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Age-related testosterone decline
Testing for syphilis

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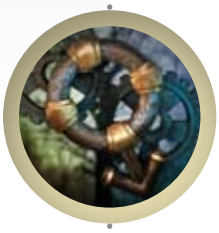

2 Age-related testosterone decline in males

Testosterone levels naturally decline with age in males. Some health professionals claim that a clinical syndrome of testosterone deficiency, or andropause, is being under diagnosed, which has led to dramatic increases in testosterone prescribing and testing in many countries. Routine measurement of testosterone levels is not indicated in older males. Testing should only be considered in males who have clinically significant signs and symptoms of late-onset hypogonadism.

10 Syphilis: testing for "the great imitator"

Over one hundred people per year in New Zealand are diagnosed with syphilis. While this only represents a small number of patients, the incidence of syphilis is increasing. Syphilis is most infectious in the earlier stages, therefore prompt identification and treatment is required to prevent transmission. Recognising the signs and risk factors and incorporating syphilis testing into sexual health checks is essential.

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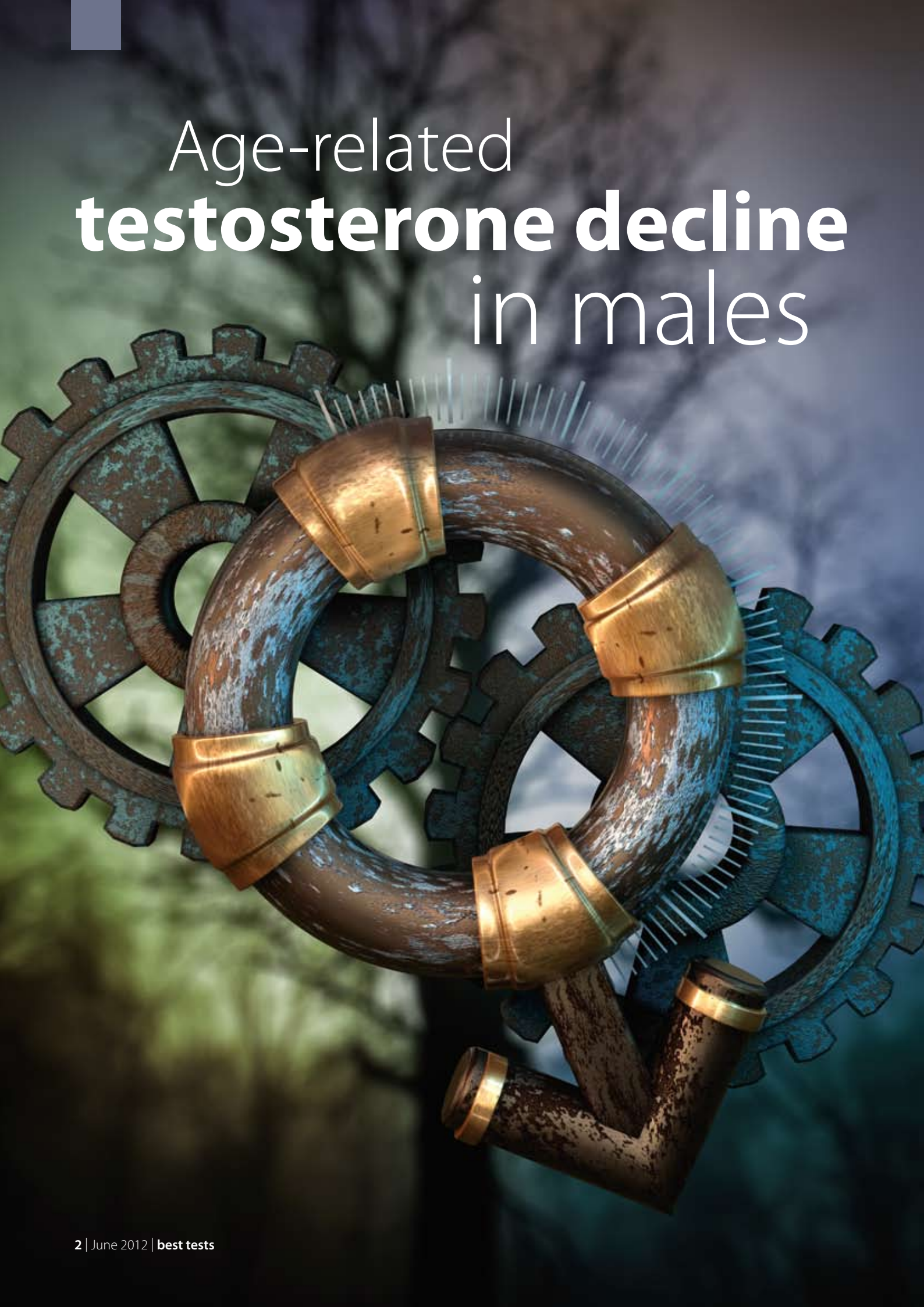
Age-related **testosterone decline** in males



The symptoms of male late-onset testosterone deficiency are non-specific and can be difficult to distinguish from changes related to natural ageing. There is often uncertainty as to when the measurement of testosterone is indicated. Testing should only be considered in males who have clinically significant symptoms and signs of late-onset hypogonadism.

Testosterone and ageing

Testosterone production in males is regulated by the hypothalamic-pituitary-gonadal (HPG) axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) which causes the anterior pituitary to produce luteinising hormone (LH) and follicle stimulating hormone (FSH). LH then stimulates Leydig cells in the testes to produce testosterone. The process is controlled by a negative feedback loop, with testosterone inhibiting the frequency and amplitude of hypothalamic and anterior pituitary secretions. The majority of testosterone is inactivated in the liver and excreted by the kidneys, approximately 4% is converted to dihydrotestosterone via a reductase enzyme and 0.2% to oestradiol via the enzyme aromatase.[1]

Testosterone levels in males decline at the rate of approximately 1% per year from age forty years.[2] Interpretation of the clinical significance of this is controversial. Some health professionals (predominantly in North America) claim that a clinical syndrome, referred to as "andropause", is being under diagnosed. Conversely, other health professionals describe this age-related decline in testosterone as merely a barometer of natural ageing. There is therefore no consensus on the prevalence of clinically significant testosterone deficiency in the older male population.

The two schools of thought have also resulted in discrepancies in prescribing practice in different countries. Between 1994 and 2003, testosterone prescription sales in the United States increased by 1700%, while remaining relatively constant in Europe.[3, 4] Increases in the volume of testosterone prescriptions have been recently reported in Australia,[5] however, this trend is not apparent in New Zealand.

Significant increases in the volume of testosterone prescribed means a similar increase in laboratory testing of testosterone and other hormones. This article provides guidance on when it is appropriate to investigate suspected late-onset hypogonadism in males aged over 40 years.

Testosterone deficiency in older males

Testosterone deficiency that occurs in association with advancing age is termed late-onset hypogonadism. The symptoms of late-onset hypogonadism (Table 1, over page) are often non-specific, with a weak overall association with testosterone levels.[8] A 2010 study of over 3000 males aged 40 to 79 years found that the combined sexual symptoms of poor morning erection, low sexual desire and erectile dysfunction (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance) were useful in diagnosing testosterone deficiency, in combination with laboratory testing of testosterone levels.[8]

Primary and secondary hypogonadism

Late-onset hypogonadism can result from primary or secondary causes, which can be due to congenital abnormalities or acquired disease. In some cases, both

"Andropause" and disease mongering

Recent articles in the Medical Journal of Australia suggest that testosterone is being over prescribed in Australia due to successful marketing by pharmaceutical companies.[6, 7]

From 1992 – 2010 the volume of testosterone prescribed per month in Australia increased by 1.5 to 4.3 times (depending on the State).[5] It was concluded that improved diagnosis of testosterone deficiency is unlikely to account for the majority of this increase and that it is more likely that it is being driven by the use of testosterone for non-approved indications, such as "andropause" and male sexual dysfunction.

primary and secondary causes are present, particularly in people with long-term systemic diseases such as chronic kidney disease, cirrhosis or chronic lung disease.

Primary hypogonadism is when there is decreased testosterone production due to a testicular abnormality. This may occur, for example, after infection or chemotherapy and in a small percentage of males with advancing age. Primary hypogonadism is characterised by elevated LH due to the reduced negative feedback effect of testosterone.

Secondary hypogonadism results from disorders of the hypothalamic-pituitary axis, e.g. tumours, or congenital or genetic conditions. Secondary hypogonadism is characterised by low, or lower than expected, serum LH levels in combination with low testosterone levels.

Measuring testosterone levels

Measurement of total serum testosterone (see panel opposite) is generally sufficient to diagnose testosterone deficiency. Assays which directly measure free testosterone are not recommended due to poor reliability, although free testosterone can be calculated through additional testing in rare cases where unusually high or

Table 1: Signs and symptoms associated with testosterone deficiency in males[9]

More specific	Less specific
Decreased or absent early morning erection	Decreased energy, motivation and confidence (vitality)
Reduced libido	Depressed mood
Erectile dysfunction	Poor concentration and memory
Breast discomfort, gynaecomastia	Sleep disturbance and increased sleepiness
Loss of facial, axillary and pubic hair	Mild anaemia
Testicular atrophy	Reduced muscle bulk and strength
Infertility	Increased body fat
Height loss, low velocity fractures, low bone mineral density	Decreased physical performance
Hot flushes, sweats	

N.B. All of these signs and symptoms can be indicative of causes other than hypogonadism. Signs and symptoms should be interpreted in the context of the entire clinical picture.

low sex hormone-binding globulin (SHBG) levels may be expected, e.g. patients with hyperthyroidism, cirrhosis or taking anticonvulsants.[10]

Who should be considered for testing?

Testosterone testing should only be considered for males who display symptoms and signs clinically suggestive of hypogonadism. Routine testosterone testing in older males is not recommended, as the results in the absence of symptoms are unlikely to influence management.

Before considering investigating for late-onset hypogonadism, rule out factors that can cause a transitory drop in testosterone levels and may explain the current symptoms. This includes co-existing acute or chronic illness, long-term use of medicines, e.g. opioids or corticosteroids, high alcohol intake, illicit drug use, eating disorders or excessive exercise.[9]

Erectile dysfunction is common in males aged over 40 years and may be a reason for patients to request a testosterone test.[12] However, routine testing of testosterone levels in males with erectile dysfunction in the absence of other symptoms of late-onset hypogonadism is not recommended.[13] Although late-onset hypogonadism and erectile dysfunction both become more common with age (and will often co-exist), the two disorders have distinct pathophysiology and erectile dysfunction is only rarely ever caused by low testosterone levels.[9] Erectile dysfunction is most frequently caused by neurological or vascular disease, some medicines (e.g. antidepressants or antihypertensives) or psychosexual factors.[13] Testosterone treatment for erectile dysfunction is only effective (and indicated) if the cause is a testosterone deficiency.[9, 13]

For further information see: "Selected topics in Men's Health" Best Tests (Sept, 2010) and "Erectile dysfunction", BPJ 12 (Apr, 2008).

Obesity in males is associated with decreased testosterone levels.[14] However, testing of testosterone levels in obese males, who do not display symptoms of hypogonadism, is not recommended, as treatment in the absence of symptoms is unlikely to be of significant benefit. The relationship between obesity and hypogonadism is complex as low testosterone is both a cause and consequence of obesity.[15]

Free, bio-available and total testosterone

Only 1 – 2% of circulating testosterone is not bound to protein. This fraction is termed free testosterone.[11] Approximately 40 – 50% of circulating testosterone is weakly bound to albumin.[11] The free and albumin-bound testosterone is referred to as bio-available. The remaining testosterone in circulation is strongly bound to SHBG. The amount of SHBG in circulation therefore influences the amount of bio-available testosterone. SHBG can be altered by factors such as age, hepatic cirrhosis and hepatitis, hyperthyroidism, obesity and the use of anticonvulsants.[9] Total testosterone refers to circulating, bio-available and SHBG-bound testosterone.

Investigating testosterone concentration

Blood samples should be taken in the early morning as serum levels in males, particularly younger males, vary throughout the day, e.g. highest at 8 am and lowest at 8 pm.[16] The reference range for total serum testosterone concentration in adult males differs between laboratories. An approximate range is 8 – 35 nmol/L, however, if there is doubt the reporting laboratory should be consulted. Work is currently in progress internationally to standardise testosterone assays and reference ranges.

Interpreting serum testosterone results

If a single early morning testosterone level is within the reference range then no further testing is required.

Testosterone levels below the reference range should be considered in the context of the patient's symptoms. Low testosterone levels require at least one repeat test, as 30% of males with a mildly subnormal level will have a normal level when the test is repeated.[17] Acute illness or recent alcohol intake can also affect testosterone levels.

The level of testosterone below which adverse health outcomes emerge in older men is unknown.[8] However, it is generally agreed that clinically relevant symptoms and a testosterone level below 8 nmol/L are required for a diagnosis of late-onset hypogonadism.[8]

If a low testosterone level is detected, **serum LH** should be measured, along with the confirmatory testosterone test. Serum LH and FSH can be used to distinguish primary from secondary hypogonadism. However, unless fertility is an issue, measurement of LH levels alone is sufficient.[15] LH and testosterone levels can be interpreted as follows:

- Primary hypogonadism is suggested by elevated LH levels and a consistently low or borderline testosterone level.

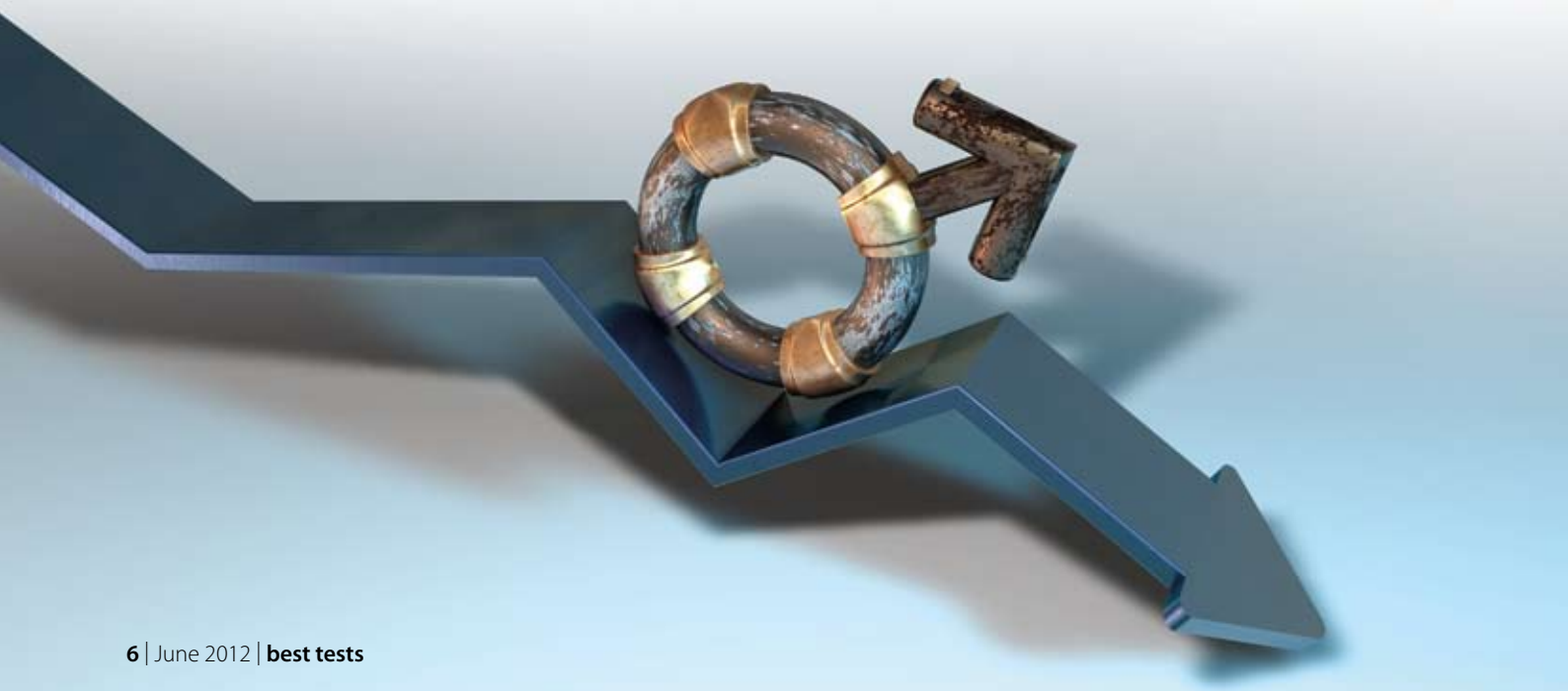
  N.B. the testosterone reference range is population based, therefore for some individuals the serum testosterone may fall within the reference range, but is low for them – as revealed by the high LH.

- Secondary hypogonadism is suggested by low LH or an inappropriately normal LH in the context of consistently low testosterone levels

- Low LH with a clearly normal testosterone level suggests significant illness or exogenous supplementation

Where secondary hypogonadism is suspected, a **serum prolactin** test should be requested as prolactinoma is a common type of pituitary tumour, which may be the cause of secondary hypogonadism.

All patients with suspected hypogonadism should be referred to an endocrinologist to confirm the diagnosis and to discuss treatment options. In patients with suspected secondary hypogonadism, assessment for anterior pituitary dysfunction and MRI may be considered to exclude the possibility of pituitary tumours.[9] Testosterone replacement should not be commenced until assessment has taken place, as treatment is likely to suppress endogenous production of testosterone and alter any subsequent testosterone measurement.



Testosterone replacement for late-onset hypogonadism in males

A three month trial of testosterone replacement may be considered in patients with clinically significant symptoms of hypogonadism and reproducible biochemical evidence of a testosterone deficiency, following a detailed discussion of the risks and benefits of treatment.[9] It is recommended that testosterone is initiated in consultation with an endocrinologist. Testosterone replacement treatment for hypogonadism is likely to be life-long if it provides benefit to the patient (after the treatment trial).

Before testosterone treatment is commenced a clinical history of prostate symptoms should be taken, a digital rectal examination of the prostate conducted and PSA and full blood count (to assess haematocrit) requested.

Testosterone replacement is generally not appropriate for males who have: [9]

- Diagnosed prostate or breast cancer
- Palpable prostate nodule or induration, or PSA > 4 ug/L (> 3 ug/L in males with an elevated risk of prostate cancer, e.g. first-degree relative with prostate cancer)
- Severe lower urinary tract symptoms associated with benign prostatic hypertrophy
- An elevated haematocrit (> 50%)
- Untreated severe sleep apnoea
- Poorly controlled heart failure

There is no convincing evidence that testosterone treatment is causally associated with the development of new prostate cancer, however, occult prostate cancer should be actively excluded before treatment begins.

Testosterone should not be prescribed to males who wish to conceive or to treat male infertility. Testosterone within the testes is required for spermatogenesis, however, exogenous testosterone will decrease sperm production through the negative feedback effect of testosterone on gonadotropins.[9]

Testosterone replacement treatment is not indicated for males with testosterone levels which are intermittently low, or with low levels caused by medicines or lifestyle factors (e.g. drug or alcohol misuse, excessive exercise).[9]

Evidence of adverse effects associated with testosterone replacement

A 2010 meta-analysis of studies of adult men with low testosterone levels found that testosterone treatment was associated with a three-fold increase in the risk of polycythaemia and small, but significant reductions in HDL cholesterol.[19] However, the same analysis did not find significant effects on all-cause mortality, prostatic or urological outcomes or cardiovascular events. In contrast, the Testosterone in Older Men with Mobility Limitations (TOM) trial found significantly increased cardiovascular-related adverse effects in 23 of 106 men receiving testosterone treatment, compared to six of 103 receiving placebo. This resulted in the trial being halted early. However, this study has been criticised for its small sample size and the potentially elevated cardiovascular risk of participants at baseline.

The most significant adverse effects associated with testosterone treatment are prostatic hypertrophy and polycythaemia, which may occur within three months of treatment initiation.[9, 18] Mild hyperbilirubinaemia has also been reported.

Prescribing testosterone

In New Zealand, testosterone is available in the following forms:

- Orally as testosterone undecanoate, e.g. initially 120 – 160 mg daily for two to three weeks, followed by a maintenance dose of 40 – 120 mg daily.[20] This preparation is poorly absorbed and should be taken in divided doses with food. Depending on baseline testosterone levels, treatment may be started at a lower dose to reduce the risk of adverse effects.
- Testosterone patches, e.g. two 2.5 mg/day patches applied before bed.[21] This often causes local skin irritation and can be poorly tolerated.
- Injectable (intramuscular) – either long-acting testosterone cypionate or testosterone esters, e.g. 50 – 400 mg testosterone cypionate every two to four weeks.[22] Reandron is a very long-acting injectable form of testosterone undecanoate, which has the advantage of 10 – 12 weekly administration, but is not subsidised.

Prescriptions for oral and injectable testosterone require consultation with and recommendation from an endocrinologist (or other relevant specialist) in order to be subsidised. Testosterone patches are fully-subsidised, without restriction. However, it is recommended that any testosterone preparations are prescribed in consultation with an endocrinologist.

Follow-up is recommended after three months in order to assess the effect of treatment, ask about adverse effects and alter the dose if necessary.

Testosterone replacement treatment, particularly injections, can be associated with a placebo effect, therefore a second follow-up three months later is recommended to ensure that any benefits of treatment are sustained.

Within the first three to six months of treatment, a PSA test and a digital prostate examination should occur. This should be repeated annually if treatment continues.[15] If the PSA is significantly elevated then discussion with an urologist is recommended.

The role of testosterone measurement in patients on testosterone treatment is not clear. Routine monitoring of testosterone levels is not required. However, in patients using injectable preparations, it may be useful to determine their trough level immediately prior to administering their next dose. The target testosterone concentration is in the mid-normal range. For example a concentration of 14 to 24 nmol/L is recommended for patients receiving testosterone cypionate injections.[9]

Androgen misuse

Unexpected testosterone, LH, FSH and SHBG levels can result from illicit use of androgens ("anabolic steroids"). Classic symptoms include truncal acne, excessive muscularity, testicular atrophy and gynaecomastia, usually in association with obsessive and intense exercise regimens. Consider asking specific questions regarding androgen misuse to males who display these behaviours and signs.

Males who are currently using androgens may have elevated testosterone and suppressed LH, FSH and SHBG. Suppression of testosterone as well as LH, FSH and SHBG can indicate a recent history of androgen misuse.[4] The rate of recovery from HPG axis suppression is dependent on the duration and severity of the misuse, but will generally occur within 12 months after cessation of androgens.[4]

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References

1. Allan CA, McLachlan RI. Testosterone deficiency in men. Diagnosis and management. Aust Fam Physician 2003;32(6):422–7.

2. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 2002;87(2):589–98.

3. Bhasin S, Singh AB, Mac RP, et al. Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. J Androl 2003;24(3):299–311.

4. Handelsman DJ. Androgen misuse and abuse. Best Pract Res Clin Endocrinol Metab 2011;25(2):377–89.

5. Handelsman DJ. Pharmacoepidemiology of testosterone prescribing in Australia, 1992-2010. Med J Aust 2012;196(10):642–5.

6. Katelaris A. Testosterone up. A case of disease mongering? Med J Aust 2012;196(10):611.

7. Vitry AI, Mintzes B. Disease mongering and low testosterone in men: the tale of two regulatory failures. Med J Aust 2012;196(10):619–21.

8. Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363(2):123–35.

9. The Endocrine Society. Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95(6):2536–59.

10. Editor: Kyle C. A handbook for the interpretation of laboratory tests. 4th ed. Diagnostic Medlab; 2008.

11. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev 2005;26(6):833–76.

12. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994;151(1):54–61.

13. Jack G, Zeitlin SI. The role of routine serum testosterone testing: routine hormone analysis is not indicated as an initial screening test in the evaluation of erectile dysfunction. Rev Urol 2004;6(4):203–6.

14. Mulligan T, Frick MF, Zuraw QC, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract 2006;60(7):762–9.

15. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. Int J Clin Pract 2010;64(6):682–96.

16. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983;56(6):1278–81.

17. Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay J. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol (Oxf) 2007;67(6):853–62.

18. Snyder PJ, Peachey H, Berlin JA, et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85(8):2670–7.

19. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95(6):2560–75.

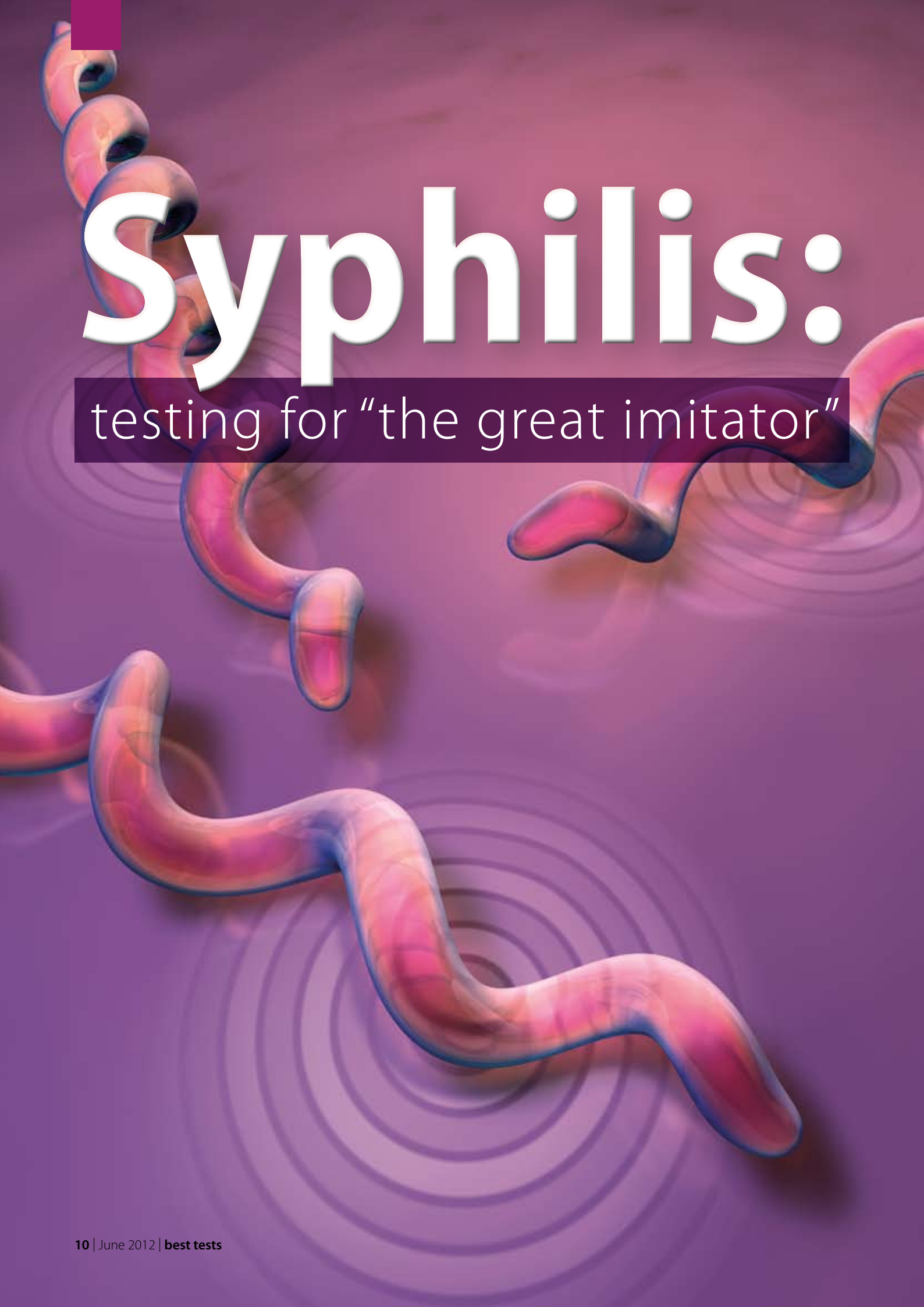
20. Arrow Pharmaceuticals Limited. Testosterone - Medicine data sheet. 2010. Available from: www.medsafe.govt.nz (Accessed Jun, 2012).

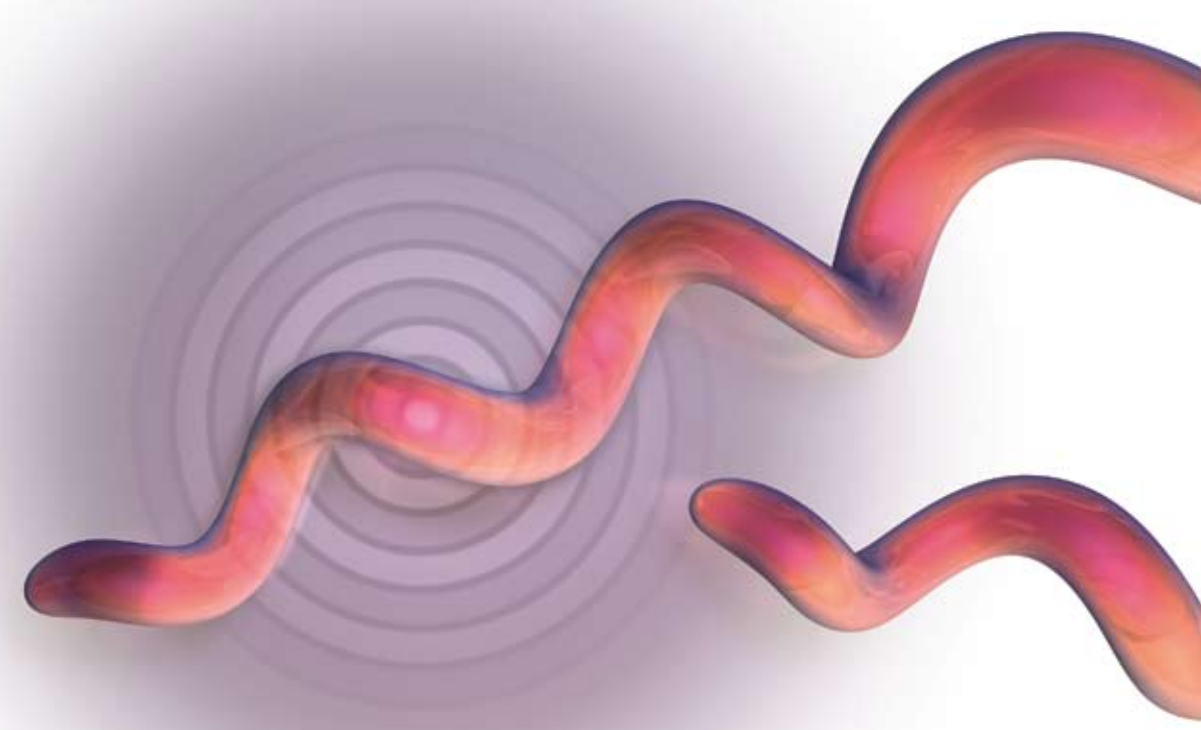
21. Hospira NZ Limited. Androderm. 2009. Available from: www.medsafe.govt.nz (Accessed Jun, 2012).

22. Pfizer New Zealand Ltd. Depo Testosterone: Testosterone cypinoate injection. 2011. Available from: www.medsafe.govt.nz (Accessed Jun, 2012).

Syphilis:

testing for "the great imitator"





The incidence of syphilis in New Zealand has increased dramatically over the last decade. As syphilis is highly infectious in the early stages, prompt identification is important. However, the perceived rarity of syphilis, combined with often non-specific symptoms, mean this can be difficult. Recognising the signs and risk factors and incorporating syphilis testing into sexual health checks, is essential for controlling the growing number of new syphilis infections.

A recent increase in new syphilis infections

Syphilis is a sexually transmitted infection caused by the spirochete (spiral shaped) bacterium *Treponema pallidum*. It is unknown where and when syphilis first emerged, but one theory is that explorers carried syphilis from the "New World" back to Europe with them in the 1400s, where it spread so quickly it became known as the Great Pox. Many famous historical figures are thought to have had syphilis, including Vincent van Gogh, Adolf Hitler and Leo Tolstoy, and prostitutes infected with syphilis are most likely the origin of the "femme fatale" character in literature. It was not until the discovery of penicillin in the 1940s that the prevalence of syphilis began to decline.[1]

In New Zealand, less than 20 cases of syphilis were being reported each year by the early 2000's.[2] However, the incidence of syphilis is now beginning to increase again, with the most recent data showing that 119 cases were reported by sexual health clinics in New Zealand in 2010.[3, 4] While in absolute terms these numbers are low, they represent a 600% increase in prevalence in less than a decade. Similar increases have been occurring worldwide and have been attributed to factors such as decreases in the resources allocated to the diagnosis and control of syphilis, increased international travel and increases in the number of men who have sex with men.[1]

Although syphilis is still a relatively rare condition, it should be considered as part of a sexual health check. Syphilis in New Zealand is most commonly seen in men who have sex with men (in particular, HIV positive men), in heterosexual people who have sex while overseas, particularly in South East Asia and Africa and in immigrants, particularly those from the Asia-Pacific region.

The symptoms of syphilis

Syphilis is termed the "great imitator", as symptoms are often non-specific or mimic other infectious or immune mediated conditions, e.g, the rash seen in secondary syphilis may resemble pityriasis rosea. Approximately 50% of people with syphilis are asymptomatic.

The progression of syphilis is divided into three stages; primary, secondary and tertiary. An asymptomatic latent period, which may last more than a decade, separates the secondary and tertiary stages. The time between infection and development of initial symptoms is on average 21 days, but ranges from 10 – 90 days.[5] People with syphilis are highly infectious during the primary and secondary stages, with infectivity declining in the latent and tertiary stages. Syphilis spirochetes are able to pass through intact mucous membranes and compromised skin, so are transmissible via kissing and vaginal, oral and anal sex.[1] Consistent condom use reduces, but does not eliminate, the risk of syphilis infection.[6] It is estimated that the rate of transmission between people with primary or secondary syphilis and their sexual partners is 30%.[1]

Primary syphilis

The initial stage of syphilis is typically marked by the appearance of a single chancre (ulcer-like lesion), although multiple lesions may be present (Figure 1).[7] The chancre is firm, painless and can vary in size up to approximately 3 cm. It generally appears at the site of disease transmission, and therefore may not be noticed by the patient if it is inside the vagina, anus or oral cavity. Non-tender lymphadenopathy may develop near the site of the chancre.

The chancre typically resolves within four to eight weeks and does not require localised treatment, although antibiotic treatment to prevent syphilis infection from progressing is necessary (Page 16).[7]

Secondary syphilis

Secondary syphilis develops three weeks to three months after the appearance of primary syphilis, if left untreated.[7] Secondary syphilis is characterised by skin rashes and mucous membrane lesions. The typical rash is a widespread, symmetrical eruption of slightly scaly, reddish brown plaques (Figure 2) that also occurs on the palms of the hands and the soles of the feet (Figures 3). However, rashes may be non-specific, appear on other parts of the body or resemble rashes caused by other conditions, such as pityriasis rosea. Rashes may be so faint that they are not noticed.

Condylomata lata may also be present. These are moist, grey, pink or white, raised, wart-like lesions or plaques

Figure 1: Penile chancre in primary syphilis (Supplied by Dermnet NZ)

Figure 2: Disseminated rash in secondary syphilis Pox (Supplied by Dermnet NZ /Dr John Adams)

which are highly infectious areas of concentrated spirochete particulates. They can occur on the penis (Figure 4), vulva, rectum, mouth, throat, larynx, inner thighs, armpits and under breasts.[7]

Other symptoms of secondary syphilis are non-specific and include flu-like symptoms, such as lymphadenopathy, tiredness, headache, sore throat, fever and weight loss.[7, 8]

The rashes and lesions associated with secondary syphilis typically resolve within two to six weeks. Antibiotic treatment reduces the duration of symptoms and prevents progression to tertiary disease.[8]

Tertiary syphilis

Approximately one-third of untreated people will develop tertiary syphilis. This stage occurs after a latent period, when infection is identifiable on serological testing but the patient does not have symptoms or signs. The tertiary stage usually appears within three to ten years after syphilis was first acquired, although it can appear up to 40 years later.[1]

Signs, symptoms and long term sequelae of tertiary syphilis include:[1,7]

- Neurological infection (neurosyphilis): numbness in arms, legs and face, paralysis, gradual blindness, changes in mental state and eventually dementia
- Cardiovascular disease: classically chronic inflammation of the aorta resulting in aneurysm formation, aortic valve incompetence and, in the longer term, congestive heart failure
- Granulomatous lesions (gummas): painless rubbery nodules mostly seen on the skin, mouth and throat that may ulcerate, or form as lesions in the long bones, which typically cause bone pain at night

The Oslo study estimated the probability of dying as a result of untreated syphilis to be 17% in males and 8% in females after 40 years infection.[9] The infamous Tuskagee study, which exploited a vulnerable patient population and withheld treatment after it became available, found that after 20 years of follow up, cardiovascular disease or neurosyphilis was the primary cause of death in 30% of African American males with syphilis.[10]

Figure 3: Characteristic rash on the foot in secondary syphilis. (Supplied by Dr Edward Coughlan)

Figure 4: Condylomata lata in secondary syphilis (Supplied by Dermnet NZ/Dr John Adams)

Yaws in the Asia Pacific region

Treponemal bacteria are responsible for a number of diseases other than syphilis, such as yaws, bejel and pinta. All have similar symptoms and outcomes to syphilis, but are not sexually transmitted.[12] These diseases are endemic to many tropical regions, but World Health Organisation eradication efforts have led to a greatly reduced number of people with new infections.[12]

Yaws is likely to be the most common non-syphilitic treponemal infection to be seen in immigrants to New Zealand, particularly those from the Pacific and Asia. While the likelihood of seeing a patient with yaws is very low, many may have been exposed to this infection during childhood. The antibodies produced by the immune system in response to yaws remain present for life.[12] As such, people with a previous yaws infection will always return a reactive result on specific serology testing (Page 15). This should be taken into consideration if investigating for syphilis in a patient who has immigrated from a country or region with an increased prevalence of any tropical treponemal disease.

Determining the risk of exposure to syphilis

As part of a sexual health check, ask about behaviours or factors that may increase a person's risk of exposure to syphilis.

People with an increased risk of syphilis include those who:

- Originate from a country where syphilis is common, e.g. Sub-Saharan Africa, Asia-Pacific (especially Fiji), South America or Eastern Europe
- Have had sex with a person from a county where syphilis is prevalent
- Are male and have had sex with other males
- Are HIV positive or have had sex with someone who is HIV positive
- Have multiple sexual partners
- Have had sexual contact with a person diagnosed with syphilis

Patients at increased risk should be examined for signs and symptoms of syphilis. Syphilis serology (opposite) should be requested, along with other STI investigations, including HIV.[7] Ulcer-forming genital diseases, such as syphilis, increase the likelihood of transmission of HIV and other STIs by five to ten times.[5, 11]

Specific signs which indicate an increased likelihood of syphilis include:

- Chancre (microscopy required, Page 16)
- Condyloma lata
- Rash on the palms of hands and on the soles of feet (strongly suggestive of secondary syphilis)
- Rash on the torso or lymphadenopathy not attributable to another condition

Laboratory testing for suspected syphilis

Syphilis serology should be requested in patients at increased risk or with clinical features suggestive of syphilis. Patients with a suspected chancre should also be referred to a sexual health clinic or laboratory for assessment and microbiological examination of the lesion.

N.B. Syphilis serology is also included in the first antenatal

screen in women who are pregnant and is required as part of an immigration medical examination.

Serological testing

There are two types of syphilis serology test – non-specific (non-treponemal) serology and specific (treponemal) serology. Non-specific tests detect antibodies that bind to antigens that are, or are similar to, those expressed by *Treponema pallidum* or expressed on host tissues during infection. These tests, such as the Rapid Plasma Reagin (RPR) and Venereal Disease Research Laboratory (VDRL) test, were traditionally used as screening tests for syphilis, and to measure disease activity and response to treatment.[13] They are inexpensive to perform (compared to specific tests) but have a high false-positive rate, particularly in women who are pregnant, in people with cancers, autoimmune disorders, co-morbid viral infections, in older people and in people who use illicit drugs.[7, 14]

Specific tests detect antibodies that bind to proteins derived from *Treponema pallidum*. These tests, such as the *Treponemal pallidum* Particle Agglutination (TTPA), *Treponema pallidum* Haemagglutination (TPHA) and Fluorescent Treponemal Antibody (FTA) test, have commonly been used to confirm the diagnosis of syphilis.[13] They are more expensive than non-specific tests, but have a low false-positive rate. More recently, the Enzyme immunoassay (EIA) and derivative immunoassays, such as the Chemiluminescent Microparticle Immunoassay (CMIA), that use specific *Treponema pallidum* antigens, have been developed. These tests are less expensive and have altered the way serology is used for testing for syphilis.

The approach generally used by laboratories in New Zealand is to perform an initial test with EIA. If this is positive, the diagnosis is confirmed using TPPA. Disease activity is then determined using RPR.[14, 15] Depending on the patient-management system in use and the methodology of the local laboratory, clinicians either select "syphilis serology" on the laboratory request form or request the individual tests.

Interpreting syphilis serology

Syphilis serology results should be interpreted within the overall clinical picture, i.e. clinical examination, patient history and risk profile. Table 1 (over page) may be useful in aiding interpretation.

Antenatal screening and congenital syphilis

Congenital syphilis occurs when infection is passed vertically from mother to infant in-utero. The risk of transfer in-utero is approximately 75 – 95% in a mother with primary syphilis. The risk of a mother passing infection to a foetus remains for up to seven years post infection, if untreated.[8] The mother does not need to be symptomatic to pass on the infection.

Serology testing for syphilis is included in the first antenatal screen. Testing should be repeated at 28 weeks and prior to delivery in women with a high risk of syphilis infection, such as recent immigrants from high-risk countries.[5]

EIA, TPPA and RPR results are expressed as "reactive" or "non-reactive". RPR results also include a titre, with higher titres indicating greater disease activity. N.B. People who have had a past treponemal infection, including non-venereal infections such as yaws, will remain reactive on specific treponemal tests for their lifetime.[7, 14]

Discussion with a sexual health or infectious disease physician is recommended if results are contradictory or difficult to interpret.

Referral for microscopy is required for patients with a chancre

If a patient presents with a suspected chancre, they should be referred to a sexual health clinic or laboratory for assessment and examination of the exudate from the lesion. Dark field microscopy is used to detect bacterium particulates (spirochetes).[7]

Exudate from oral and anal chancres cannot be reliably examined with standard dark-field microscopy due to the likelihood of contamination. Direct fluorescent antibody (DFA) stains for microscopy can be used,[16] however, the availability of this method is variable.

Topical treatment should not be applied to the chancre and systemic antibiotics should not be prescribed until the sample has been taken as this may alter the results.[16]

Syphilis serology should also be requested.

Management of syphilis: refer for treatment

Patients who have tested positive for syphilis should be referred urgently to a sexual health or infectious disease physician for treatment.[14]

Benzathine benzylpenicillin* injection is the first-line treatment for syphilis at all stages. Tetracyclines, some macrolides and cephalosporins can be used as an alternative if the patient is allergic to penicillin. Penicillin is the only recommended treatment in women who are pregnant. Skin testing for penicillin allergy followed by de-sensitisation is recommended for pregnant women with a history of penicillin allergy.[7]

Table 1: Interpreting syphilis serology

EIA	TPPA	RPR	Interpretation
Non-Reactive	Not tested	Not tested	No evidence of syphilis, or too early, retest in one month if strong suspicion based on clinical evidence
Reactive	Non-Reactive	Non-Reactive	Possible early primary, latent or false-positive, retest in one month
Reactive	Non-Reactive	Reactive	Probable early primary, false positive possible but unlikely, retest in two weeks
Reactive	Reactive	Non-Reactive	Evidence of past infection or possible latent infection, history will help to differentiate
Reactive	Reactive	Reactive	Current syphilis

* Originally published as Penicillin G

Effective treatment usually results in a decline in RPR titres, although a return to pre-infection levels may take many years.

Follow-up and partner notification

Sexual partner notification is necessary for all people diagnosed with syphilis. This is usually carried out by the sexual health clinic.

If the patient has primary syphilis, all sexual partners within the last three months should be contacted, offered testing and begun on empiric treatment, regardless of serology results.[14]

If the patient has secondary syphilis, all sexual partners within the last six months should be contacted and offered testing. Empiric treatment should be commenced if sexual contact has been within the last three months, regardless of serology results.

If the patient has early-latent syphilis or syphilis of unknown duration with an RPR titre of 1:32 or more, all sexual partners within the last 12 months should be contacted and offered testing. Empirical treatment should be commenced if sexual contact has been within the last three months regardless of serology results.[14]

In most cases, patients with late-latent or tertiary syphilis are unable to transmit syphilis infection. Current partners and children of women with late-latent or tertiary syphilis should be tested.

Syphilis is not a Notifiable Disease, but surveillance of cases is performed by Environmental Science and Research Ltd (ESR) through voluntary reporting by laboratories and sexual health clinics.

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References

1. Walker G. Antibiotics for syphilis diagnosed during pregnancy. Cochrane Database of Syst Rev 2010;(3):CD001143.

2. The Environmental Institute of Science and Research (ESR). Sexually transmitted infections in New Zealand: 2001. Ministry of Health; 2002. Available from: www.surv.esr.cri.nz (Accessed Jun, 2012).

3. The Environmental Institute of Science and Research (ESR). Sexually transmitted infections in New Zealand: 2003. Ministry of Health; 2004. Available from: www.surv.esr.cri.nz (Accessed Jun, 2012).

4. The Environmental Institute of Science and Research (ESR). Sexually transmitted infections in New Zealand: 2010. Ministry of Health; 2011. Available from: www.surv.esr.cri.nz (Accessed Jun, 2012).

5. Kollmann TR, Dobson S. Chapter 16 - Syphilis. Infectious Diseases of the Fetus and Newborn (7th Ed). Philadelphia: W.B. Saunders; 2011. p.524–63.

6. Koss C, Dunne E, Warner L. A systematic review of epidemiologic studies assessing condom use and risk of syphilis. Sex Transm Dis 2009;36(7):401–5.

7. Ngan V. Syphilis. DermNet NZ. 2011. Available from: www.dermnetnz.org/bacterial/syphilis (Accessed Jun, 2012).

8. Longo D, Fauci A, Kasper D, et al. Harrison's principles of internal medicine. 18th ed. New York: Mc Graw Hill Medical; 2012. p. 1384-8.

9. Clark EG, Danbolt N. The Oslo study of the natural history of untreated syphilis: An epidemiologic investigation based on a restudy of the Boeck-Bruusgaard material a review and appraisal. J Chronic Dis. 1955;2(3):311–44.

10. Olansky S. Untreated syphilis in the male Negro: Twenty years of clincial observation of untreated syphilitic and presumably non-syphilitics groups. J Chronic Dis. 4(177):1956.

11. Karp G, Schlaeffer F, Jotkowitz A, Riesenberg K. Syphilis and HIV co-infection. Euro J Int Med 2009;20(1):9–13.

12. Lal S, Dhariwal AC. Yaws, Pinta, and Endemic Syphilis. Int Encyclo Pub Health. Oxford: Academic Press; 2008. p. 651–7.

13. Hoover K, Radolf J. Serodiagnosis of syphilis in the recombinant era: Reversal of fortune. J Infect Dis 2011;204(9):1295–6.

14. The New Zealand Sexual Health Society (NZSHS). Syphilis. NZSHS: Auckland; 2009. Available from: www.nzshs.org/treatment_guidelines/Syphilis_2009.pdf (Accessed Jun, 2012).

15. Editor: Kyle C. A handbook for the interpretation of laboratory tests. 4th ed. Diagnostic Medlab; 2008.

16. Brown D, Frank J. Diagnosis and management of syphilis. Am Fam Physician 2003;68(2):283–90.

QUIZ FEEDBACK

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March 2012

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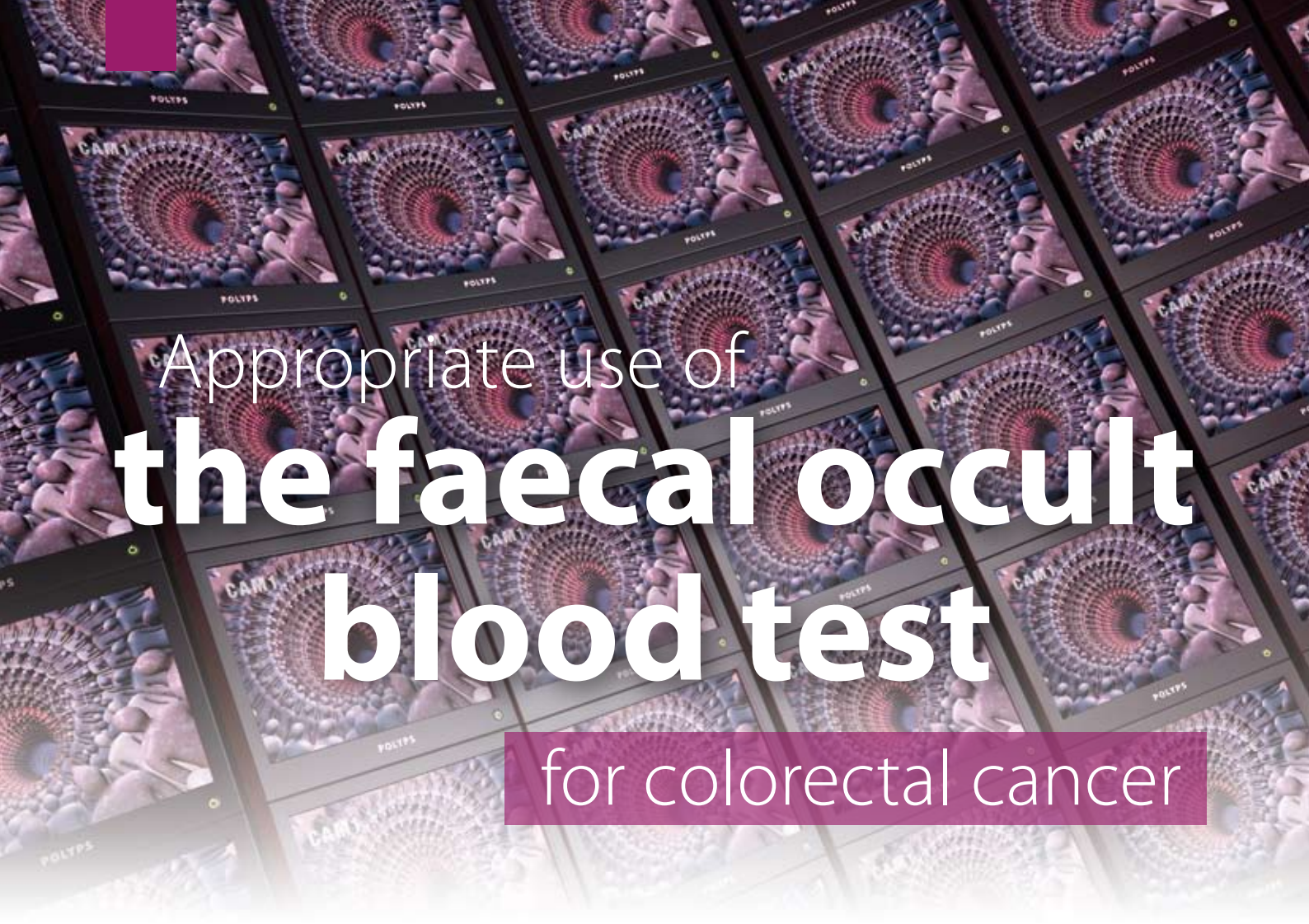


Appropriate use of the faecal occult blood test for colorectal cancer

What is a faecal occult blood test?

A faecal occult blood test (FOBT) detects the presence of haemoglobin in the faeces, which may indicate colorectal adenomas or cancers.

There are two types of FOBT; gFOBT which involves the use of a guaiac impregnated card and iFOBT in which haemoglobin is detected immunologically. The relative sensitivity of these tests is influenced by the amount of haemoglobin present in the faeces.

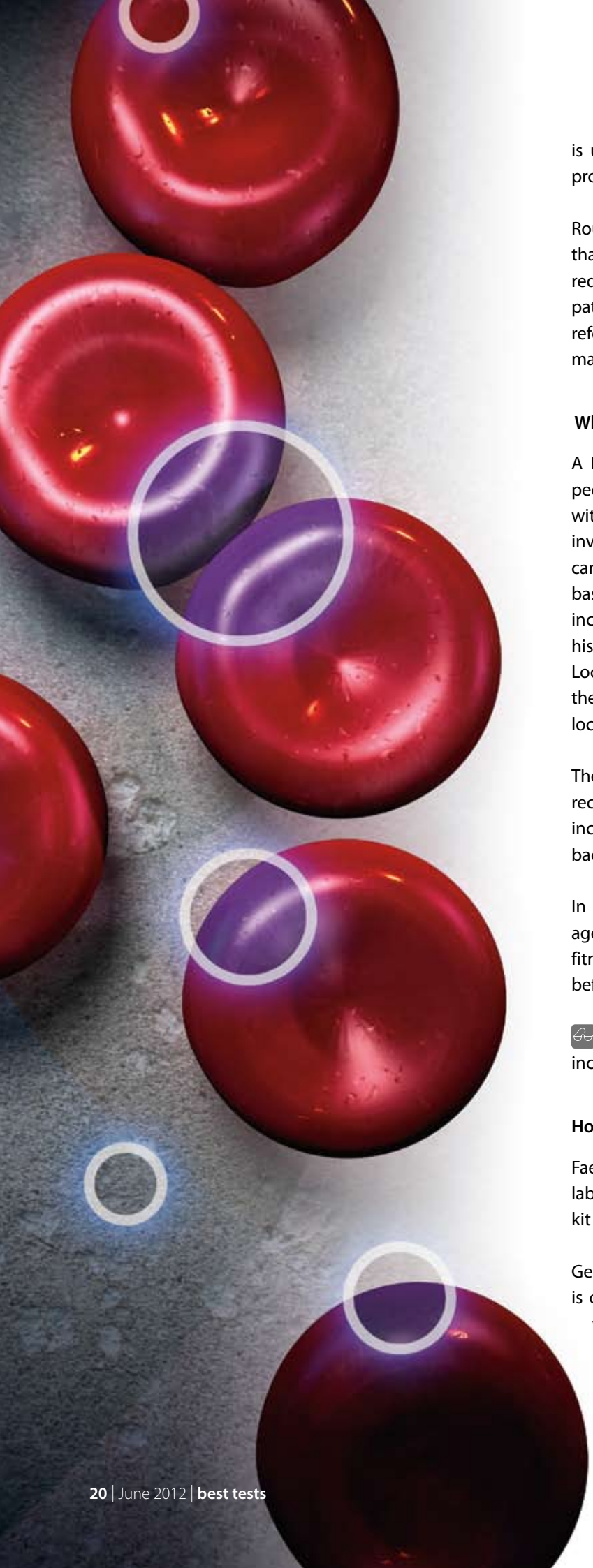
In New Zealand, laboratories use either gFOBT, iFOBT or gFOBT in conjunction with iFOBT as a confirmatory test. Laboratories using gFOBT alone may require the patient to undertake dietary restrictions two days prior to testing. This should be discussed with individual laboratories. It is not necessary to specify the type of test when requesting a FOBT.

Are faecal occult blood tests effective?

There is evidence that FOBT is an effective method for screening for colorectal cancer. A 2007 Cochrane meta-analysis found that iFOBT or gFOBT screening in people aged 45 to 75 years prevents approximately one in six deaths due to colorectal cancer.[1] However, approximately 80% of positive FOBT results are false-positives as there are many other causes for gastrointestinal bleeding, such as haemorrhoids or anal fissures. This can lead to anxiety and potentially unnecessary invasive procedures, e.g. colonoscopy.[1]

When should a faecal occult blood test be requested?

There is currently no national FOBT screening programme for colorectal cancer in New Zealand, however, a four year pilot in the Waitemata District Health Board region



is underway. This will determine if a national screening programme is appropriate for New Zealand.

Routine use of FOBT is not recommended, until such a time that a screening programme is established. The decision to request a FOBT should be made on an individual basis in patients aged over 50 years, whose risk does not indicate referral for colonoscopy, based on colorectal cancer management guidelines.[2]

When is a faecal occult blood test not appropriate?

A FOBT is not recommended as a surveillance tool for people at increased risk of colorectal cancer or for people with a previous history of colorectal cancer, or as an investigation tool for people with symptoms of colorectal cancer. Symptomatic people should be referred on the basis of risk, symptoms and clinical examination. People at increased risk of colorectal cancer, or who have a previous history of colorectal cancer require regular colonoscopy.[2] Local resourcing of colonoscopy services may influence the pathway of evaluation. This should be discussed with local DHBs.

The use of FOBT in people aged under 50 years is not recommended. The proportion of false-positive results increases significantly in this age group, because the background rates of colorectal cancer are lower.

In people aged over 50 years, factors such as advanced age, co-morbidities, reduced life expectancy or reduced fitness for invasive procedures should be considered before requesting a FOBT.

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

How is the sample collected?

Faecal sample collection methods vary depending on the laboratory and whether or not a purpose-made collection kit is used. Check with your local laboratory.

Generally, a sample from two or three bowel movements is collected by the patient with a spatula, brush or cloth which is then stored in separate specimen containers, or applied to the cardboard patches of a kit. The sample should then be delivered to the laboratory as soon as practically possible.

How should the results of a faecal occult blood test be managed?

A positive result

A patient with a positive FOBT result requires further investigation, including clinical examination for benign causes of bleeding, and is likely to require referral for a colonoscopy. There is no need to repeat the FOBT.

A negative result

A negative result does not guarantee that an adenoma or cancer is absent, as the lesions may not be bleeding or the bleeding may be intermittent. The FOBT does not need to be repeated, but the patient should be instructed to report any persistent change in bowel symptoms.

All patients, regardless of FOBT results, should be encouraged to make healthy lifestyle choices including; avoiding excessive consumption of red and processed meats, high-fat dairy products and highly refined grains, starches and sugars, maintaining a healthy body weight, undertaking regular exercise, not smoking and drinking less than two standard units of alcohol per day.

References

1. Hewitson P, Glasziou P, Irwig L, et al. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev 2007;(1):CD001216.

2. New Zealand Guidelines Group (NZGG). Guidance on surveillance for people at increased risk of colorectal cancer. Wellington: NZGG; 2012. Available from: www.nzgg.org.nz (Accessed Jun, 2012).

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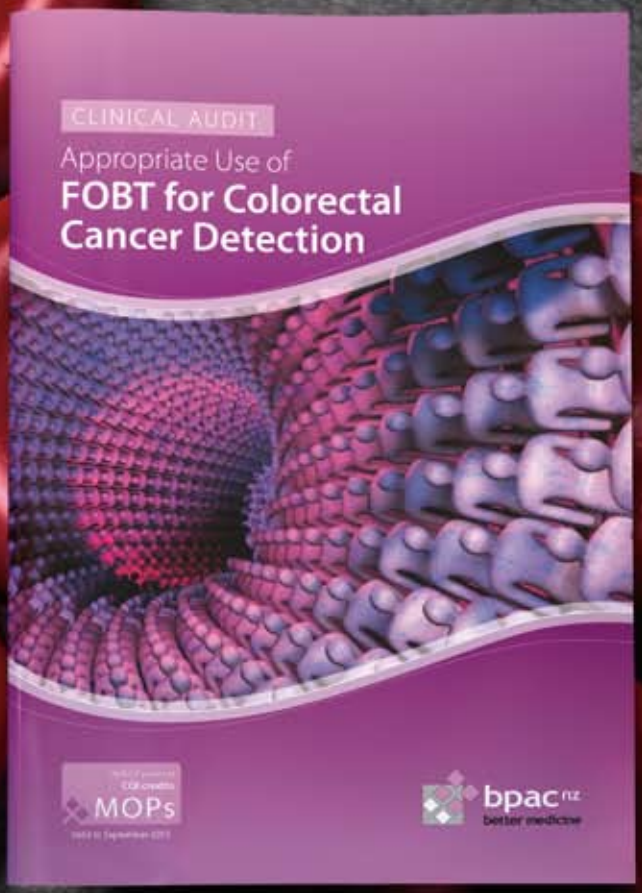

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