

BNP | Haemochromatosis | Vitamin D

Testing in Primary care

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BNP testing in primary care

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Vitamin D testing in primary care

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All information is intended for use by competent health care professionals and should be utilised in conjunction with pertinent clinical data.

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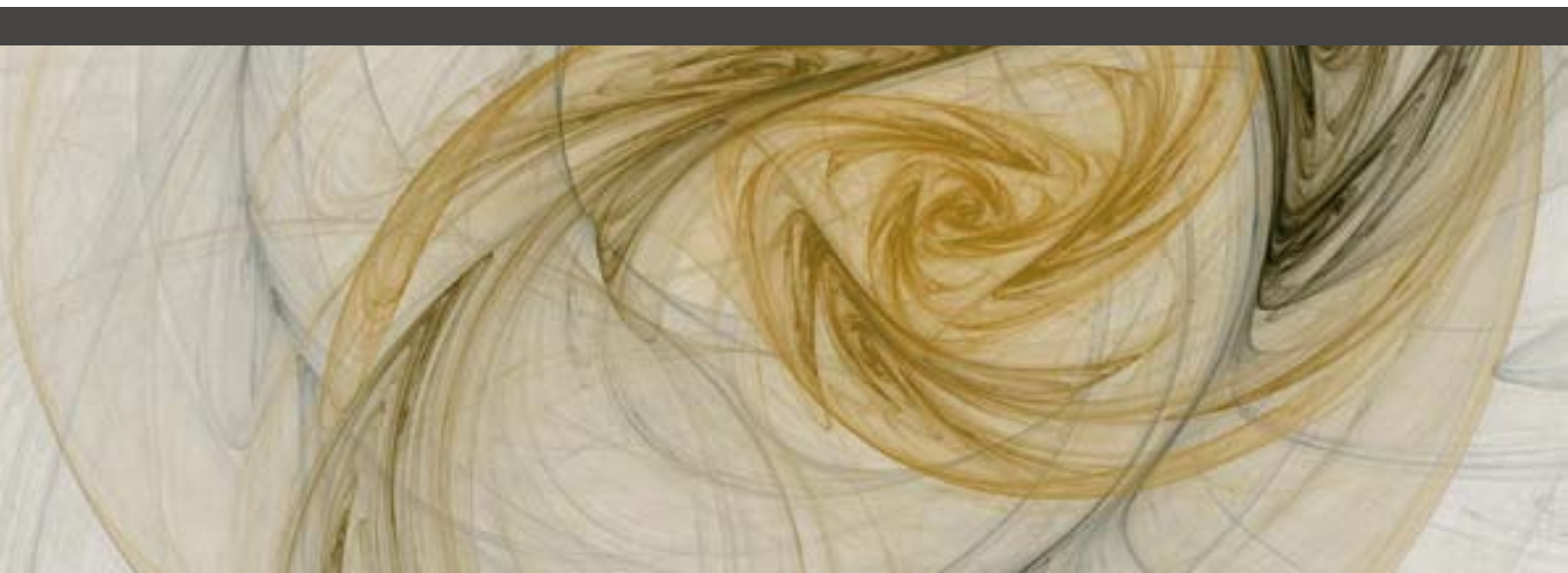
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BNP testing in primary care

Our key recommendations are:

1. BNP is useful as a 'rule-out' test of heart failure when a patient presents with acute dyspnoea and the diagnosis is not clear
2. The use of BNP testing in the diagnosis and management of heart failure in primary care is promising although not yet established

Introduction - Assays of B-type natriuretic peptides

B-type natriuretic peptide (BNP) assays have become important aids in the diagnosis and perhaps more importantly, the exclusion of heart failure. Normal levels virtually exclude the diagnosis of heart failure and very high levels effectively confirm the diagnosis; intermediate levels require confirmation by echocardiography.

These peptides are released into the circulation by distended ventricular walls as the active peptide, BNP, and the inactive peptide, NT-proBNP. Assays may be performed on either but there are no conversion factors for comparison between these measures. Furthermore, there is variability in the type of assay used and availability of testing across the country.

Underlying pathophysiology

BNP is synthesised and stored in ventricular myocytes and secreted in response to ventricular distension, Figure 1. It is cleaved into equimolar proportions of biologically active BNP and inactive NT-proBNP. BNP has a half-life of 20 minutes before it is inactivated whereas NT-proBNP has a half-life of 120 minutes and is excreted by the kidneys.

BNP is involved in the regulation of salt and water excretion and the maintenance of blood pressure. It inhibits the Renin-Angiotensin-Aldosterone System (RAAS) and the Sympathetic Nervous System (SNS).

Estimation of both BNP and NT-proBNP can be used in the assessment of heart failure but values obtained with different assays are not comparable. The gender and age of the individual being tested also effects plasma levels.

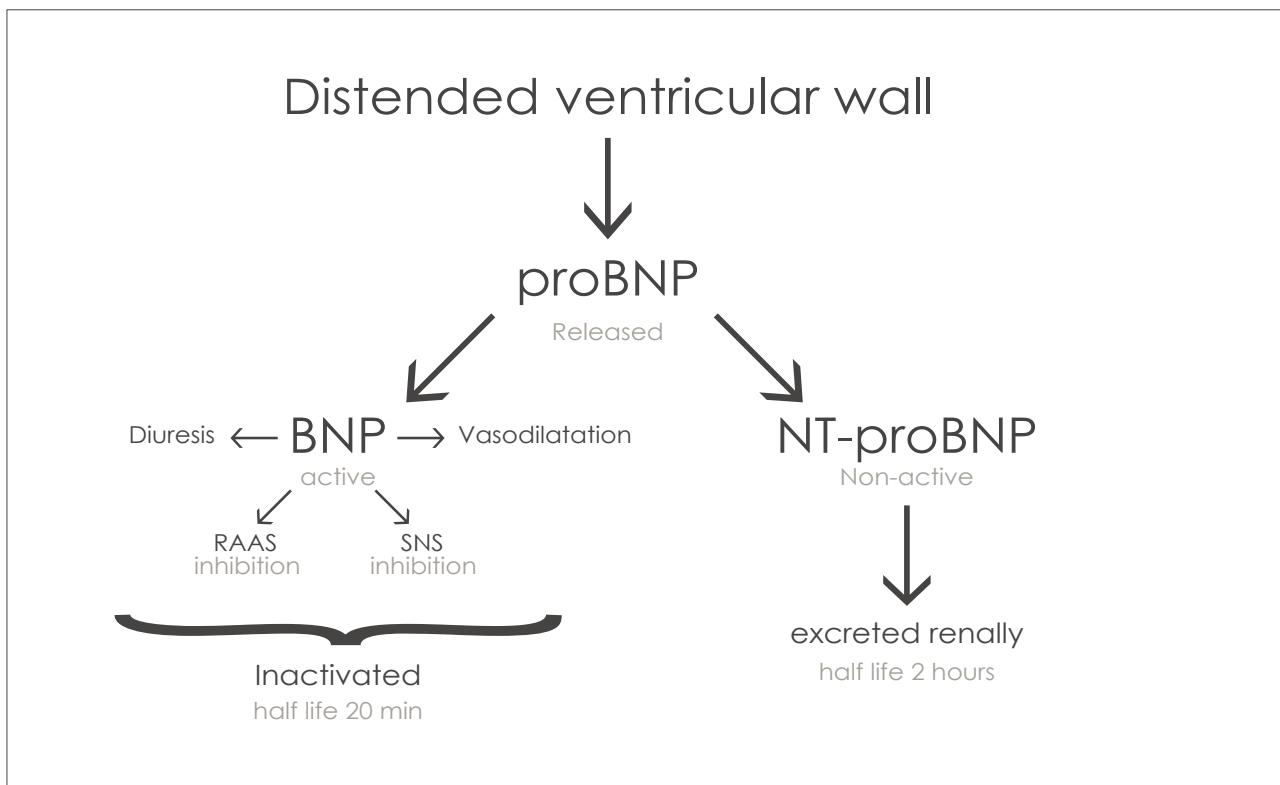
As a result of these variations, cut-off values for results should ideally be agreed locally depending on the type of assay being used and the characteristics of the population being tested.

Results should include a low cut-off value below which heart failure is unlikely and a high cut-off value above which heart failure is likely. The high cut-off should preferably have age dependent values.

BNP is a non-specific biomarker. As well as being raised in heart failure, it may also be raised in atrial fibrillation, left ventricular hypertrophy, acute coronary syndromes, acute pulmonary embolus, cor pulmonale, and renal failure. A useful future role may develop for BNP in the diagnosis and prediction of outcomes from these conditions.

BNP levels may be decreased by hypothyroidism, treatment with diuretics, vasodilators or ACE inhibitors. A raised BNP does not exclude other chest/heart problems in addition to heart failure, for example a patient may have heart failure and pneumonia.

Figure 1: Release of BNP



BNP* is useful as a 'rule-out' test of heart failure when a patient presents with acute dyspnoea and the diagnosis is not clear

When a patient has acute dyspnoea, elevated BNP levels have good sensitivity for heart failure; in trials, approximately 90-95% of people with acute dyspnoea caused by heart failure had an elevated BNP. However, because there are other causes of elevated BNP, such as acute pulmonary embolus or cor pulmonale, only about 70-80% of people with acute dyspnoea, with an elevated BNP, have heart failure. Therefore, the demonstrated strength of BNP is its ability to rule-out heart failure as the cause of a patient's dyspnoea¹, see Figure 2.

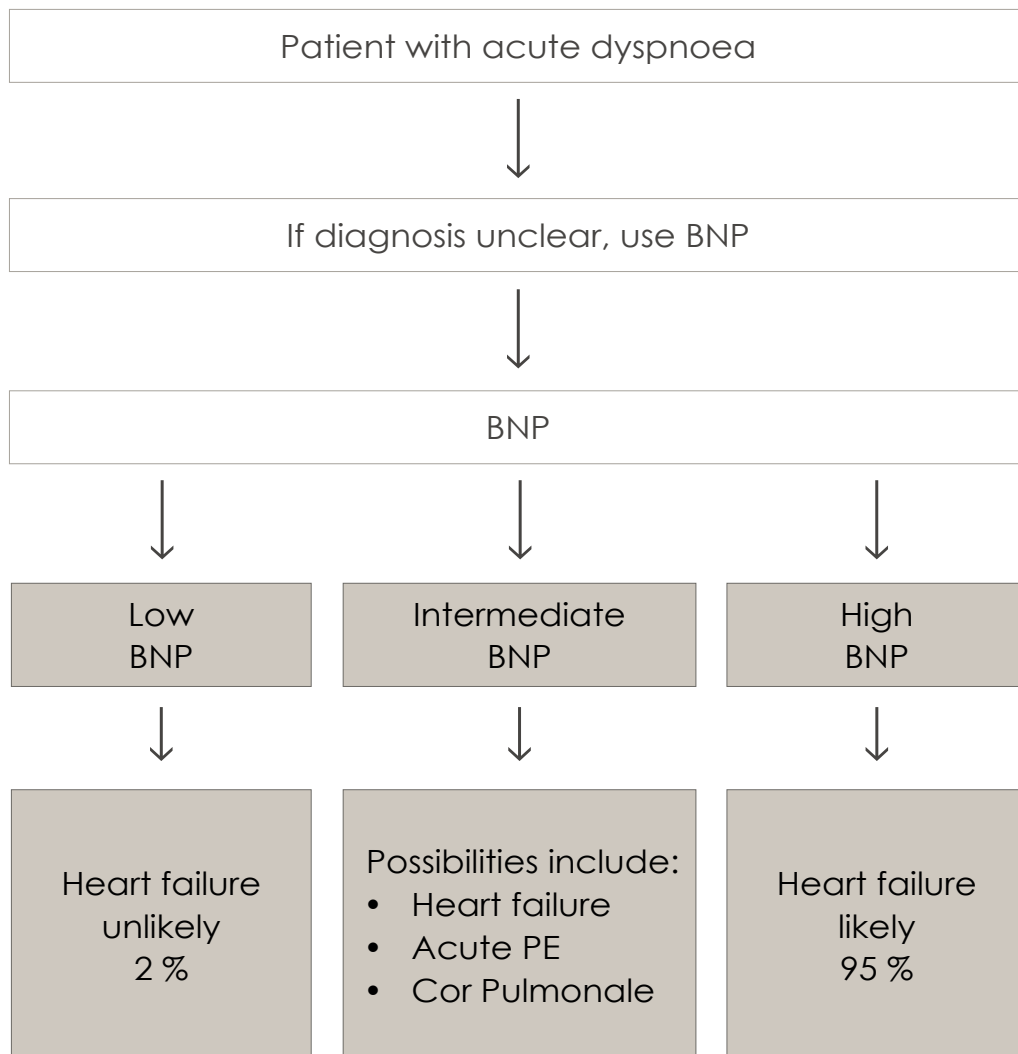
People with very high BNP levels on presentation for urgent care with dyspnoea appear to be highly likely to have heart failure rather than pulmonary causes of dyspnoea, severe rather than mild heart failure, and cardiac rather than other causes for dependent oedema².

Of course BNP can only guide the immediate management of acute dyspnoea when there is rapid turnaround of results.

**We have used BNP to refer to both the active peptide and the inactive NT-proBNP as either of these assays can be used in the diagnosis of heart failure. However there are important differences and in some publications BNP is used to refer to the B-type natriuretic peptides in general and in others specifically to the active peptide.*

Figure 2: Interpretation of BNP results in acute dyspnoea

It is important the result is interpreted using the ranges provided by the testing laboratory. Laboratory ranges for low, intermediate and high results vary between laboratories and the particular assay used.



The use of BNP testing in the diagnosis and management of heart failure in primary care is promising although not yet established

Untreated heart failure has a worse prognosis than most cancers. Early diagnosis is likely to lead to appropriate treatment and improved prognosis. However, diagnosis is difficult in primary care. People presenting to primary care with symptoms suggestive of heart failure have different characteristics to people presenting to emergency departments with dyspnoea. They are less likely to have heart failure and those that do often have earlier and less severe disease.

Clinical findings in heart failure are neither sensitive nor specific and GPs in New Zealand, like GPs in many other countries, do not have direct access to echocardiography. The place of BNP testing as an additional diagnostic tool in this setting has been suggested but as yet the best test or combination of tests for the diagnosis of mild heart failure in primary care is not known. A summary of the European Society of Cardiologists recommendations for the diagnosis of chronic heart failure³ is included on page 6.

a. BNP and ECG are equally effective for initial diagnostic work up of suspected chronic heart failure

People with heart failure frequently have abnormal ECGs, which may show ischaemic changes, left ventricular hypertrophy or arrhythmias. A systematic review⁴ found that BNP and ECG have similar sensitivity and only small differences in specificity in the diagnosis of chronic heart failure. One study reviewed, assessed people who presented to UK general practices with new symptoms, which the GPs suspected were due to heart failure⁵. The findings are presented in Table 1.

chronic heart failure and that there is no evidence to justify combined use of both these tests. The choice is made by issues such as relative cost and availability.

The value of ECG is in identifying people who need further cardiac investigations. It can not be used to diagnose heart failure.

In addition, the authors of the systematic review concluded that combining BNP and ECG does not improve sensitivity above performing either of these tests alone. They recommend that, on current evidence, either BNP or ECG be used as part of the diagnostic work up of individuals with suspected

Table 1: Sensitivity and specificity in people presenting to primary care with symptoms suggestive of heart failure.

Test Criteria	Sensitivity	Specificity
BNP > 100 pg/ml	79 %	72 %
Abnormal ECG	81 %	60 %



b. The role of BNP in identifying patients with asymptomatic ventricular dysfunction not yet determined

Studies of the role of BNP in the identification of people with asymptomatic ventricular dysfunction show a high degree of heterogeneity with sensitivities ranging between 28% and 92% and specificities between 44% and 97%. As a result its role in the screening of asymptomatic patients for left ventricular dysfunction cannot currently be recommended. It seems likely that BNP will find a place in the screening of well-defined high-risk groups where the pre-test probability is high.

c. No clear role yet for BNP in diagnosing heart failure in those already on therapy

Because the clinical diagnosis of heart failure is difficult, it has been suggested that approximately one third of people currently on treatment for heart failure do not have it. Unfortunately BNP is not currently useful in identifying these people. Low levels may mean the patient does not have heart failure but could also be the result of effective treatment or the direct influence of drugs, including hypotensive agents and frusemide, on BNP levels. It is not appropriate to use BNP for this indication until trials have established its utility.

d. Evidence for the use of BNP levels to guide therapy in primary care still inconclusive

The evidence for the use of BNP to monitor progress and guide therapy in people with heart failure managed in primary care is still not conclusive but some trials have produced encouraging results. Raised BNP levels are highly predictive of unfavourable outcomes and early indications are that they may be useful in guiding treatment. However, the results of large prospective trials are awaited before definite conclusions can be reached⁶.

Review of methods for the diagnosis of heart failure in primary care³

Symptoms and signs

- Important as they alert clinician to the possibility of heart failure.
- Poor relationship between symptoms and severity of cardiac dysfunction.
- Symptoms useful for monitoring effects of therapy.

Electrocardiogram

- If the ECG is completely normal, heart failure, especially due to LV systolic dysfunction, is unlikely.

Chest X-ray

- CXR is useful to detect cardiomegaly and pulmonary congestion; however, it only has predictive value in the context of typical signs and symptoms and in abnormal ECG.

Haematology and biochemistry

- Routine diagnostic evaluation includes: complete blood count, electrolytes, creatinine, glucose, liver enzymes, and urinalysis.
- Tests of thyroid function may be indicated.
- In acute exacerbations, acute myocardial infarction is excluded by troponin analysis.

Natriuretic peptides

- Plasma concentrations of BNP and NT-proBNP are helpful in the diagnosis of heart failure.
- A low-normal concentration in an untreated patient makes heart failure unlikely as the cause of symptoms.
- In clinical practice today, the place of BNP and NT-proBNP is as 'rule out' tests to exclude significant cardiac disease, particularly in primary care but also in certain aspects of secondary care (e.g. the emergency room and clinics.) A normal result should obviate the need for further cardiological tests such as echocardiography.
- BNP and NT-proBNP have considerable prognostic potential, although evaluation of their role in treatment monitoring remains to be determined.
- The diagnostic potential of natriuretic peptides is less clear cut when systolic function is normal.
- Other common cardiac abnormalities that may cause elevated natriuretic peptide levels include left ventricular hypertrophy, valvular heart disease, acute or chronic ischaemia or hypertension, and pulmonary embolism.

Echocardiography

- Echocardiography is the preferred method for the documentation of cardiac dysfunction at rest.

Pulmonary function

- Measurements of lung function are of little value in diagnosing CHF. However, they are useful in excluding respiratory causes of breathlessness. Spirometry can be useful to evaluate the extent of obstructive airways disease which is a common comorbidity in patients with heart failure.

Exercise testing

- In clinical practice, exercise testing is of limited value for the diagnosis of heart failure. However, a normal maximal exercise test in a patient not receiving treatment for heart failure excludes heart failure as a diagnosis.
- The main applications of exercise testing in CHF are focused more on functional and treatment assessment and on prognostic stratification.

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Haemochromatosis testing in primary care

Defining haemochromatosis

Hereditary haemochromatosis (HH) is the most commonly identified genetic disorder in the Caucasian population. Over 90% of people with HH have a mutation in the HFE gene which controls the absorption of iron from the G.I. tract. Other mutations may also cause HH in Caucasians and other ethnic groups.

Although its geographic distribution is worldwide, the common genetic mutation (C282Y) is most frequent in individuals of northern European origin, particularly of Nordic or Celtic ancestry. In New Zealand and Australia, it is estimated between 1 in 7 and 1 in 10 people are carriers, and 1 in 200 are homozygous for the most common mutation found on the HFE gene¹.

The genetic mutation causes enhanced iron absorption, resulting in raised serum transferrin (iron) saturation and progressive iron accumulation with age, reflected by a rising serum ferritin. If untreated, many patients develop excessive iron deposition that causes organ damage, e.g. to the liver, pancreas, heart and gonads. Haemochromatosis is diagnosed by DNA testing for the HFE gene C282Y mutation. In Caucasian people who develop clinical features of haemochromatosis, over 90% are homozygous for this mutation. Additional HFE gene mutations, for example, H63D and S65C, have now been identified and may result in overload when present as compound heterozygotes with the C282Y mutation, e.g. C282Y/H63D. In the remaining patients with evidence of iron overload, no HFE gene mutation can be identified; this percentage is higher in other ethnic groups. Alternative strategies are required to make the diagnosis in these patients including quantitative phlebotomy or liver biopsy. Specialist referral is recommended.

Our key recommendations are:

1. Serum transferrin saturation (iron saturation) and ferritin are the best initial tests for hereditary haemochromatosis
2. Population screening of asymptomatic individuals for haemochromatosis is currently not recommended
3. Transferrin saturation, ferritin and HFE gene testing are indicated in first degree adult family members of people with haemochromatosis
4. People with haemochromatosis are monitored with transferrin saturation and ferritin

Serum transferrin saturation (iron saturation) and ferritin are the best initial tests for hereditary haemochromatosis

The most common symptoms associated with haemochromatosis are vague and nonspecific; they include fatigue or weakness, arthralgias, and impotence. Sometimes weight loss, abdominal pain and hyperpigmented skin may also be noted. A large proportion of people with C282Y will have no symptoms of haemochromatosis¹. One controversial study² found the symptoms commonly associated with haemochromatosis are no more common in people with HH than in people that do not have HH. However, with the high consumption of meat in Australasia, which provides iron, the penetrance of HH is sufficiently high that testing is recommended; nearly 20% of asymptomatic males detected through screening had hepatic fibrosis¹.

Historically, a cluster of signs such as diabetes, arthropathies, arrhythmias, impotence, skin pigmentation and cirrhosis, were associated with haemochromatosis. These features, which suggest significant end-organ damage are now rare, presumably due to earlier detection of the disease.

In many cases haemochromatosis will be considered in the differential diagnosis, following a laboratory report with unexplained results, e.g. elevated transferrin saturation and/or ferritin, elevated transaminases, or unexplained abnormal liver panel.

Increased transferrin saturation is usually the earliest change, but may be falsely normal or low in unwell patients.

Ferritin levels rise as iron stores accumulate. However, a raised ferritin level is not specific for HH as it may be raised by other factors, such as the acute phase response, liver steatosis (fatty liver), other forms of liver inflammation, alcoholism, and some chronic anaemias.

A high ferritin with low or low-normal transferrin saturation is not typically due to iron overload.

Because both ferritin and transferrin saturation tests are temporarily affected by inflammation, abnormalities should be re-checked on a fasting test when the patient is well. This improves the accuracy of the results.

There is no clear consensus on the level of transferrin saturation which would warrant HFE gene testing. The levels suggested are usually around 50%^{4,5}. The trigger level may be lower in women than men. If ferritin levels are raised with a normal transferrin, the majority of these will have other causes such as hepatic steatosis or alcohol. If other causes have been excluded HH may be considered.

Abnormalities should be confirmed in a well patient (preferably fasting) before requesting an HFE gene test

It is now recognised that the clinical presentation and severity of iron overload varies between patients, even between siblings, who are homozygous for the C282Y HFE gene mutation. Presumably other genetic and environmental factors influence iron accumulation, but these are not well defined at present.

When haemochromatosis is suspected, tests should be requested in a cascade manner, with each result suggesting the path of further testing. Figure 1, page 12, shows an algorithm for investigating haemochromatosis.

Population screening of asymptomatic individuals for haemochromatosis is currently not recommended

Although haemochromatosis may fulfil the WHO criteria for population screening, it has not been widely supported³ because of doubts about the cost-effectiveness of such an approach.

Transferrin saturation, ferritin and HFE gene testing are indicated in first degree adult family members of people with haemochromatosis

Once a person is identified as having the HFE gene mutation, studies of first degree relatives are suggested. Adult relatives should be offered screening using transferrin saturation, ferritin and HFE gene testing, as shown in Figure 1.

HFE gene testing is included in the initial testing in this situation because negative iron studies will need retesting periodically, whereas negative gene testing never needs repeating because genetic status will never change. Furthermore, iron studies may not show characteristic changes in pre-menopausal women and children.

Because accumulation of iron overload usually takes decades to develop, there is no need to perform tests on children when a first degree relative is identified with the C282Y mutation, although younger patients may be tested if the patient and parents want certainty about the diagnosis. A reasonable approach would be to delay testing until the child is 20 years old. In most cases iron overload would not be evident until the person reached 30-40 years for men or at menopause for women, although there are exceptions. Alternatively, the partner of an affected individual could be tested to assess their carrier status, which would then determine whether the children were at risk of inheriting the HFE gene mutation from both parents.

Prior to testing, it is important that patients are counselled on the implications of the testing, including the potential consequences on their ability to obtain life and medical insurance.



People with haemochromatosis are monitored with transferrin saturation and ferritin

Treatment of haemochromatosis can prevent progression of iron overload which may further lead to cirrhosis. The mainstay of treatment for haemochromatosis is therapeutic phlebotomy. Studies have shown that the life expectancy for patients with haemochromatosis who undergo adequate venesection is equivalent to age matched controls except for those patients with cirrhosis or diabetes mellitus as a complication of their iron overload⁶.

To determine development of iron overload, all patients homozygous for the C282Y mutation should have transferrin saturation and ferritin performed 1-2 yearly, depending on degree of elevation and past rapidity of rise.

When the serum ferritin is consistently elevated* in a homozygous C282Y patient, therapeutic phlebotomy is indicated. 500 mL of blood is removed weekly until iron depletion is achieved; this can be expected to take 6 to 24 months. Patients undergoing regular phlebotomy should have regular checks of ferritin, transferrin saturation and haemoglobin, with the target level for the serum ferritin < 50 µg/L.

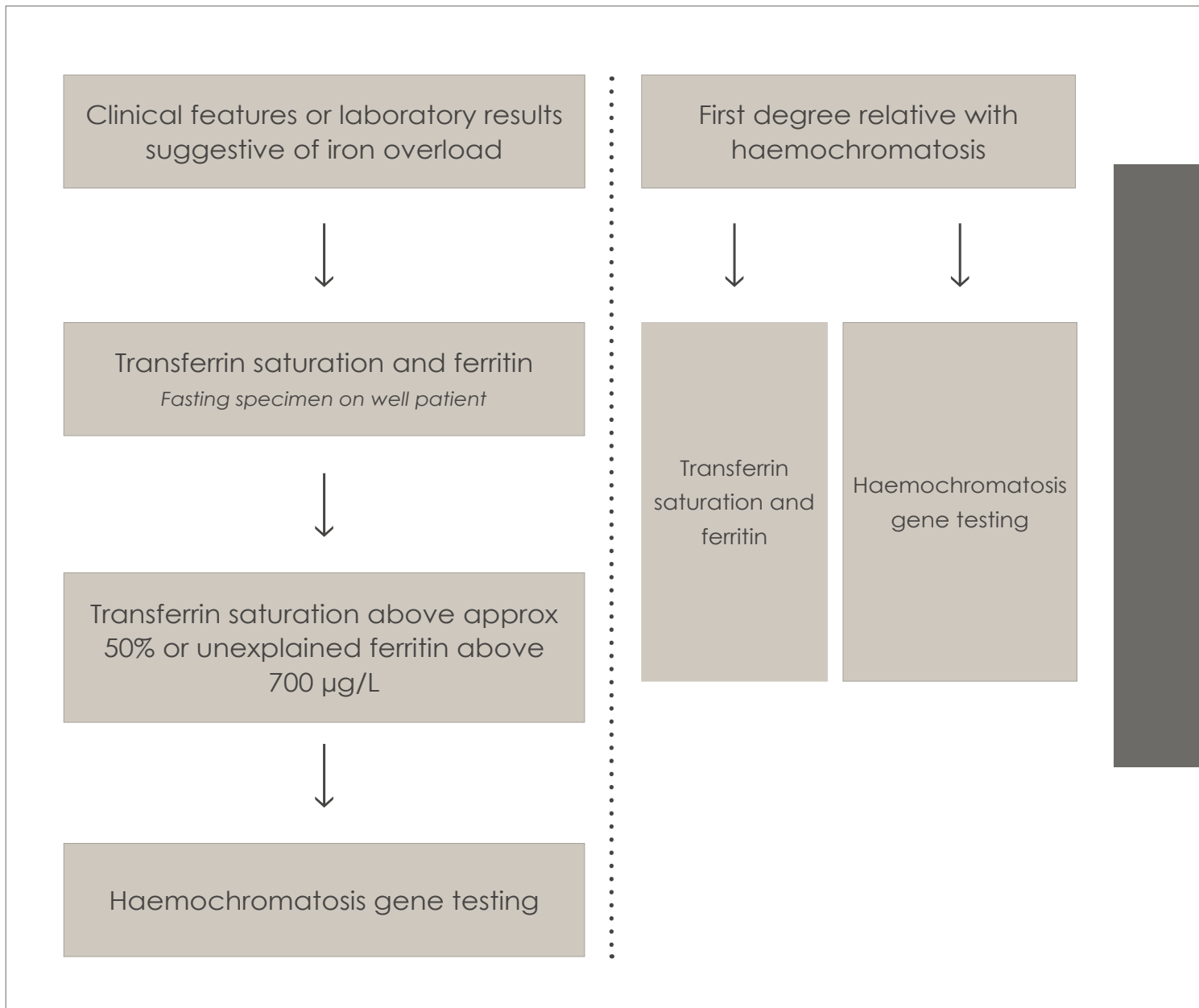
Once the target level has been achieved, phlebotomies at 3-4 monthly intervals are usually required to maintain low normal iron stores in these patients.

It is usually recommended that patients with serum ferritin of >1000 µg/L or abnormal liver enzymes have a liver biopsy to assess whether liver fibrosis is present.

Because genetic status will never change, testing for C282Y mutation never needs to be repeated.

**There is variation in opinions of what level constitutes the level at which this is indicated.*

Figure 1: Algorithms for investigating haemochromatosis



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Vitamin D testing in primary care

Introduction

Although rickets and osteomalacia are now rare in New Zealand there is concern that low vitamin D levels in older adults are contributing to bone loss and consequent fractures. Low levels of vitamin D are common in older adults but measurement of vitamin D is expensive. As an alternative to widespread testing, there is international interest in vitamin D supplementation for older people. However, there is no international consensus on how to deal with this issue¹. In this article, we discuss a reasonable approach to vitamin D supplementation and testing.

Our key recommendations are:

1. Increased sun exposure is advisable for people at high risk of vitamin D insufficiency due to inadequate exposure.
2. Vitamin D and calcium supplementation is appropriate for people at high risk who cannot increase their sun exposure.
3. Routine testing of vitamin D levels is not usually necessary prior to or after starting vitamin D supplementation.
4. Vitamin D testing is appropriate for people with:
 - a. Unexplained raised serum alkaline phosphatase or low calcium or phosphate.
 - b. Atypical osteoporosis.
 - c. Unexplained proximal limb pain in older people.
 - d. Unexplained bone pain, unusual fractures or other evidence suggesting metabolic bone disease. *Consider specialist advice for people in this category.*

Pathophysiology

The two main forms of vitamin D are vitamin D3 (cholecalciferol) produced in the skin by the action of UV light and vitamin D2 (ergocalciferol) produced by plants. Most people receive approximately 90% of their vitamin D requirements from exposure to sunlight. Food provides the remainder but adequate vitamin D is unlikely to be achieved through diet alone as the vitamin D level of most foods is extremely low. It is found in small quantities in fatty fish (salmon, herring and mackerel), liver, and eggs. Some foods, such as margarine and some low-fat milks, are fortified with vitamin D.

Vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D (25-OHD). This is the major circulating form of vitamin D and undergoes further hydroxylation in the kidney to the active metabolite 1,25-dihydroxyvitamin D (calcitriol).

Calcitriol stimulates intestinal calcium absorption, decreases parathyroid hormone secretion, stimulates osteoclastic bone resorption, stimulates osteoblasts, decreases production of collagen type 1, influences muscle function, and stimulates cell differentiation and the immune system².

No biochemical abnormalities may be apparent on testing in mild vitamin D deficiency. As deficiency worsens, raised serum alkaline phosphatase levels may be the only abnormality as serum calcium levels are maintained by the action of parathyroid hormone, but increased bone turnover contributes to the development of osteoporosis. In severe deficiencies there are low plasma calcium and phosphate, low urine calcium and raised alkaline phosphatase. Severe prolonged deficiencies cause rickets or osteomalacia.

Apart from its classical functions, roles are being explored for vitamin D in reducing the risks of autoimmune diseases such as type 1 diabetes and cancers such as of the prostate, colon and breast.

Adequate exposure to sunlight is required to maintain vitamin D levels:

Adequate exposure to sunlight to maintain vitamin D levels can be achieved by daily exposure of hands, face and arms (around 15% of body surface) to around one third of the exposure that would produce faint erythema. Table 1 shows approximate sun exposure times required for this to occur³. These times are for people with moderately fair skin. People with dark skin require approximately 3–4 times greater exposure to achieve the same benefit. Older adults also require greater exposure as they are less efficient at producing vitamin D.

Table 1: Recommended average daily sun exposure times (minutes) which result in adequate vitamin D production

	Dec - Jan	Jul - Aug	
Region	At 10:00 or 14:00	At 10:00 or 14:00	At 12:00
Auckland	6 - 8	30 - 47	24
Christchurch	6 - 9	49 - 97	40

Times for New Zealand were calculated from ultraviolet data averaged over 2 years provided by the National Institute of Water and Atmospheric Research.

Due to the known risks of skin cancer from excess UV light, deliberate exposure to sunlight in the summer months between 10:00 and 14:00 (or 11:00 and 15:00 day-light saving time) is not advised. With this proviso in mind, it is appropriate to advise people at risk of low vitamin D levels because of inadequate sun exposure to increase their exposure up to the recommended dose. It may not be possible to obtain these levels of sun exposure in some parts of New Zealand in the winter and early spring. In addition, exposure through glass is not effective.

Who is at risk of low vitamin D levels?

Groups in whom low vitamin D levels have been documented include³:

- Older people in residential care
- Older people admitted to hospital
- Patients with hip fracture
- Dark-skinned men and women (particularly if veiled)
- Mothers of infants with rickets
- People unable to obtain regular sun exposure for any reason

People with abnormal gut function or malabsorption, which reduce access to dietary sources of vitamin D, are at risk during the winter months or other times of inadequate sun exposure. People with reduced synthesis or enhanced degradation of the active metabolite because of, for example, hepatic or renal disease or drugs such as rifampicin and multiple anticonvulsant drug therapy, are also at risk. Those with severe renal disease are unable to make the active form of vitamin D (calcitriol) and may require treatment with activated vitamin D.

Supplementation may be given without testing for asymptomatic people at risk of low vitamin D because it is safe and relatively inexpensive, whereas testing is expensive

For people at risk, supplementation may be given without testing

For asymptomatic people who are at risk of low vitamin D levels who cannot achieve adequate sun exposure, supplementation may be given without testing. Supplementation reduces the risks of fractures in the elderly, particularly those in institutions but must be combined with an adequate calcium intake⁴. Although there is some evidence that vitamin D supplementation reduces fracture rates in other groups at risk of vitamin D deficiency, the evidence is conflicting^{5,6,7,8}.

Vitamin D supplementation equivalent to an oral daily dose of >700 IU is needed to reduce fracture rates. However, the body stores vitamin D efficiently and higher doses of supplements can be given at longer intervals.

A reasonable approach is to offer vitamin D supplementation to asymptomatic people at high risk of vitamin D insufficiency, in particular older adults in residential care. An appropriate dose is a single tablet of cholecalciferol 1.25 mg (50,000 IU) monthly by mouth. This dose is effective and not associated with risk of toxicity. For vitamin D supplementation to be effective, an adequate calcium intake is required (1.5 g daily). For elderly people this will usually require supplementation.

Vitamin D supplementation can reasonably be offered to any individual commencing anti-resorptive therapy for osteoporosis.

Over the counter vitamin D products may have other ingredients, such as vitamin A, which can be toxic in higher doses and should be used only with caution.

Testing is expensive and likely to be positive in people at high risk

Vitamin D levels of those most at risk of fractures (i.e. older people in residential care) are usually low, even in the absence of other biochemical studies. Depending on the criteria used for vitamin D deficiency, a study of over 65 year olds in England found that up to 80% of those in residential care were deficient⁹. As testing is expensive and supplementation is safe, it is reasonable to supplement asymptomatic at risk people without testing.

When is vitamin D testing appropriate

In adults, severe vitamin D deficiency presents with deep bone pain, diffuse muscle pain, hip pain, proximal weakness, fractures with minimal trauma and pseudofractures on x-ray. In the elderly it may mimic common musculoskeletal diseases or they may report difficulty with gait, walking up stairs, and getting out of a chair.

If there is clinical suspicion of severe symptomatic vitamin D deficiency it is appropriate to investigate with serum calcium, phosphate, alkaline phosphatase and vitamin D levels plus other tests as indicated. Specialist treatment is recommended for people identified as having metabolic bone disease other than simple vitamin D deficiency.

25-hydroxyvitamin D is almost always the most appropriate measure of vitamin D status. Measurement of 1,25-dihydroxyvitamin D is rarely required—it is very expensive and results do not provide a good reflection of vitamin D status. It may be indicated in some cases of sarcoidosis but it should be considered a specialist only test.

People identified as having severe deficiency of vitamin D are usually suitable for higher booster doses of vitamin D before reverting to maintenance doses. An appropriate booster dose for people with 25-OHD of less than 30 nmol/L is ten cholecalciferol 1.25 mg tablets either as a stat dose or one tablet daily for ten days. This dose should not be continued as a maintenance dose. Although vitamin D therapy is generally safe, people on higher doses may require a follow up serum calcium. Serum vitamin D levels should be checked at 3 – 4 months, as further treatment may be needed.

Vitamin D testing is appropriate for people with:

- a. Unexplained raised serum alkaline phosphatase or low calcium or phosphate
- b. Atypical osteoporosis
- c. Unexplained proximal limb pain in older people
- d. Unexplained bone pain, unusual fractures or other evidence suggesting metabolic bone disease. *Consider specialist advice for people in this category*

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