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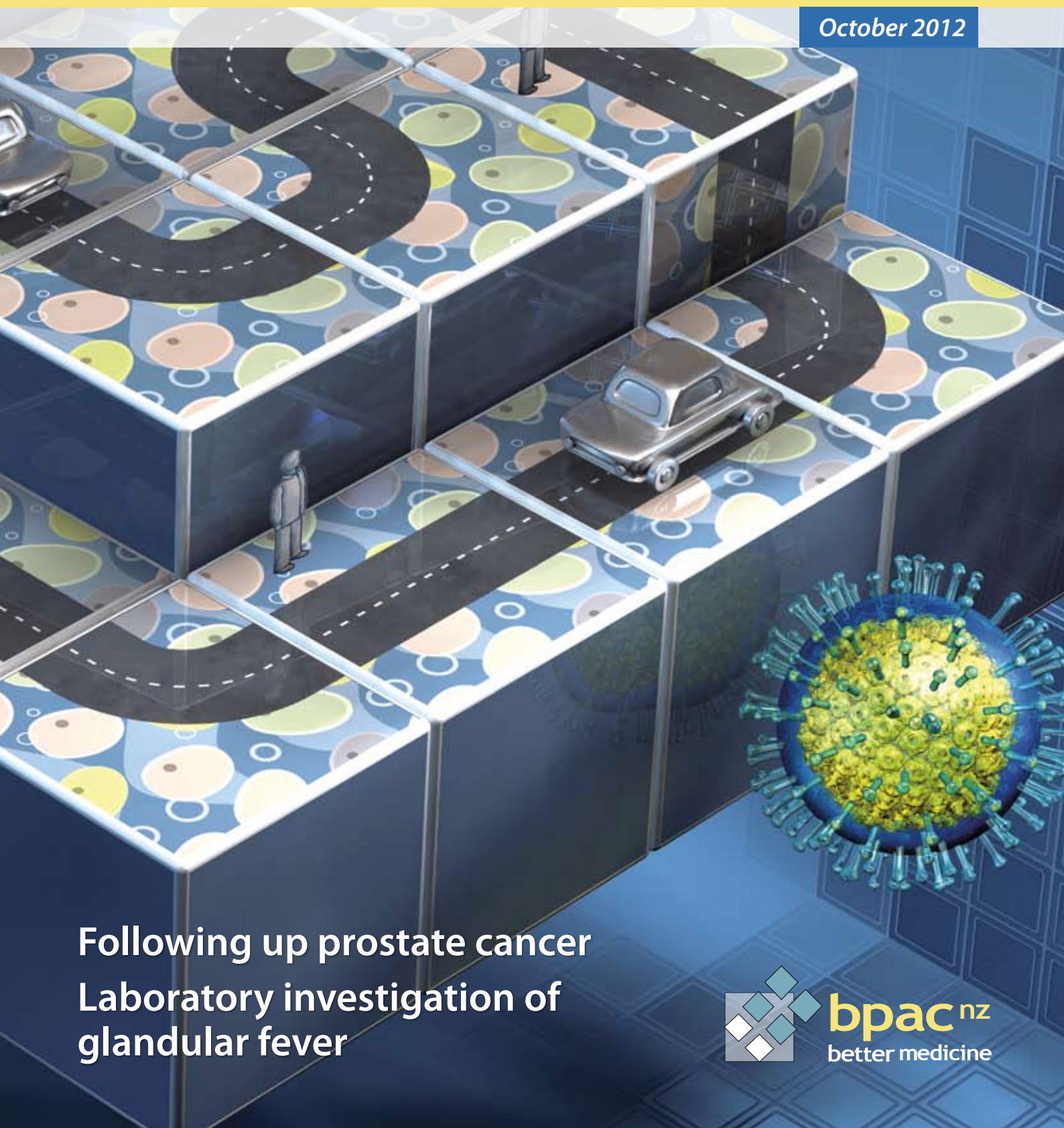

Following up prostate cancer

Laboratory investigation of glandular fever

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A new model for Cancer Care in New Zealand

An ageing population, earlier diagnosis and advances in oncology treatment are contributing to a rising number of cancer survivors in New Zealand.* This is placing an unsustainable pressure on oncology services, which has led to the announcement of a new national framework for managing people with cancer. The new model of care focuses on a wider level of involvement in cancer care, for a more diverse range of clinicians, using a tiered approach to treatment, based on patient needs. It is likely that primary care clinicians will play a significant role in this new framework, which is to be implemented within the next three to five years.

The changing face of cancer care

Cancer care centres in New Zealand are under pressure due to limited resources and the increasing need for their services. Over the next 15 years it is predicted this demand will increase significantly.[1] Despite a decrease in age-standardised cancer incidence rates, the need for cancer services is increasing due to an ageing population, earlier diagnosis, improved survival rates and the availability of newer, more targeted chemotherapy medicines. Two-thirds of people diagnosed with cancer can now expect to live beyond five years, and 80% of people with prostate and breast cancer will be long-term survivors.[2] The result is that more people are living with a diagnosis of cancer and requiring ongoing treatment, surveillance and support.

Medical Oncology National Implementation Plan

To ease the burden on oncology services, and ensure that services are sustainable for the future, a plan has been devised to set a new national framework for managing cancer treatment and follow-up.[3] The plan is to be implemented over the next three to five years.

The plan is separated into three main activities:

1. Devise a four-level service centre model, i.e. set up a system where patients can be directed to one of four types of cancer care service, depending on the complexity of their treatment
2. Establish the workforce needs, i.e. determine the requirements for staffing of the cancer service centres, which will involve oncologists, other clinical and non-clinical roles
3. Define a framework for assessing cancer treatment needs, i.e. formulate a consistent approach to directing patients to the appropriate level of cancer service centre, based on tumour type

Establishing the workforce

In the next 12 months, work will be undertaken on identifying cancer care services that can be devolved

* Survivorship is the term widely used to refer to the period after a patient has completed their cancer treatment, until either recurrence of the cancer or death.

to other clinicians (i.e. non-oncologists). This means defining the scope of practice, training and qualification requirements of the clinicians involved, as well as establishing support and supervisory systems. It is hoped that these clinical roles will be implemented in 2013/14.

A tumour specific approach

The five most common cancers in New Zealand (colorectal, breast, prostate, melanoma and lung) account for 90% of cancer treatment volumes, and an estimated 70% of oncology treatments are considered routine.[3] In order to stratify cancer treatment from routine to complex, eight tumour types have been identified. The treatment that a patient with cancer receives, and therefore the place that this treatment is undertaken, will be determined by nationally consistent protocols, based on tumour type.

Cancer service centres

It is proposed that four levels of cancer care service centres are established, to meet the differing treatment needs of patients. General Practitioners and other primary care clinicians are most likely to be involved in Level 1 and 2 centres.

Level 1 cancer care service centres will offer non-complex, low-risk, day-based chemotherapy treatment, as well as education and support for patients and their families/whānau, and follow-up services. In some cases, it is possible that these centres would be part of an integrated general practice clinic, with General Practitioners and nurses involved in provision of treatment and follow-up management. Clinicians would receive appropriate post-graduate theoretical and practical training in order to deliver these services.

Level 2 cancer care service centres will offer all the Level 1 services, plus outpatient clinic care by Senior Medical Officers and Medical Oncologists. In addition, a complex needs co-ordinator will provide support for primary care clinicians caring for patients with cancer.

Level 3 and 4 cancer care services centres provide more complex day-treatment and inpatient (hospital) care.

A streamlined referral process

Although not all primary care clinicians will be a part of delivering specific cancer treatments, all will continue to play a key role in surveillance and detection of cancer, and referral to cancer services.

Improved diagnosis and referral standards will lessen the workload of clinicians providing cancer care. National standards will be devised to ensure that referrals are appropriate, timely and directed to the correct pathway, and clinicians will be given guidance on what supporting information and investigations should accompany the referral.

Roles within the referral pathway will be defined, based on treatment needs. The First Specialist Assessment of patients with cancer categorised as "non-complex" or standard, may potentially be carried out by a General Practitioner or nurse (with training in oncology). Primary care clinicians may also be involved in counselling, education and pre- and post-clinic follow-up, e.g. additional investigations and referrals.

Follow-up after cancer treatment

It is anticipated that General Practitioners (with training in oncology) will have a key involvement in follow-up of patients after cancer treatment, and monitoring for recurrence or other adverse effects of treatment. Protocols will be established for delivering this care and referral pathways and additional support put in place.

Where to now?

The exact specifications of the Medical Oncology National Implementation Plan will unfold over the next 12 months and beyond. The Ministry of Health has set aside funding to support the national and regional infrastructure required to establish and deliver these services. Written communication and face-to-face meetings will take place to discuss and inform key stakeholders of the progress of the implementation plan.

In the meantime, cancer care services will continue to be delivered throughout New Zealand by the six major cancer networks, and primary care clinicians should continue to provide cancer detection, referral and follow-up support as required.

 For further information see: "Medical oncology implementation plan 2012/13", available from: **www.health.govt.nz** Keyword search: oncology

The role of primary care in the management of people with cancer

The requirements for the care of people with cancer fit well within the strengths of primary care, and have many similarities with the management of long-term conditions. A systematic review found no difference in patient wellbeing, psychological morbidity or satisfaction between primary and secondary care follow-up of people with breast cancer.[4]

Primary care practitioners are well placed to:

- Provide education and psychosocial support to patients and their families/whānau, which may include referral to community support agencies, e.g. Māori health providers, hospice care, counselling services
- Help to monitor patients' haematological and biochemical status during chemotherapy
- Manage medicines and common chemotherapy and radiotherapy adverse effects
- Perform surveillance to detect cancer recurrence, both local and metastatic
- Anticipate and manage transitions, e.g. from the curative to palliative phase

What are the specific challenges for primary care?

Continuity of care and effective communication are both critical in establishing a partnership between providers for cancer management. Care plans must be established to ensure agreed understanding of surveillance programmes for individual patients, and criteria and pathways for re-entry back into cancer care services when required.

Information technology will play an important role in managing patients with cancer within the practice. Decision support tools can improve interpretation of cancer markers, and practice based cancer registers can enable pathways of care for surveillance and follow up.

Disparities in cancer-related health outcomes already exist for Māori and people in lower socioeconomic groups.[5, 6] There is evidence that Māori males have a decreased incidence of cancer (all types), yet have increased mortality from cancer, greater than all other ethnicities in New Zealand.[7] It is important that the implementation of a new framework does not further compound the problem. Although the Medical Oncology National Implementation plan does not make specific recommendations for reducing disparities, the nationally consistent guidelines for care that will be developed and implemented have the potential to help to address this problem and ensure that the right level of treatment and follow-up is available to every patient with cancer. Primary care clinicians have an important role in ensuring that, in particular, Māori and people in lower socioeconomic groups access cancer care services and that appropriate support is provided to them and their whānau.

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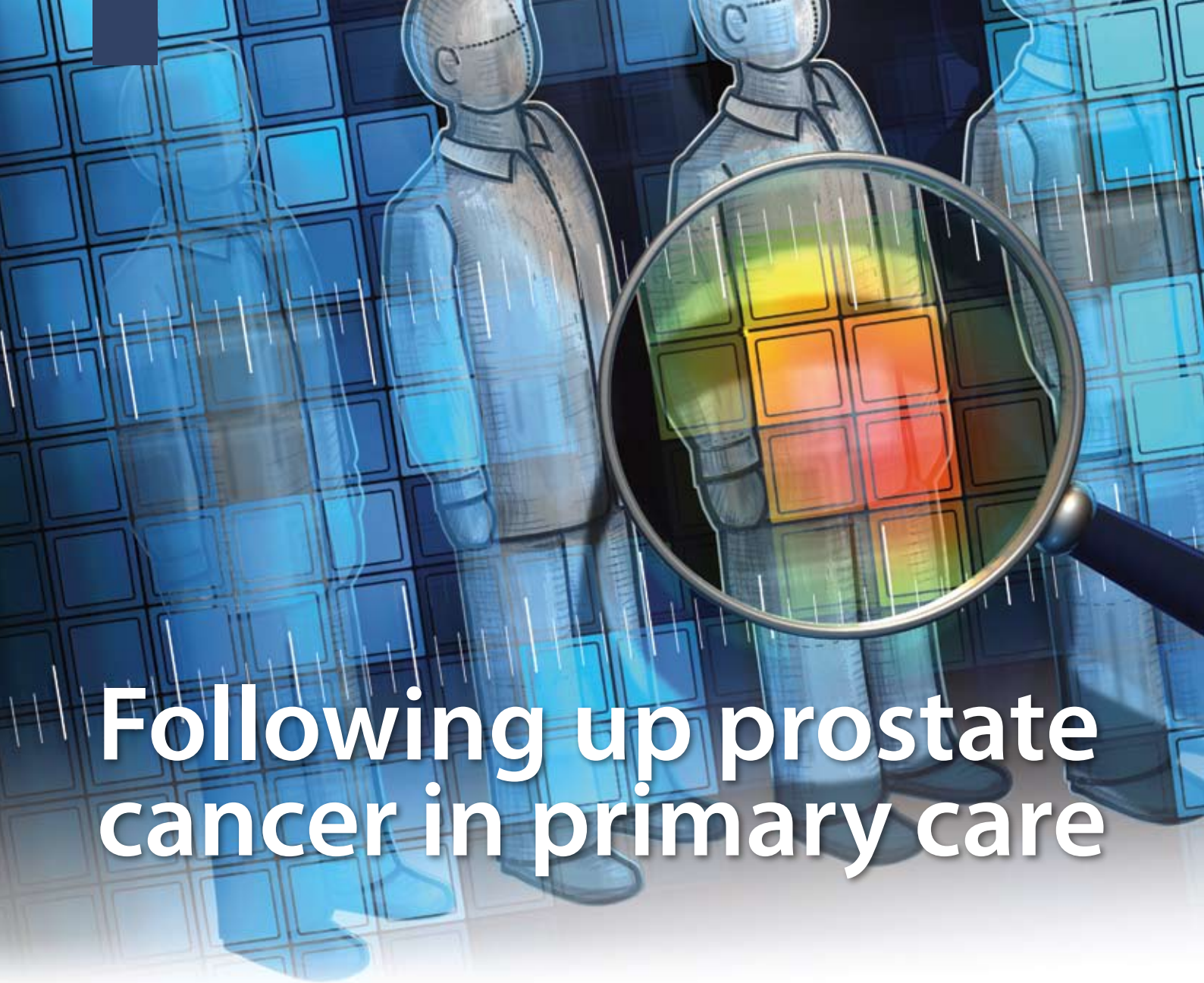

Following up prostate cancer in primary care

Cancer services in New Zealand are undergoing major changes over the next few years. Primary care clinicians are likely to have a much greater involvement in providing management for their patients with cancer, especially in regards to follow-up after cancer treatment has been completed. Many General Practitioners already manage patients after prostate cancer. We give guidance on interpreting PSA levels for surveillance, and other associated follow-up tests.

Prostate cancer is one of the most common cancers in New Zealand

In 2009, prostate cancer had the greatest incidence of all cancers in New Zealand, accounting for 16.1% of cancer registrations (30.2% of all male registrations).[1] Although prostate cancer is the third most common cause of cancer death in males, it has a favourable survival ratio: between 2004 and 2009, 91.3% of men with prostate cancer survived past five years, compared with 61.8% of people with colorectal cancer.[2]

There are a number of different options for treatment of localised prostate cancer, that vary depending on the health and age of the patient, the stage of the disease (largely determined by biopsy results and prostate-specific antigen [PSA] level), and personal preference. These options include surgery and/or radiotherapy with intent to cure, hormone treatment or monitoring for progression of disease.

The majority of men with a diagnosis of localised prostate cancer undergo definitive treatment, e.g. radical prostatectomy, external beam radiotherapy or brachytherapy (internal radiotherapy using radioactive "seeds") with intent to cure.

Follow-up treatment after definitive treatment for localised prostate cancer includes:

- Patient and family/whānau education and psychosocial support
- Clinical assessment for local or distant recurrence, primarily with PSA testing
- Ongoing assessment and treatment of adverse effects secondary to the definitive treatment, such as urinary incontinence, erectile dysfunction
- Monitoring of long-term adverse effects from the definitive treatment

Because prostate cancer is generally slow growing, some patients with low-risk localised cancer may be offered "active surveillance" through regular PSA testing and have definitive treatment only if there is evidence of progression of the cancer. Men are considered to be at low risk if they have a:[3]

- PSA level of < 10 ug/L, and
- Gleason score (histological grade) of ≤ 6, and
- Clinical stage of T1-T2a (confirmed tumour involving no more than one half of the prostate gland)

A "watchful waiting" approach may be taken in men with prostate cancer who are unsuitable for radical treatment, e.g. those with disseminated disease, co-morbidities precluding radical treatment, or older men with limited life expectancy where the cancer is unlikely to progress significantly over this time.[3] If PSA levels begin to rise rapidly, or if symptoms develop, hormonal treatment (e.g. androgen blockade) is the preferred treatment option.[3]

Androgenic hormones can stimulate prostate cancer growth, therefore androgen deprivation treatment (or androgen blockade) may also be used in various other circumstances, such as an addition to radical radiotherapy, pre- or post- surgery or as a means of treating metastatic prostate cancer.[3]

Table 1 summarises the follow-up procedures for the different treatment options for men diagnosed with localised prostate cancer.

Surveillance Tests

A rise in serum PSA is usually the only indication of a recurrence in men who have been treated for localised prostate cancer with radical prostatectomy or radiotherapy. Although the role of PSA for prostate cancer screening is not clear and often controversial, PSA is a reliable and sensitive tumour marker that increases in the majority of men with recurrent cancer. However, there is little evidence that determines the frequency that PSA should be requested after definitive treatment, and the significance and extent of the increase in the PSA level depends on the type of definitive treatment. Most clinicians are guided by the PSA velocity (the rate of the change) and the grade of the tumour rather than by absolute levels.

PSA testing intervals

Men who have undergone radical prostatectomy or radiotherapy should have their PSA level checked:[3]

- Six weeks after treatment (unless adjuvant hormonal treatment is being given)
- At least every six months for the first two years
- Then annually

Men in an active surveillance protocol should have their PSA level checked regularly, e.g. every six months, however, the PSA velocity should be used to guide the frequency of testing.

Men who adopt a watchful waiting approach (no intention to cure) should have their PSA measured at least annually, as guided by the velocity of change.[3]

The significance of an increase in PSA

An increasing PSA level after treatment is regarded as a biochemical recurrence of cancer. Regardless of the initial treatment, it is estimated that one-third to one-half of patients will have a biochemical recurrence.[5] The significance of this recurrence, however, is not always clear, e.g. it does not necessarily indicate metastatic disease, which is estimated to occur in less than one-third of patients that have rising PSA levels after radical prostatectomy.[5]

Velocity and the PSA doubling time are used to guide further investigation and treatment during monitoring. Velocity refers to the rate of change over time between

PSA measurements. The PSA doubling time is the length of time for PSA to double based on an exponential growth pattern. PSA doubling time has been shown to be a strong predictor of clinical progression and cancer mortality.[5] A man with a PSA level that has doubled slowly, e.g. over 12 months, is more likely to have local recurrence and a less aggressive tumour than a man with a PSA doubling time of less than six months.[5, 6]

The measurement and use of PSA velocity and doubling time to guide management has been described as "an art, not a science" because the ideal number of times that PSA should be tested and the time period between these tests has not been determined.[6] NICE guidelines (United Kingdom) recommend that a minimum of three PSA measurements be carried out over a least a six-month period to estimate the PSA doubling time.[3]

Rises in PSA level must also be interpreted in the context of the specific treatment received. During a radical prostatectomy, almost all the prostate tissue is removed and PSA should become undetectable within three to six weeks. PSA levels > 0.2 ug/L (or > 0.05 ug/L if an ultrasensitive PSA assay is used) after this time, would indicate that there may be residual or recurrent cancer, and this should be discussed with an urologist.[5, 7]

Table1: Summary guideline for primary care follow-up in men following diagnosis of localised prostate cancer[3]

Treatment	Follow-up testing frequency	Comments
Watchful waiting	■ PSA testing at least annually ■ Clinical assessment	DRE is not recommended if the PSA level remains at baseline levels
Active surveillance	■ PSA testing	Frequency of PSA testing is not clear. Three to six monthly testing may be appropriate but testing should be guided by the rate of change (velocity). DRE is not recommended if the PSA level remains at baseline levels although some guidelines recommend 6 –12 monthly DRE[4]
Radical prostatectomy or radiotherapy	■ PSA testing starting from six weeks at the earliest, and at least every six months for the first two years, and then annually ■ Clinical assessment	DRE is not usually indicated if the PSA remains undetectable as it is unlikely to change the clinical outcome, however, DRE can be of value in detecting local relapse particularly in people with high grade tumours where PSA may be misleading NICE guidelines recommend sigmoidscopy to check for colorectal cancer every five years for men who have received radical radiotherapy, however, this should be determined on an individual patient basis
Hormonal treatment	■ Baseline DEXA scan and then follow-up DEXA scan at 12 months or earlier (six months) if appropriate ■ Reassess cardiovascular risk, e.g. lipids and HbA_{1c}	DEXA scans are indicated for men treated with androgen blockade

DRE = Digital rectal examination PSA = Prostate specific antigen

The fall in PSA levels after radical radiotherapy is much slower, and may take 18 months to four years to reach the lowest point. An increase in PSA level of > 2 ug/L (or > 0.05 ug/L if ultrasensitive assay is used) after radical radiotherapy, warrants discussion with a radiation oncologist, but this can generally only be assessed two to three years after treatment.[5, 7] A further complicating factor is the PSA bounce phenomenon, which is a benign rise in PSA levels in some patients after radiotherapy (most commonly brachytherapy) due to apoptosis (cell death). This tends to resolve spontaneously within 12 months.[8]

N.B. 5α-reductase inhibitors such as finasteride and dutasteride lower PSA levels by approximately 50%. PSA results should be doubled to get an indication of the patient's true PSA level, if they have been using these medicines.[5, 7]

The Memorial Sloan-Kettering Cancer Centre has an online nomogram to calculate PSA doubling times, see: **http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx**

Clinical assessment

A clinical assessment should include history and examination to check:

- Adverse effects of treatments such as urinary and sexual dysfunction after radical prostatectomy and bowel problems after radiotherapy
- Symptoms that might suggest local recurrence, although usually men are initially asymptomatic and any recurrence is likely to be first detected by an increase in PSA
- Symptoms that may suggest metastatic spread such as bone pain or weight loss
- Psychosocial aspects

Guidelines vary in their recommendations as to whether a digital rectal examination (DRE) should be part of routine follow-up.[9] After radical prostatectomy, DRE is not particularly useful as early local recurrence is not usually able to be felt. A DRE should detect an empty prostatic fossa. After radical radiotherapy, the scar tissue that remains may not be able to be distinguished on DRE from areas that may have residual or recurrent cancer. DRE is therefore of limited clinical value and clinicians usually rely on the PSA level for monitoring recurrence. The exception is in patients with high grade prostate cancers (e.g. Gleason 9 or 10) as the PSA level in these patients may not be representative of the clinical situation.[9]

Associated Tests

Patients should be referred for an isotope bone scan if symptoms and rising PSA trends are suggestive of metastatic disease.[3]

Men who report lower gastrointestinal tract symptoms after radiotherapy should be investigated due to the risk of radiation-induced enteropathy or secondary malignancies. The NICE guidelines recommend flexible sigmoidoscopy every five years for men who have previously received radical radiotherapy.[3]

There are no consistent guidelines in relation to bone mineral density scanning for men using androgen deprivation therapy. A baseline DEXA scan should be performed. In general, the follow-up DEXA scan should occur at 12 months, or earlier (six months) if the baseline DEXA scan suggests pre-existing osteopenia or a borderline result.[10]

STOP PRESS: Prostate Cancer Taskforce release working document

The Prostate Cancer Taskforce, commissioned by the Ministry of Health, has developed recommendations for the diagnosis and management of prostate cancer in men in New Zealand. This document has now been released to the health sector for further consultation. The Taskforce recommends that General Practice has a central role in providing information about PSA testing, and supporting men after an initial diagnosis of prostate cancer, and through subsequent treatment. There is a strong focus throughout the recommendations on achieving equity for Māori in the rate of prostate cancer testing and treatment.

The consultation document is currently available on the RNZCGP website (members only section): w**ww.rnzcgp.org.nz/consultation-requests-2**

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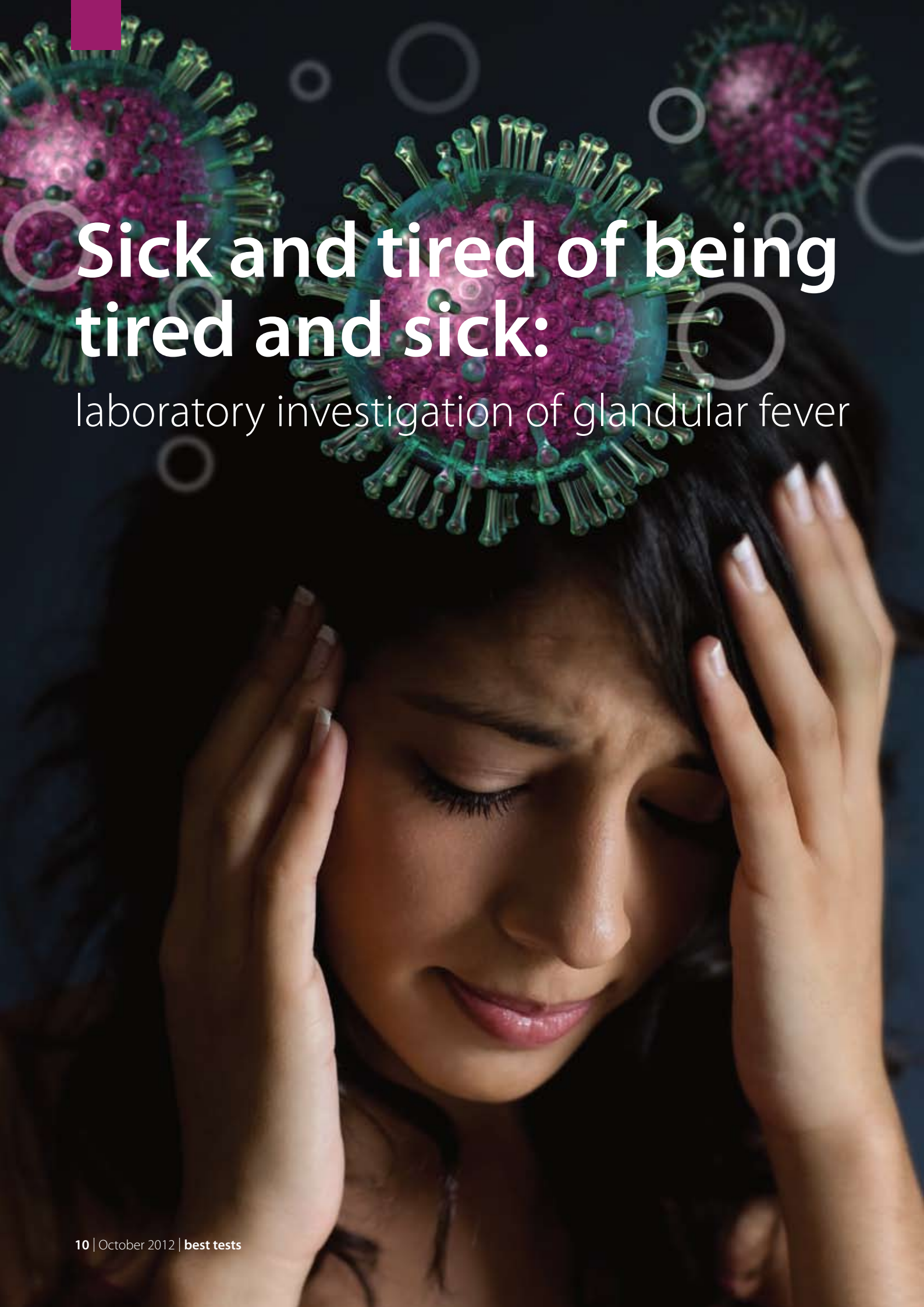
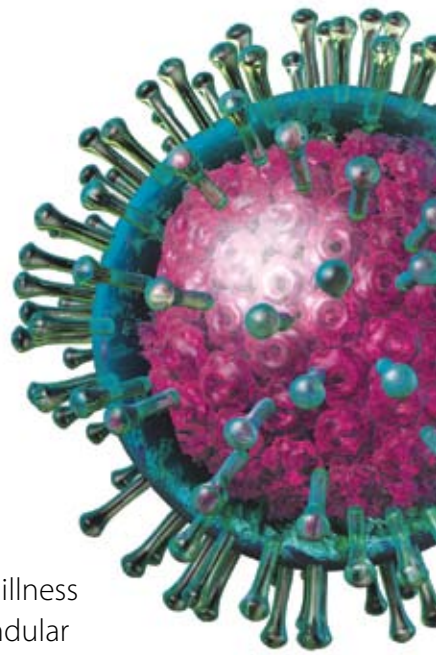
Sick and tired of being tired and sick:

laboratory investigation of glandular fever





Glandular fever (infectious mononucleosis) is a common, potentially debilitating illness that is most frequently seen in adolescents and young adults. A diagnosis of glandular fever can usually be made clinically, but laboratory testing is indicated if the clinical picture is unclear or where the risks of morbidity are high. The most appropriate testing regimen is dependent on age, history and symptoms.

The natural history of glandular fever

Infectious mononucleosis, commonly referred to as glandular fever, is a clinical syndrome comprising fever, pharyngitis and lymphadenopathy associated with atypical lymphocytosis. Acute Epstein-Barr virus (EBV) infection causes heterophile antibody positive infectious mononucleosis and accounts for approximately 90% of infectious mononucleosis cases.[1] Other important causes of infectious mononucleosis include cytomegalovirus, toxoplasmosis and acute HIV infection.

EBV is a member of the herpes virus family. As with other herpes viruses, EBV is a lifelong, predominantly latent and asymptomatic infection. EBV is spread primarily through saliva, which has led to glandular fever being called the "kissing disease", although droplet spread and the sharing of food and drink bottles contributes to transmission. There is no annual cycle of infection, and there is no difference in the incidence between males and females or between ethnicities.[1]

Epidemiological surveys indicate that more than 90% of adults worldwide are seropositive for EBV.[1] Approximately 50% of people contract the virus prior to age five years and have few, if any, symptoms.[1] Classic symptoms of glandular fever arise when acute EBV infection occurs in adolescents or young adults. The symptoms seen in older people may be less specific, although potentially more severe.[1]

Approximately 30 – 50% of adolescents or young adults exposed to EBV develop symptomatic glandular fever, following an incubation period of 30 – 50 days.[1] Symptoms persist for two to three months, although fatigue may be present for up to six months. An infected person sheds large numbers of viral particles for up to one year post-infection, after which time infectivity gradually declines.[1] Periodic viral shedding, and thus increased infectivity, occurs regularly throughout life, making attempts to limit the spread of glandular fever ineffective.

How to recognise glandular fever

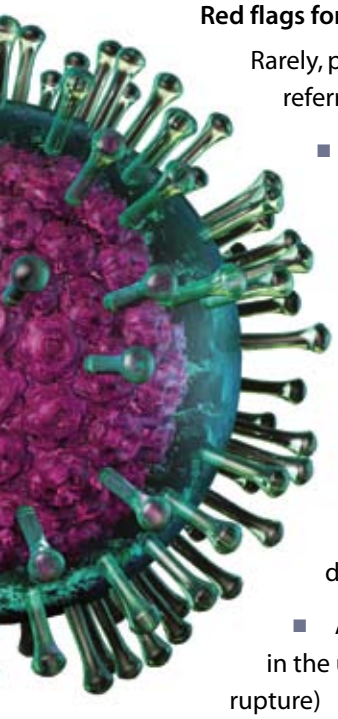
In many cases, glandular fever can be diagnosed clinically.[1] The classic symptoms are sore throat (usually with exudate), fever, enlarged cervical lymph nodes and fatigue. Headache, myalgia and chills are also common. Presentation many differ depending on the age of the patient. People aged 15 – 25 years are likely to have typical symptoms. Others have less specific symptoms; mild fever may be the only symptom in a child, and presentation of sore throat in a young child is unlikely to be glandular fever.[1] Older adults are more likely to present with abdominal discomfort and jaundice and have less obvious pharyngitis and lymphadenopathy.

On examination, signs of glandular fever include:[2]

- Lymphadenopathy – seen in almost all patients, posterior cervical lymphadenopathy is most common
- Pharyngitis – often with significant exudate and tonsil inflammation
- Fever
- Splenomegaly – detected in approximately half of patients on examination, but present in most
- Hepatomegaly –present in approximately 10 – 15% of patients, jaundice also may be present
- Palatal petechiae – also seen in streptococcal pharyngitis, but not viral pharyngitis
- Periorbital oedema
- Rash – present in less than 10% of patients, may be scarletiniform, morbilliform, urticarial or erythema multiforme-like

Recurrence of symptomatic glandular fever is unlikely

Recurrent glandular fever is unlikely.[3] Therefore, for most patients, a previous diagnosis of EBV infection will rule out glandular fever, but sometimes causes of infectious mononucleosis other than EBV should be considered. While the virus may reactivate periodically, reactivation is not associated with clinically significant symptoms except in people who are immunocompromised.[4]



Red flags for hospitalisation

Rarely, patients with glandular fever will require referral to hospital. Red flags include:

- Severe pharyngeal pain
- Excessive pharyngeal inflammation causing airway obstruction
- Insufficient fluid intake (signs of moderate to severe dehydration)
- Quinsy – inflammation of the tonsils to the extent that swallowing is not possible (can be seen on examination or if the patient is dribbling)
- Acute abdominal pain, particularly in the upper left quadrant (possible splenic rupture)

Other causes of sore throat should be considered

In some cases, glandular fever is clinically indistinguishable from other causes of sore throat. Streptococcal and viral pharyngitis should always be considered.

Viral pharyngitis is the most likely alternative diagnosis to glandular fever. The most frequent causes are adenovirus and influenza. Patients are likely to present with less severe lymphadenopathy and pharyngitis compared to those with glandular fever. Pharyngeal exudate is also likely to be less prominent. If the patient has palatal petechiae viral pharyngitis is unlikely: the patient has either glandular fever or streptococcal pharyngitis.

Streptococcal pharyngitis is more likely to be the cause of a sore throat in a younger child than glandular fever. Conversely, significant streptococcal pharyngitis rarely occurs in people aged over 15 years.[5] Streptococcal pharyngitis should be suspected in people from areas of New Zealand where there is an increased risk of rheumatic fever, and especially in those of Māori or Pacific ethnicity. It is reasonable to perform a throat swab when streptococcal pharyngitis is suspected, or consider empiric antibiotic treatment, particularly in high-risk areas.

Differentiating clinically between streptococcal pharyngitis and glandular fever is difficult. People with streptococcal infections have a reduced likelihood of hepatosplenomegaly and have less prominent fatigue compared to those with glandular fever. Lymphadenopathy in streptococcal pharyngitis is usually anterior cervical and submandibular, compared to posterior cervical for glandular fever.[2]

For further information see: "Rheumatic fever in Māori: what can we do better", BPJ 37 (Aug, 2011).

Testing for glandular fever

Laboratory investigation of glandular fever may not be necessary where the patient's clinical features suggest a diagnosis. Testing is recommended, however, wherever the clinical picture is unclear or an incorrect diagnosis has the potential to cause significant morbidity. Women who are pregnant and people who are immunocompromised should always have laboratory investigations requested, as the consequences of a missed diagnosis of acute HIV, toxoplasmosis or cytomegalovirus infection are more

Other causes of infectious mononucleosis

Acute EBV infection accounts for approximately 90% of infectious mononucleosis. Other causes should be considered when a patient, with suspected glandular fever, has an atypical presentation or risk factors for other causes are present. History, clinical presentation and, when indicated, testing may be required to help differentiate between the causes of infectious mononucleosis.

Diagnosis	Distinguishing features
Cytomegalovirus	Pharyngitis, fever, malaise, splenomegaly and lymphadenopathy. May be asymptomatic.
Acute HIV infection	Symptoms may be less specific and also include mucocutaneous ulceration, rash, headache or diarrhoea. If risk factors are present, HIV should be considered and laboratory testing arranged.
Viral hepatitis	Fever, abdominal pain, jaundice and malaise. Hepatomegaly is common. Pharyngitis, lymphadenopathy and splenomegaly are less likely.
Toxoplasmosis	Fever, lymphadenopathy and rash, but rarely pharyngitis. Transmission is usually via cat faeces or undercooked meat.
Human herpes virus-6	More common in young children (roseola, sixth disease). Fever of three to five days, widespread rash of macules and papules.

significant and may result in adverse foetal outcomes and increased morbidity and mortality.

When testing is indicated, the recommended tests are a full blood count (FBC) and a heterophile antibody test, followed by serology if the diagnosis remains unclear. Viral culture is not performed for diagnosis. (See Page 15 for specific recommendations for testing in children, older adults, women who are pregnant and people who are immunocompromised).

Start with a full blood count and a heterophile antibody test

A full blood count, when combined with findings from a clinical examination, can be highly suggestive of glandular fever.

The white blood cell count in a person with glandular fever averages between 12 – 18 x 10^9/L, with more than 50% being mononuclear lymphocytes.[1, 6] Atypical lymphocytes appear in the first week of symptomatic illness, increase to more than 20% of the total white blood cell count in the second week, and then decline over several weeks. A blood film with at least 10% atypical lymphocytes in a symptomatic person has a sensitivity of 75% and a specificity of 92% for the diagnosis of infectious mononucleosis, although not necessarily EBV infection.[1, 7] The differential diagnosis of atypical lymphocytosis includes acute viral infections, toxoplasmosis and drug hypersensitivity reactions.

Glandular fever is unlikely in a patient with a normal or reduced total white blood cells and lymphocytes, but patients who are tested within one week of symptom onset are less likely to have increased atypical lymphocytosis.

Heterophile antibody tests are used to confirm that glandular fever is due to acute EBV infection and to therefore rule out other causes of raised atypical lymphocyte counts.

Heterophile antibodies are a group of immunoglobulin M (IgM) antibodies induced by acute EBV infection that react to red blood cell antigens from other species. Heterophile

antibodies are present at clinically significant levels by the time of symptom onset and peak between two and five weeks later. Identifiable levels of heterophile antibodies may persist in a person with glandular fever for up to one year.

The presence of heterophile antibodies in a symptomatic adolescent or young adult has a sensitivity of approximately 90%, and specificity of almost 100% for glandular fever.[3] However, false-negatives occur in 25% of people early in the course of their illness (e.g. in the first week).[1] False-positives rates of 2 – 3% may be seen in patients with HIV infection, rubella, systemic lupus erythematosus and leukaemia, and older people or women who are pregnant.

Heterophile tests may be listed on laboratory request forms as Monospot, heterophile antibodies, infectious mononucleosis screen or Paul-Bunnell.

Throat swabs for pharyngitis should be taken where there is doubt about the differentiation of glandular fever from streptococcal pharyngitis. Practitioners should take into account the incidence of rheumatic fever in their area, and the likelihood of adverse sequelae of a missed diagnosis of streptococcal pharyngitis. The New Zealand sore throat guidelines state that the threshold for throat swab should be lower in a symptomatic patient with two or more of the follow features:[5]

- Māori or Pacific ethnicity
- Age 3 – 45 years (with the highest pre-test probability of a positive result in the age 3 – 14 year group)
- Living in lower socioeconomic areas of the North Island
- Past history of rheumatic fever

However, a positive result for streptococcus on a throat swab does not indicate whether there is an active infection or asymptomatic carriage, in which case glandular fever is still possible. Approximately 30% of people with primary glandular fever will have a non-symptomatic streptococcus carriage.[1]

Liver function tests are not routinely recommended as a diagnostic test for glandular fever. Tests are abnormal in more than 80% of people with glandular fever, but acute liver failure associated with EBV is very rare.[8] In addition, abnormalities in liver tests can be expected in all forms of infectious mononucleosis and in many other illnesses.

Liver tests should be considered for patients presenting with jaundice or significant hepatomegaly.[2] If measured, aspartate transaminase (AST) and alanine transaminase (ALT) levels more than ten times the upper limit of normal indicate that glandular fever is unlikely, and acute viral hepatitis should be considered.[7] Normal liver tests do not exclude glandular fever.

Where the diagnosis remains unclear, serology is recommended

If an initial FBC and heterophile tests fail to indicate glandular fever, specific EBV serology may be requested. Alternatively, FBC and heterophile tests may be repeated after seven days, followed by EBV serology if results are inconclusive.[9]

EBV serology tests provide a stage-specific diagnosis. The majority of the population is seropositive, so identifying a primary infection is important. The tests measure the activity of three kinds of antibody: viral capsid antigen (VCA) IgM and VCA IgG antibodies and anti-EB nuclear antigen (EBNA) antibodies.

VCA IgM antibodies are usually present at clinical levels from the outset of symptoms of glandular fever, and persist for two to four months before declining (Figure 1).[3] VCA IgG antibodies appear later than VCA IgM antibodies but persist for a much greater time, often for life.[3] EBNA antibodies appear six to twelve weeks after the onset of symptoms and also persist for life.[3]

The absence of EBNA antibodies indicates that the person has not had a previous glandular fever infection. VCA IgM and VCA IgG antibodies can then indicate if there is a current infection. An avidity test on the VCA IgG antibodies gives an indication of the time since infection – low avidity indicates recent infection and high avidity more than six to eight weeks since the acute infection.

The presence of EBNA antibodies indicates previous EBV infection. In a non-immunocompromised person this excludes acute EBV infection as an explanation for the current symptoms. In this case the initial diagnosis should be reconsidered, and other potential causes of infectious mononucleosis investigated.

Testing in older adults, children and people who are immunocompromised or pregnant

Specific EBV serology and FBC are recommended as the first-line tests for women who are pregnant, people who are immunocompromised, children and older people. Heterophile antibody tests are not necessary (and are also not used in children).

People who are immunocompromised and women who are pregnant should have specific EBV serology tests. It is necessary to confidently exclude other forms of infectious mononucleosis, as they are associated with adverse foetal outcomes.[1] Given the risks associated with primary cytomegalovirus and toxoplasmosis during pregnancy and the risk of mother-to-child transmission of HIV, definitive testing for other causes of infectious mononucleosis (i.e. tests for cytomegalovirus, toxoplasmosis and HIV) is also indicated in pregnant women presenting with infectious mononucleosis.[1]

Children and older adults require serology testing because heterophile antibody tests are less accurate outside of the age 12 – 25 year group. Heterophile antibody tests are likely to be falsely-negative in 50 – 75% of children, and older adults may remain reactive from a past infection or be falsely positive.[1]

The treatment of glandular fever

The management of glandular fever includes supportive treatment, identifying patients at immediate risk of complications, and education on the illness and expected symptom duration.

Women who are pregnant are not at an increased risk from glandular fever, but severe glandular fever during pregnancy may be associated with lower birth weight and pre-term delivery.[10]

Management at home

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) can be used to manage pain and fever. Consider prescribing liquid forms of these medicines to patients who are having difficulty swallowing. Corticosteroid and

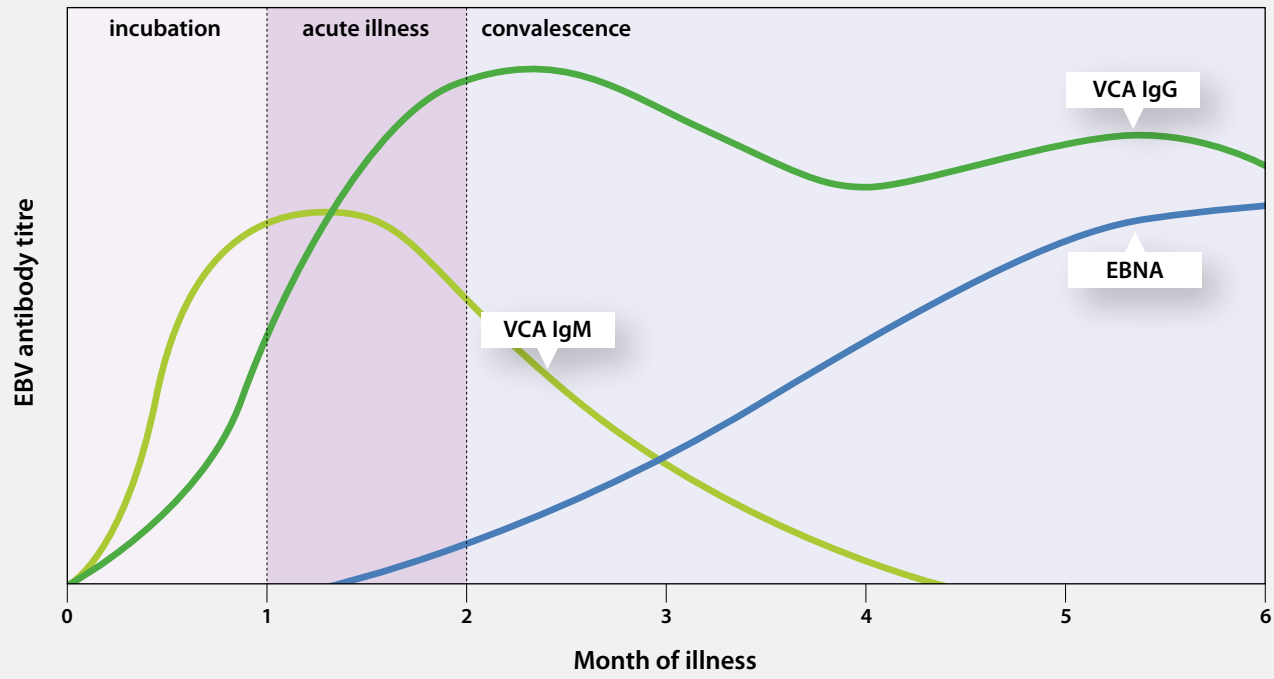


Figure 1: The antibody profile of EBV serology testing

antiviral treatment for EBV is not recommended due to a lack of evidence of clinical efficacy.[1] There is also no conclusive evidence for the effectiveness of alternative treatments such as vitamin C or B.

Adequate fluid and nutritional intake should be encouraged as anorexia and difficulty eating is present in many people with glandular fever. Alcohol consumption should be restricted.

Patients should be counselled on the likely time scale of the illness. Most symptoms will resolve within one month, but fatigue may be present for two to three months. Adequate sleep and rest is important for recovery, but complete bed rest should be discouraged. A recommendation for restriction from work or school may be considered for patients who are very unwell.

Measures or advice to limit the spread of infection are unlikely to be effective. Advice not to kiss or share food or drink bottles and to practice hand hygiene while symptomatic is sensible, but most people with glandular fever will remain contagious for at least one year following the onset of symptoms and will then become periodically re-infective throughout their lives. Usually, most people are seropositive for EBV and re-exposure does not carry a risk of symptom recurrence.

Amoxicillin may cause significant adverse effects

Amoxicillin should not be used in people with glandular fever, even where concurrent bacterial infection is suspected. Approximately 80 – 90% of people with acute EBV infection treated with amoxicillin (or ampicillin – not available in New Zealand) develop a red, diffuse maculopapular rash, similar to the morbiliform rash seen in measles infection.[2]

There is no specific guidance on how long amoxicillin should be avoided for, but most reactions occur during the acute illness phase. Patients with glandular fever treated with amoxicillin, who develop a rash, should not be recorded as having a beta-lactam allergy as this can adversely affect future antibiotic choices.

N.B. If a streptococcal infection cannot be ruled out, and empiric antibiotic treatment is indicated, penicillin V or erythromycin should be used.

Complications associated with glandular fever

The majority of people with glandular fever will have few, if any, long-term complications other than fatigue. However, glandular fever can be associated with a number of acute complications, including haematological and neurological complications, hepatitis, splenic rupture and upper airway obstruction.

Haematological complications will be present in approximately 25% – 50% of people with glandular fever, but are mild enough that they are unlikely to be apparent.[1] The most common haematological complications include haemolytic anaemia, thrombocytopenia, aplastic anaemia, purpura and haemolytic-uraemic syndrome. Neurological complications are rare, occurring in 1 – 5% of people, and urgent referral to hospital is required.[1] Neurological symptoms associated with glandular fever include facial-nerve palsy, meningocephalitis, aseptic meningitis, transverse myelitis, peripheral neuritis, cerebellitis, and optic neuritis.

Glandular fever is associated with a risk of splenic rupture

Splenic rupture is an extremely rare, but life-threatening complication of glandular fever. Patients should be advised to avoid strenuous activity and contact sport for at least three weeks after symptom onset.[1] Rupture of the spleen has been reported to occur in approximately 0.1 – 0.5% of people with glandular fever, and is not necessarily associated with trauma.[11] Risk peaks in the second to third week of the illness, but may persist for two months. Ultrasound to detect splenomegaly or the extent to which it is present, is not recommended as there is no direct relationship between the size of the spleen and the likelihood of rupture.[2]

Any patient that presents with acute abdominal pain, particularly in the upper left quadrant, within one to two months of a diagnosis of glandular fever should be referred to hospital.

Follow-up is usually not required

Most people with glandular fever make a full recovery. Fatigue sufficient to cause functional impairment will generally resolve within two to three months. Patients that display debilitating fatigue beyond this time should be assessed for other conditions such as depression, an

endocrine disorder or chronic fatigue. N.B. There is only limited evidence of a causal link between glandular fever and chronic fatigue syndrome.[12]

For further information about fatigue, see: "The laboratory investigation of tiredness", bpac[nz] (Feb, 2006).

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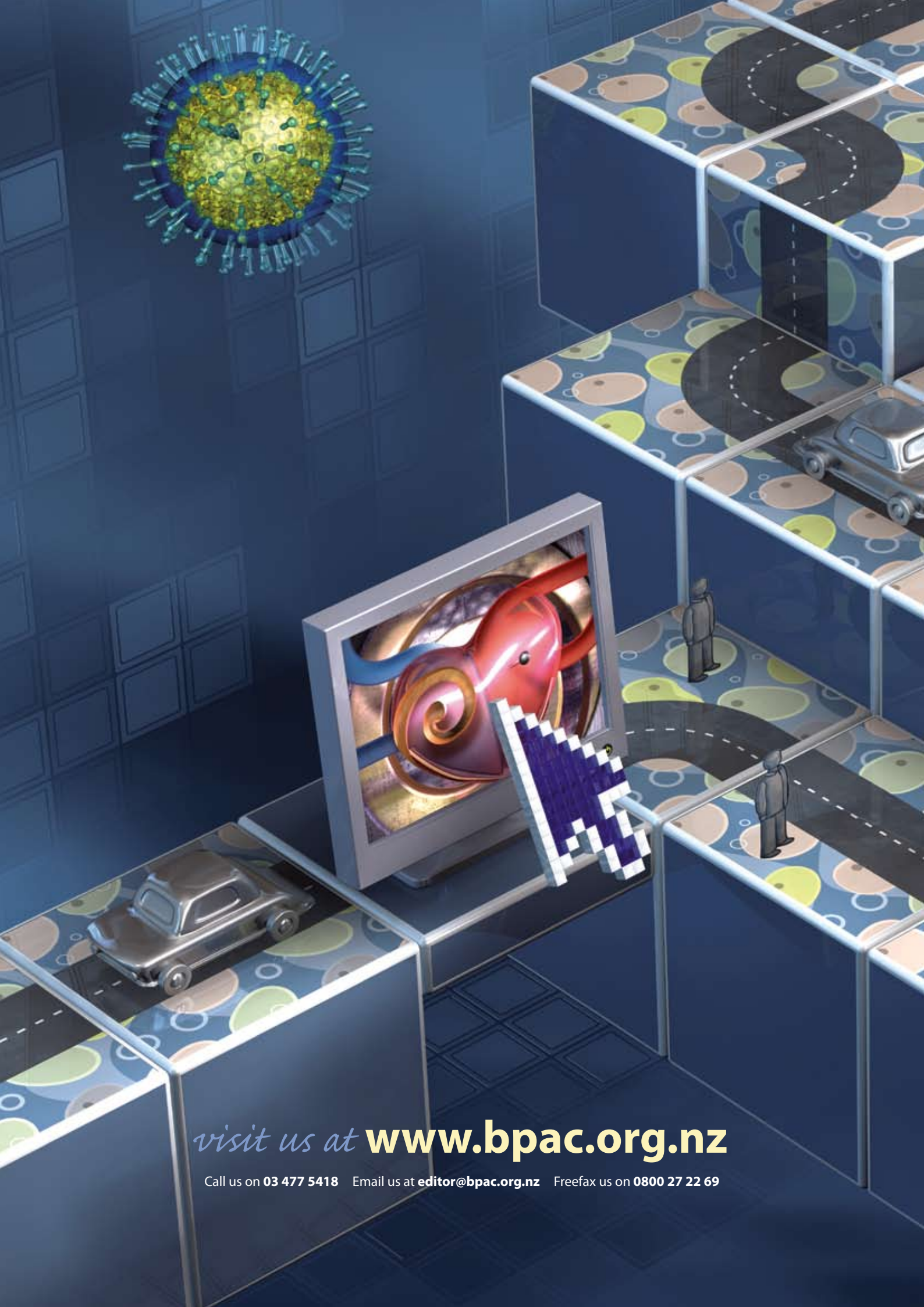

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