing all toys during an infectious disease outbreak.[10]

There appears to be no evidence that freezing soft toys reduces bacterial contamination, although this practice has been shown to reduce house dust mite concentrations.[17]

N.B. The covers of magazines from general practice waiting rooms have been shown to have low rates of bacterial contamination.[18]

What to do during a highly infectious pandemic

Pandemics occur when an infectious disease outbreak spreads throughout populations across a large region, e.g. multiple continents or worldwide. There have been a number of notable examples over the past few years including the H1N1 influenza (swine flu) pandemic in 2009 and the severe acute respiratory distress (SARS) pandemic in 2002 – 2003. Although the current outbreak of Ebola virus has not reached New Zealand, the Ministry of Health is releasing frequent updates with advice on infection control and prevention measures.

For further information on Ebola virus see: **www.health.govt.nz/our-work/diseases-and-conditions/ebola-update/ebola-information-health-professionals**

During pandemics, it is important that primary healthcare workers are aware of strategies that can prevent the pandemic spreading. These strategies will depend on the nature of the pandemic illness, and can include:[20]

- Using and promoting hand hygiene, cough and sneeze etiquette (e.g. covering nose and mouth when sneezing and using tissues) and distancing (one metre gaps where possible)
- Asking patients if they have any infectious symptoms when they phone the practice for an appointment and discouraging all non-urgent visits. If patients do have symptoms, they can be asked to wear a mask when entering the practice (a box of masks can be placed at the practice entrance). Masks should be replaced when they become damp.
- Having educational material about the pandemic on the entrance doorway of the practice and on the walls of the waiting room
- Having alcohol-based hand rubs available in the waiting room and on the reception counter
- Encouraging all practice staff to wear masks. Whether masks need to be worn at all times, or just when treating patients, will depend on the pandemic illness and the discretion of the healthcare worker.
- Wearing gloves at all times when dealing with patients
- Ensuring the practice has adequate ventilation as some pathogens, e.g. influenza, spread more rapidly in confined environments
- Having a separate triage area set up for patients with symptoms of the pandemic illness
- Treating all waste that has been in contact with a patient as potentially infectious
- Using additional protective equipment if necessary, e.g. it may be necessary to use full protective equipment, i.e. goggles, gowns, face shields, N95 respirators, if dealing with patients with suspected highly infectious, deadly diseases, e.g. SARS
- Nominating a staff member to keep up to date with what is happening with the pandemic both globally and nationally

How to minimise risk after exposure – keeping healthcare workers safe

Despite following recommended precautions and prevention strategies, personal exposures to body fluids do sometimes occur. A number of different body fluids can be involved, e.g. blood, respiratory secretions and faecal matter. Blood-borne pathogens are present in larger quantities in blood than in other fluids and therefore exposure to blood is associated with the most significant risk of transmission.[21] Needlestick injuries are generally regarded as posing the greatest risk of transmission of blood-borne pathogens, particularly after a skin penetration injury with a sharp hollow-bore needle that has recently been removed from an infected patient. Needlestick injuries are, however, relatively rare in general practice and a number of other exposures to body fluids, e.g. via mucosal surfaces or respiratory droplets, are more likely to be encountered on a day-to-day basis.

Different body fluids are associated with different pathogens

The risk of infection for the healthcare worker exposed to body fluids depends on the type of exposure, the body fluid involved and the infectious pathogen. In addition to blood, body fluids such as respiratory secretions, faecal matter and contact with a patient's contaminated skin or mucous membranes, potentially pose an infection risk. For example, influenza, conjunctivitis and *Campylobacter* can be transmitted via these methods. Although all body fluids should be considered potentially infectious, certain fluids are generally associated with lower risks of transmission, e.g. urine and vomitus.

An example of management strategies for workers after potential body fluid exposure is available from: **www.cdhb.health.nz/Hospitals-Services/Health-Professionals/CDHB-Policies/Infection-Prevention-Control-Manual/Documents/4816%20Volume%2010%20-%20Staff%20Health%20and%20management%20of%20work-related%20infection%20risks.pdf**

Appropriate first aid can reduce the risk of transmission

First aid should be given immediately after the exposure occurs and the spill cleaned up appropriately (Page 21). In general, more extensive first aid is required when needlestick or mucosal exposures to blood have occurred. Other exposures can usually be handled with a common sense approach, including thorough washing of the exposed area and removal of any soiled clothing.

Needlestick injuries: Immediately rinse the affected area of skin with warm running water and soap for at least three minutes.[22] There is no evidence that encouraging the wound to bleed or applying an antiseptic to the wound reduces the rate of infection, but these actions are not contraindicated.[23] Caustic agents, such as hypochlorite, should not be used as they can compromise skin integrity.[10] Injuries should be covered with an appropriate dressing. The tetanus status of the exposed individual should also be checked and a tetanus booster administered if required.

Mucous membrane exposures: Any mucous membranes, e.g. the eyes, that are exposed to body fluids should be rinsed out with a large amount of water or saline for at least three minutes.[22]

Testing for HIV, hepatitis B and hepatitis C is recommended after needlestick injuries or mucosal exposure to blood

Although there are many infections which can be transmitted through body fluids the most consequential are generally considered to be HIV, hepatitis B and hepatitis C. The likelihood of transmission of these viruses after exposure to different body fluids varies and an understanding of the risks is pivotal when performing a risk assessment (Table 1). In general, testing for HIV, hepatitis B and hepatitis C should only be considered after needlestick injuries, or after mucosal or broken skin exposure. If it is decided that testing should be undertaken, blood tests for HIV, hepatitis B, hepatitis C for both the source individual and the exposed healthcare worker need to be **conducted within 24 hours and marked as urgent**. If consent is refused by either the exposed person or the source, document this, and the reasons for refusal.

Source individual: When known, the source individual should be asked for consent to test their blood for:[24]

1. HIV antibody
2. Hepatitis B surface antigen
3. Hepatitis C antibody

Exposed individual: Blood from the exposed person should be tested for:[24]

1. HIV antibody
2. Hepatitis B surface antigen
3. Hepatitis B surface antibody
4. Hepatitis C antibody

The exposed person should be reassured that the risk of infection after accidental exposures is low and advice and education should be provided that highlights the importance of:[24]

- Having blood tests as soon as possible after exposure with follow-up testing at the appropriate times (Tables 2, 3 and 4)
- Not donating blood, avoiding pregnancy and practising safe sex until all final follow-up tests have been completed and results are available
- Reporting any glandular fever-like illness for the six months after exposure

Hepatitis B testing and prophylaxis

There are a number of serological markers used to test and monitor patients for hepatitis B. The following definitions are intended to assist clinicians in understanding what these markers mean clinically to help when analysing test results (Table 2):[29]

- HBsAg – persistent or acute infection
- Anti-HBs – immunity due to vaccination or past infection
- HBeAg – highly infectious disease
- HBV DNA – circulating virus
- Anti-HBc IgM – recent infection
- Anti-HBc IgG – past/current infection

Hepatitis C testing

Management of potential hepatitis C exposures (Table 3) can be problematic as there is no known effective prophylaxis and a high proportion of people (approximately 75%) are unaware they have the disease.[27]

Most cases of hepatitis C in New Zealand are in people with a history of illicit IV substance use or a history of sexual contact with people with confirmed hepatitis C.[29] The prevalence rates of hepatitis C in illicit IV substance users in New Zealand have been reported to be as high as 70%.[29] There is also an increased risk of infection in people who underwent a blood transfusion prior to 1992, as this was when blood was first screened for hepatitis C.[30]

Table 1: Transmission risks and incidences of HIV, hepatitis B and hepatitis C in New Zealand.[21, 24 – 27]

	HIV	Hepatitis B	Hepatitis C
The number of people living with the disease in New Zealand	2000	90 000	50 000
The risk of transmission following exposure to a single needlestick or cut injury	0.3%	6 – 30%	1.8%
Fluids and tissues capable of transmitting blood borne infections			
Blood and fluids visibly contaminated with blood	Yes	Yes	Yes
Faeces, nasal secretions, sputum, sweat, tears, urine or vomit	No	No	No

N.B. Breast milk, inflammatory exudates, semen and vaginal fluids, pleural, amniotic, pericardial, peritoneal, synovial, and cerebrospinal fluids are all potentially capable of transmitting HIV, hepatitis B and hepatitis C but are less likely to be encountered in a primary care setting.

Table 2: Testing and prophylaxis for hepatitis B[24]

Exposed individual		Source individual		Action for exposed individual
HBsAg	Anti-HBs	HBsAg	Anti-HBs	
–	–	–	–	Consider hepatitis B vaccination for future protection (vaccination not needed for this exposure)
–	–	–	+	
–	+	–	–	No action required as exposed person is immune
–	+	–	+	
–	+	+	–	
–	+	**unknown**	**unknown**	
–	**past + now –**	–	+/-	Booster dose of hepatitis B vaccine recommended
–	**past + now –**	+	–	
–	–	+	–	Recommend HBIG* 400 IU IM and hepatitis B vaccination schedule. Known non-responders to hepatitis B vaccination should have two doses of HBIG. **Request HBsAg and HBsAb testing at 3, 6, and 12 months**
–	–	**unknown**	**unknown**	Consider HBIG 400 IU IM and hepatitis B vaccination schedule. **Request HBsAg and HBsAb testing at 3, 6, and 12 months**

* HBIG = hepatitis B immune globulin; obtain from the New Zealand Blood Transfusion Service.

Table 3: Testing for hepatitis C antibody[24]

Exposed individual	Source individual	Action for exposed individual
Negative or unknown	Negative or unknown	No action is usually required, but testing can be performed at 3, 6 and 12 months if there is concern the source may be incubating hepatitis C
	Positive	1. Consider hepatitis C polymerase chain reaction (PCR) testing of the source, which will also determine how infectious they are 2. If the source individual's PCR test is positive, test the exposed individual (PCR) at 1 month 3. Test all exposed individuals (PCR) at 3, 6 and 12 months. 4. Test the exposed individual if they are exhibiting signs and/or symptoms of hepatitis C 5. No prophylaxis is available. If acute infection occurs the patient should be referred for initiation of antiviral treatment

HIV testing and prophylaxis

The risk of contracting HIV after exposure to HIV-infected blood is relatively low even for needlestick injuries (Table 1). Mucous membrane exposure, e.g. eye, nose or mouth, to HIV-infected blood carries an even lower risk of infection – reported to be approximately 0.1%.[21] The transmission risk after skin exposure is lower again. A small amount of blood on intact skin is not likely to pose a risk, as no documented cases of HIV transmission have been reported after exposure to a small amount of blood on intact skin for a short period of time.[21]

Post-exposure prophylaxis is recommended if the source individual is known to be HIV positive (Table 4).

N.B. The rates of HIV infection in people who use illicit substances intravenously in New Zealand are very low and post-exposure prophylaxis is not routinely recommended after exposure to body fluids from these people, unless they are known to be HIV positive.[11, 25]

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Table 4: Testing for HIV antibodies and prophylaxis[24]

Exposed individual	Source individual	Action for exposed individual
Negative or unknown	Negative or unknown	No action is usually required, but testing can be performed at 3, 6 and 12 months if there is concern the source individual may be incubating HIV, e.g. if the source patient has undergone recent testing but it is too early to tell whether they have contracted the disease
	Positive	1. It is recommended that, when appropriate, **post-exposure prophylaxis** is initiated within one to two hours of exposure. A clinical microbiologist or infectious diseases specialist should be contacted immediately to determine whether prophylaxis is required. 2. Repeat serology testing at 3, 6 and 12 months

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