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Troponin
Urea
Cervical screening: Quiz feedback

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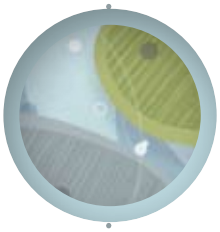

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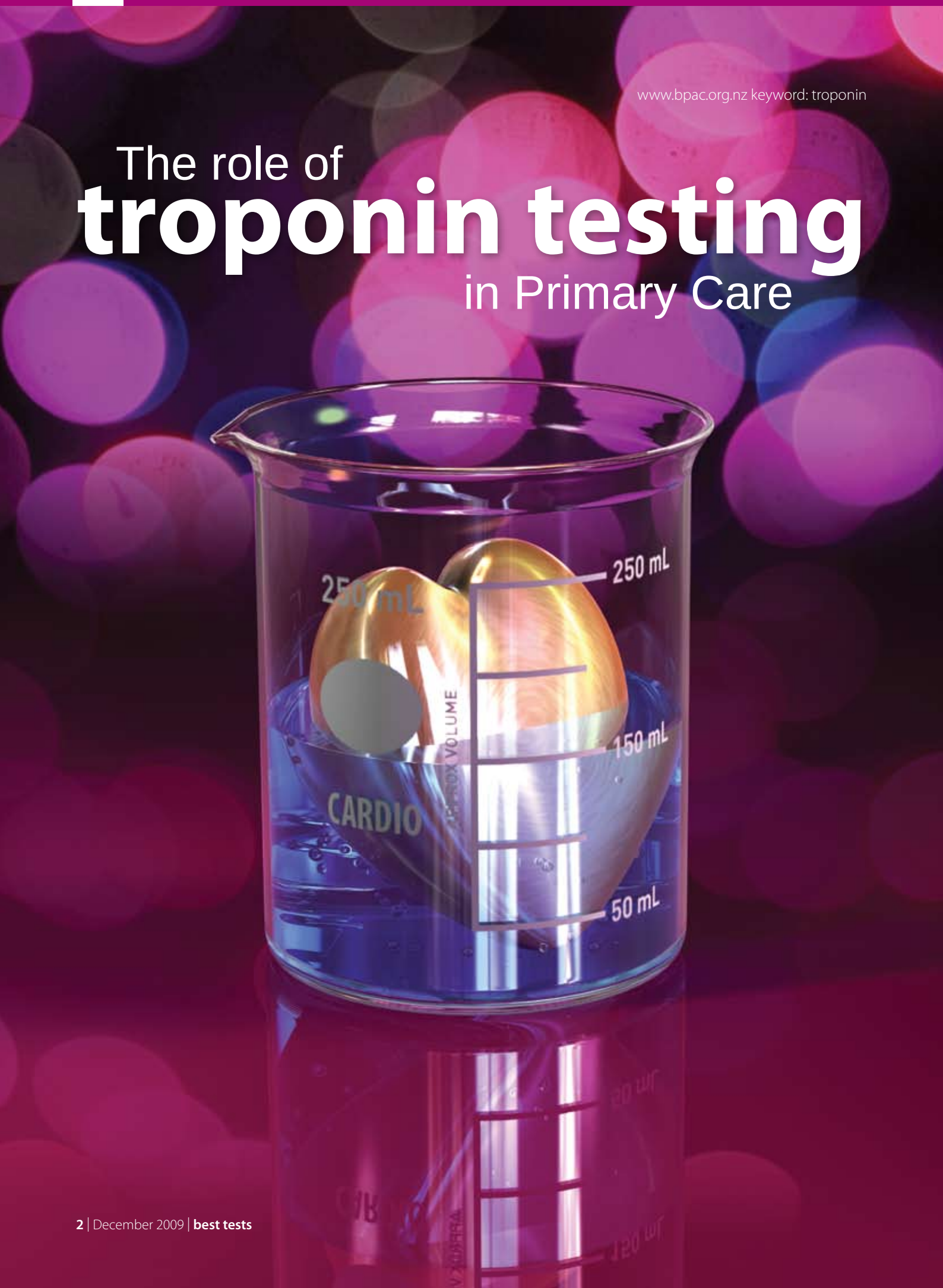
The role of troponin testing in Primary Care



Keypoints

- Where clinical suspicion of MI is high (eg typical symptoms) refer immediately: do not test troponin
- Where clinical suspicion of MI is low (eg atypical symptoms or delayed presentation): troponin may be useful
- Negative troponin from the laboratory (measured at least 10 hours from onset of symptoms) can rule out almost all myocardial events
- Positive troponin (from either a laboratory or point-of-care) is an indication for immediate referral
- Troponin has no role as a screening test for cardiovascular disease (CVD)

When is troponin useful in primary care?	
Symptoms suggestive of MI	✗ refer immediately to secondary care
As a CVD screening test	✗
Delayed presentation (typical 'Monday morning' consult)	✓
Atypical symptoms of MI	✓
No ECG changes	✓

Introduction

Troponins have overtaken the traditional 'cardiac enzymes', and can provide valuable information of the likelihood of a myocardial infarct (MI). Although troponins are recognised as having diagnostic advantages over older cardiac enzymes, it is important the test is requested appropriately. This is mainly because results are typically not useful in the first one to three hours and maximum sensitivity is not until after 10 or more hours following onset of acute MI.

Where clinical suspicion of MI is high (eg typical symptoms) refer immediately. Do not test troponins

There is almost no use for troponin in an acute presentation of possible MI in primary care. Measurements of troponin are likely to remain normal immediately after an acute MI and it takes several hours before a useful result can be obtained. Therefore, a single early negative test is not useful.

When a patient presents to primary care with acute chest pain suggestive of MI, the role of the GP is well defined. Immediate transfer to hospital/cardiac care is indicated. This should not be delayed by waiting for the troponin result.

Where clinical suspicion of MI is low (eg atypical symptoms or delayed presentation) troponin is a useful test

There are a number of situations when the GP has a less clear pathway to follow, which may include situations such as atypical symptoms, presentation several days after the onset of chest pain, or no ECG changes. For these situations, troponin may be a useful test.

A common scenario in which troponins may be useful is for patients presenting 24–72 hours after a single episode of chest pain, 'the Monday morning consult'. Measurement of troponin and an ECG will establish whether or not the chest pain was due to a MI. If there has been a MI, troponin is likely to remain elevated for up to 10 days. A positive troponin result is indication for immediate referral.

It has been estimated that approximately 20% of all MIs are unrecognised with the patient presenting with symptoms which are not initially suggestive of MI.[1,2] Atypical presentations are more common in women, people with diabetes and older people.[3] Troponins are a useful rule-out test when there is a low clinical suspicion of MI, as long as the poor sensitivity of early measurement (within the first 10 hours of the onset of symptoms) of troponin is recognised.

For patients presenting with symptoms that may be attributable to MI, but the ECG shows no ST elevation, troponin is a useful discriminatory test and has been shown to increase the proportion of patients subsequently identified with MI, and increase the accuracy of risk assessment.[4]

For patients with negative results initially, but for whom there is continuing suspicion, or there is the return of possible ischaemic symptoms, repeat testing should be considered.

A laboratory measured negative test after 10 hours effectively rules out cardiac damage.

Other causes of raised troponin level

In the presence of typical symptoms and a high suspicion of an MI, a raised troponin level confirms the diagnosis of cardiac ischaemia. However when the clinical picture is not typical, a raised troponin level is not diagnostic for ischaemic damage.

On some occasions patients may have increased troponins as a result of a process other than myocardial ischaemia leading to MI. These include severe heart failure, pulmonary embolism, myocarditis, pericarditis, cardiomyopathy, trauma and any other cause of damage to cardiac muscle.

Troponin elevations are also common in people with end-stage renal disease (where cardiac death is common), but the clinical interpretation of these results remains unclear. In patients with known renal disease who present with symptoms of MI, a single high troponin result needs to be interpreted with caution as the result could either be due to acute MI or underlying renal disease.[5]

Troponin has no role in 'screening' for CVD

Cardiologists in New Zealand have previously expressed concern[6] at the increasing use in primary care of troponin as a screening test. Some GPs are requesting troponin checks several weeks or even several months in advance. **There is no rationale for this and the practice is strongly discouraged.**

Troponin has no role as a risk marker for CVD risk assessment in primary care and there is no indication for undertaking troponin testing in asymptomatic patients. Troponin testing should be confined to symptomatic individuals only.

Laboratory versus point-of-care troponin testing

A negative troponin result is an appropriate 'rule out' test for MI, only if a laboratory method is used and if the initial symptoms occurred more than 10 hours ago. Most point-of-care methods for troponin testing do not have sufficient sensitivity to 'rule out' acute MI.

However, a positive result for troponin, whether from the laboratory or point of care, is significant, indicating myocardial damage. In the presence of typical symptoms it is strongly predictive of MI even if there are no ECG changes.

Practice tip: Can you be contacted?

Troponin is often ordered as an urgent test and may need to be acted on without delay. If ordered at the end of the day the result may only become available out of hours. This presents the laboratory with a dilemma if the referring doctor cannot be contacted easily. Best practice is to provide an out-of-hours contact, either the on call doctor or the doctor who ordered the test.

What are troponins?

Troponin is a 3-unit complex of troponin I, T and C, (T for 'tropomyosin binding', I for 'inhibitory', and C for 'calcium binding'). These are located at regular intervals along the length of actin filaments and play a key role in muscle contraction. Troponin I (TnI) and T (TnT) have cardiac specific isoforms and are used for assessing cardiac injury.[5] Apart from their proximity to each other in the troponin complex, troponin T, C and I are otherwise unrelated proteins.

Troponin testing is widely available throughout New Zealand, but there is some variation as to whether TnI or TnT is tested by individual laboratories. TnT and TnI are different tests and results cannot be used interchangeably. Different laboratories use different assays for these tests and the results between laboratories cannot be compared.

Troponins are now considered the biomarker of choice for detecting cardiac injury and have surpassed the historical 'cardiac enzymes' creatine kinase (CK), aspartate transaminase (AST) and lactate dehydrogenase (LDH), which are not specific to cardiac muscle. Testing for cardiac troponin is associated with fewer false positive and false negative results.

Serum troponin concentrations begin to rise 3–4 hours following acute MI, and remain elevated for 7–10 days for TnI and 10–14 days for TnT.[10] Results are typically not useful in the first one to three hours and maximum sensitivity is not until after 10 or more hours following onset of acute ischaemia.

The initial increase is due to troponin release from the cytoplasm, followed by the slower release of troponin from the cardiac myofilaments as they degrade. This pattern of release means that troponins can be detected in the serum for an extended period of time. See Figure 2 for a comparison of troponin release with 'traditional' cardiac enzyme release patterns.

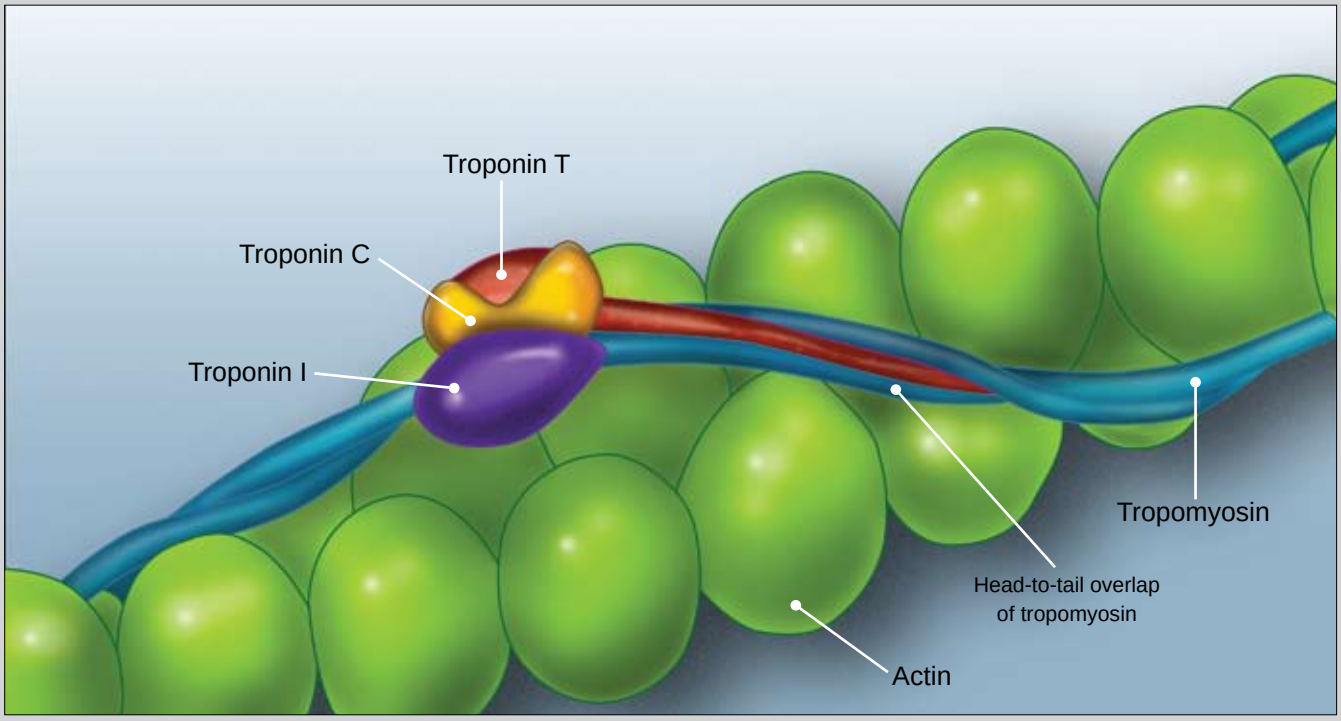


Figure 1: Troponin complex in cardiac muscle[9]

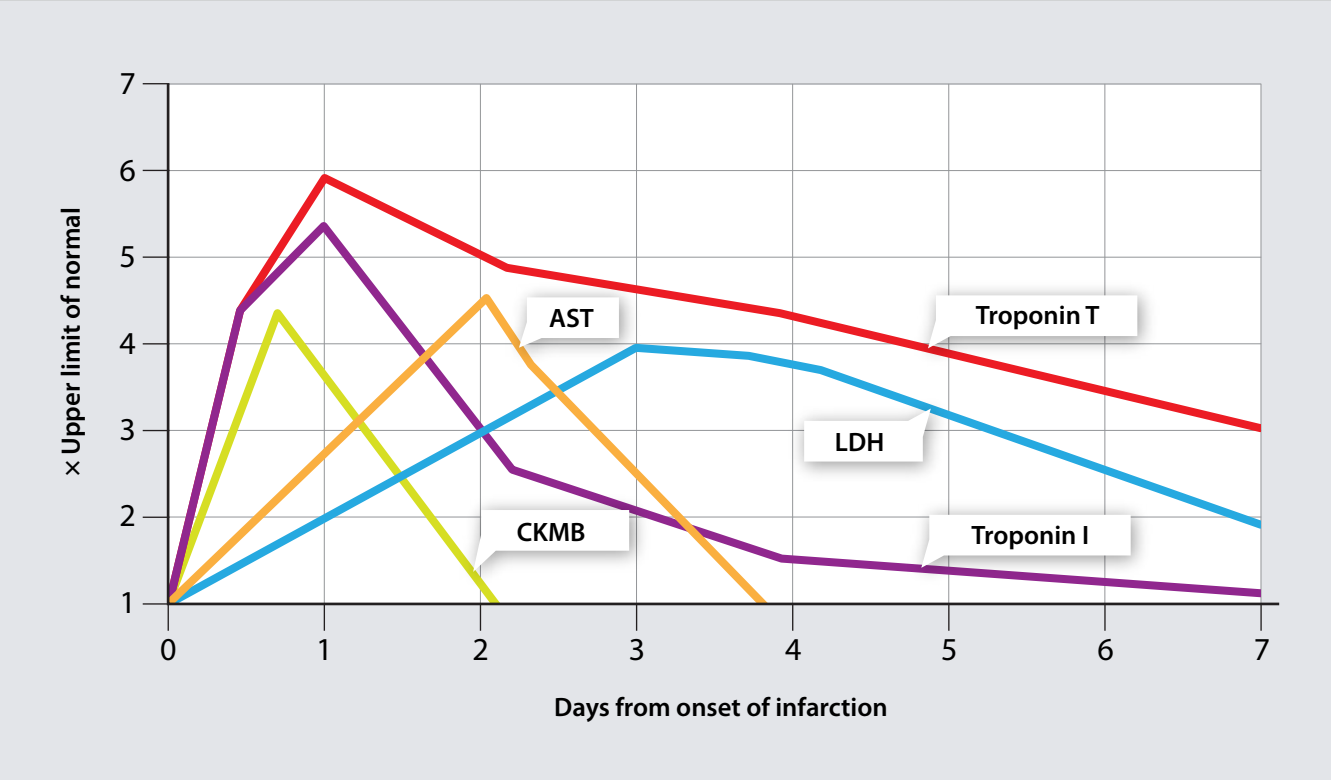


Figure 2: Temporal release patterns of troponins, CKMB, AST and LDH[11, 12]

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Should we still be measuring urea?

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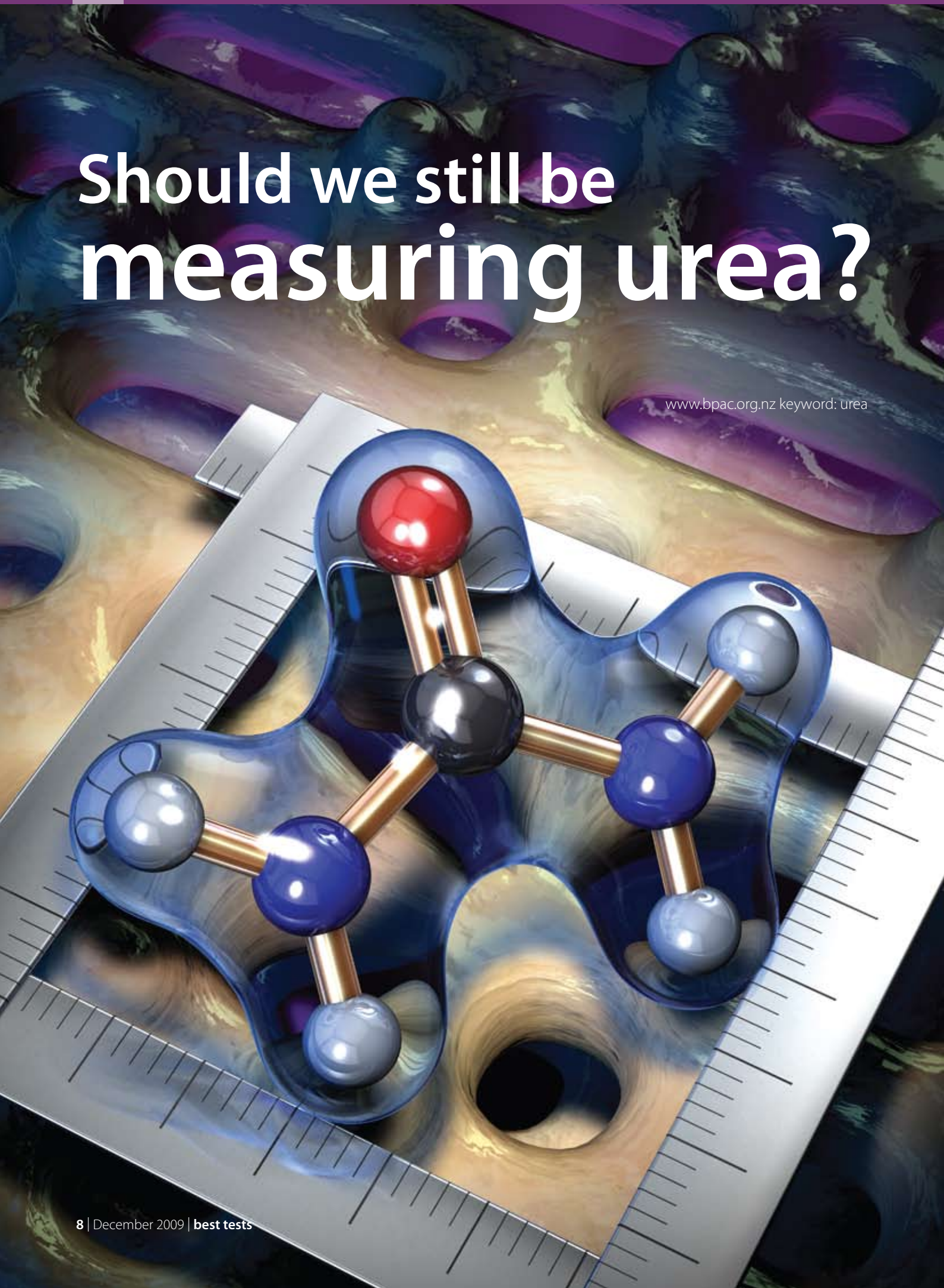


Key point:

In most situations choose eGFR or serum creatinine for assessing renal function

Over recent years the role of urea as a renal function test, has been mostly superseded by creatinine and more recently by the estimated glomerular filtration rate (eGFR). Despite urea being well recognised as less useful for routine investigation of renal function, there continues to be significant variation in the patterns of testing of urea throughout New Zealand.

Urea is a less reliable test of renal function

In the past "U&Es" (urea and electrolytes) was frequently requested for assessing renal function. Creatinine is now used in preference to urea as it has become recognised as a more constant measure of renal function (because it is an end-product of creatine metabolism in muscles). In constrast, urea is an end product of protein metabolism, therefore levels can vary for a number of reasons, see sidebar. For example, a high protein diet, tissue breakdown, major GI haemorrhage and corticosteroid therapy can lead to an increase in urea whereas a low protein diet and liver disease can lead to a reduction. Also, because 40–50% of urea filtered by the glomerulus may be reabsorbed by the tubules,[1] urea is a less useful indicator of either glomerular or tubular function

Urea is not longer indicated in most situations. Although there are some limitations with creatinine, it is considered a better measure of renal function. Furthermore, the eGFR (calculated by the laboratory) reflects renal function more accurately even when the creatinine levels are normal.

In most situations choose eGFR or serum creatinine for assessing renal function

Although creatinine is widely used as a test of renal function and is raised in chronic renal failure, it is an insensitive marker of early renal loss. In many patients with early renal dysfunction, serum levels do not increase until at least 50% of the filtration capacity is lost.

Causes of a raised urea

Pre-renal:

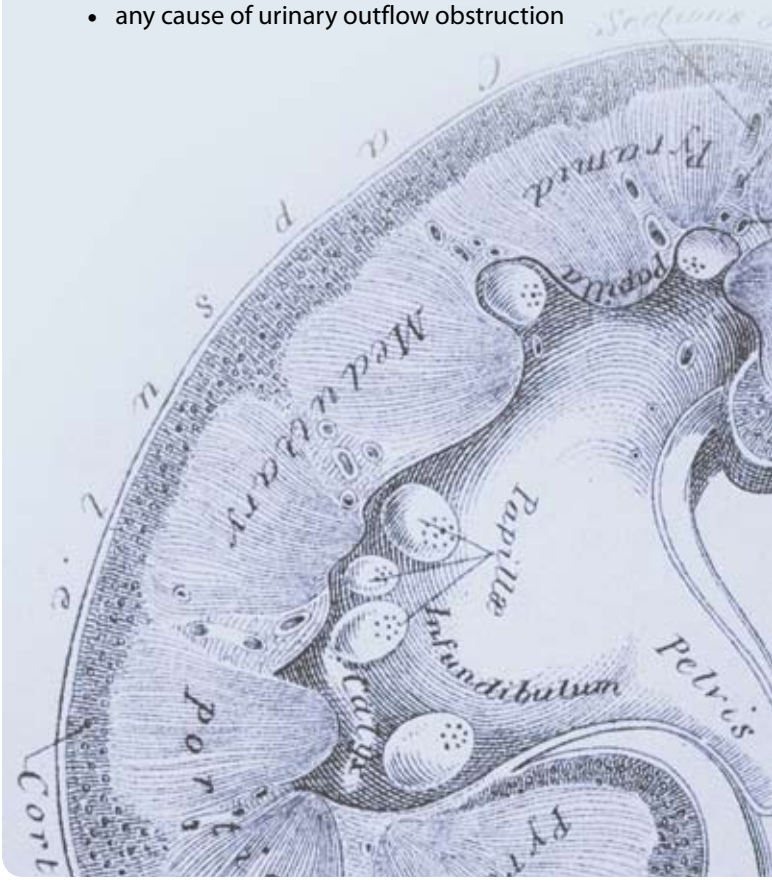
- increased hepatic production of urea:
  - high protein diet
  - gastrointestinal haemorrhage
  - increased protein catabolism – trauma, major surgery, extreme starvation with muscle breakdown
- increased renal reabsorption of urea – any cause of reduced renal perfusion, for example, congestive cardiac failure, shock, severe diarrhoea
- iatrogenic e.g. drug therapy leading to an increased production of urea – corticosteroids

Renal:

- any cause of acute or chronic renal failure

Post-renal:

- any cause of urinary outflow obstruction



eGFR has superseded creatinine measurement alone as the preferred measure of chronic renal disease because it reflects renal function more accurately even when the creatinine levels are normal. Creatinine and eGFR are recommended for screening and monitoring of patients with early loss of glomerular function.

The eGFR formula assumes a number of factors including normal diet, average weight and stable renal function, therefore it does not work in a number of situations, including:

- children under age 18
- patients with acute changes in renal function, including dialysis
- vegetarians or patients taking supplements such as creatine
- those with unusual muscle bulk, either very low (wasting diseases, amputees) or high (very obese patients or body builders)

The formula was derived in Caucasians and, while it is used for other ethnic groups, it may underestimate renal function in Māori and Pacific Island patients who have relatively higher weight and muscle bulk.

For patients on diuretics or ACE-inhibitors monitor changes in renal function with with eGFR

Any changes in renal function associated with diuretics[2] or ACE-inhibitors[3] are best monitored with eGFR (as well as electrolytes).

Confirm acute renal failure with falling eGFR or rising creatinine

If the eGFR is found to be unexpectedly low, best practice is to exclude acute renal failure by a repeat eGFR and serum creatinine. Discuss urgently with the nephrology team if acute renal failure is confirmed and there is evidence of rising blood pressure, oedema, proteinuria or haematuria.

Both urea and creatinine are increased in acute renal failure. Previously the urea:creatinine ratio was used to distinguish between pre-renal and renal causes, but this is now considered unreliable. Instead, a serum creatinine greater than 250 µmol/L is suggestive of a renal cause with 90% probability.[4]

Does urea testing have a role in Primary Care

The role of urea is limited to the following:

Urea is used for managing dialysis in end stage renal failure

Both serum urea and creatinine may be required by nephrologists for dialysis patients.

In end stage renal failure (equivalent to CKD 5), urea levels are used as a proxy measure for all the metabolites that accumulate with poor renal excretion causing the symptoms of 'uraemia'. When the decision to use peritoneal or haemo-dialysis, the prescription is adjusted on the urea levels in order to remove about two thirds of the total-body urea content during each treatment.[5]

Urea is rarely used for the assessment of hydration status

Initial assessment of dehydration is best made with clinical, rather than biochemical parameters.[6] Occasionally urea may be helpful for the assessment of dehydration in the frail elderly, when clinical indicators are less reliable.

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QUIZ FEEDBACK

Cervical Screening

Introduction

This quiz provides an opportunity to revisit the recent bpac 'best tests' that had a key focus on the adoption of liquid based cytology (LBC) and the subsequent introduction of human papillomavirus (HPV) testing.

This document provides a reminder of the advantages of using LBC, as well as the situations in which HPV will aid management. It is worth remembering that although LBC will provide some distinct advantages over conventional cytology, the biggest health gains will still be achieved by ensuring all eligible women have regular cervical smears.

The quiz feedback includes the aggregated responses from GPs that completed the quiz, comments from the GP review group and specialist commentary from Dr Peter Fitzgerald.

All general practitioners who responded to this quiz, will receive personalised feedback online and CME points. This quiz can still be completed online. Currently, there are over 30 interactive quizzes available which provide an ongoing opportunity for the accumulation of points. Visit **www.bpac.org.nz**

1.	Which of the following is true about HPV testing?		
		Your peers	GP panel
☐	HPV testing is not indicated in women under 30	91%	✓
☐	Not indicated for post menopausual women	5%	✗
☐	All LBC specimens will now also be automatically tested for HPV	9%	✗
☐	Is indicated for all women older than 30 years	17%	✗

The correct answer is that routine HPV testing is not indicated in women under 30 because of the high prevalence of HPV in this age group. However, regardless of age it may be required for the ongoing management of women who have been treated for a high-grade lesion, and for women with discordant cytology and colposcopy results. There is no indication to test all women over 30 years.

A number of respondents thought that all LBC specimens would automatically be tested for HPV. This only occurs when a woman older than 30 years is identified by the laboratory to have low grade changes in her cervical cytology.

2.	What are considered the main advantages of moving to liquid based cytology (LBC)?	Your peers	GP panel
☐	Reduction in number of unsatisfactory smears	99%	✓
☐	Quicker laboratory turnaround time	81%	✓
☐	Ability to use same sample for HPV	91%	✓
☐	Collection devices cause less trauma to the cervix	4%	✗

The main advantages of moving to LBC are:

- A reduction in number of unsatisfactory smears
- Quicker laboratory turnaround time
- The ability to use same sample for HPV

The panel felt the main practical benefit to general practice of laboratories adopting LBC, was the ability to use the same specimen for HPV testing if required. However, it was noted that the change to LBC in itself is unlikely to reduce the incidence of or mortality from cervical cancer in New Zealand. The most important factor in the short to medium term is improving screening coverage. In the long term, vaccination against HPV infection should reduce cervical cancer incidence and mortality.

3.	Which of these collection devices are recommended for use with LBC?	Your peers	GP panel
☐	Wooden spatula + cytobrush (in combination)	4%	✗
☐	Plastic spatula + cytobrush (in combination)	91%	✓
☐	Cytobrush (on its own)	11%	✗
☐	Cervibroom (on its own)	92%	✓

The plastic spatula + cytobrush (in combination) or cervibroom (on its own) are the collection devices recommended for use with LBC. Neither the cytobrush nor plastic spatula on their own are recommended and wooden spatulas are unsuitable for use with LBC. On a practical note the panel said they tended to use just the cervibroom, since it meant only one sample had to be collected.

4.	For young sexually active women, which of the following ranges best estimated the rate of acquisition of HPV infection per year?	Your peers	GP panel
☐	>80%	1%	✗
☐	60–80%	7%	✗
☐	40–60%	2%	✗
☐	20–40%	7%	✗
☐	<20%	84%	✓

HPV is one of the most common sexually transmitted infections in the world with 15–20% per year of all young sexually active women acquiring the infection per year.

5.	Which of the following is true about the LBC systems used in New Zealand?	Your peers	GP panel
☐	Is at least as sensitive as conventional cervical cytology	90%	✓
☐	Is more prone to interference from blood and cervical mucus	1%	✗
☐	Offers some advantages with recurrent inflammatory smears	91%	✓
☐	Collection devices are interchangeable between systems	5%	✗

LBC is at least as sensitive as conventional cervical cytology and offers some advantage for women with recurrent inflammatory smears. LBC can reduce the amount of obscuring blood and inflammation in cervical samples compared to conventional smears, however routine screening smears should still be avoided at the time of menses.

Note: collection devices are not interchangeable between the Surepath and Thinprep systems.

6.	Which of the following is true about collection of the specimen for cervical cytology:	Your peers	GP panel
☐	The ideal sample consists of all squamous cells	18%	✗
☐	For an abnormal looking cervix, it is important to use LBC to exclude the presence of precancerous lesions	12%	✗
☐	Cytobrush is indicated where previously no endocervical cells were obtained	90%	✓
☐	Cervibroom is indicated for post menopausal women	11%	✗

There was some concern expressed at the high proportion of respondents who answered this question incorrectly. All cervical smears should contain some endocervical cells to indicate that the squamocolumnar junction has been sampled. Squamous cell carcinoma begins as cervical intraepithelial neoplasia (CIN) at the squamocolumnar junction which is why it is important to sample this site to detect early changes. If a previous smear is reported as containing no endocervical cells, a cytobrush is recommended for the repeat smear.

It is important that if the cervix looks abnormal or there are abnormal symptoms, the women should be referred for colposcopy, irrespective of the cytology report. If the cervix looks abnormal due to known benign changes (eg nabothian cysts) referral for colposcopy may not be required.

7.	What followup is indicated for a women over 30 years found to have a low grade lesion?	Your peers	GP panel
☐	HPV testing is indicated	94%	✓
☐	Should be referred automatically for colposcopy	13%	✗
☐	Watchful waiting and retest cervical cytology in 12 months	29%	✗
☐	Confirm with conventional Pap smear	<1%	✗

Almost all respondents correctly answered that HPV testing is indicated for all women > 30 years with low grade abnormalities. This is generally initiated by the laboratory. Referral for colposcopy should be made following a positive HPV result and watchful waiting would be appropriate following a negative HPV result, with repeat HPV testing at 12 months.

8.	Which of the following areas of management are most likely to benefit from the inclusion of HPV tests?	Your peers	GP panel
☐	The triage of women 30 years and over with low grade changes	96%	✓
☐	The follow-up of women who have been treated for a high grade lesion	88%	✓
☐	Post colposcopy management of women with discordant results	89%	✓
☐	Follow-up of women under 30 years with low grade changes on first smear	8%	✗

HPV results will be of benefit when managing women who:

- Are 30 years and over with low grade changes
- have been treated for a high-grade lesion
- have discordant colposcopy and cervical cytology results

HPV testing will hopefully reduce the number of patients who receive unnecessary specialist referral and colposcopy. HPV testing is not indicated for women less than 30 years with low grade changes. Follow-up will depend on previous patient history.

More on cervical screening

Some additional questions arose out the panel discussion and these were put to cytopathologist Dr Peter Fitzgerald for his comment.

Q. Who is responsible for requesting HPV testing?

A. The laboratory is responsible for performing HPV testing in women over the age of 30 years with ASCUS/LSIL cytology. When HPV testing is used as proof of cure, the smear taker is responsible for gaining patient consent and requesting the test. And when there is discordance between laboratory results and colposcopy, the colposcopists are responsible for requesting HPV testing.

Q. How long is the LBC sample stored for, and can HPV testing be requested at a later date?

A. The vials may be used for HPV testing for several months after the sample is taken. However for most laboratories storage beyond about 4 weeks is not practical.

Q. Do the laboratories perform HPV testing if it is requested as part of an STI screen?

A. HPV is not an appropriate test for STI screening, as it is only indicated for triage in conjunction with cervical cytology. Current HPV testing in New Zealand is only designed for use within an organised cervical screening program.

Please note: We no longer send out printed personalised quiz feedback. Personalised feedback is now available from **www.bpac.org.nz**. GPs who completed this quiz will receive an email with access instructions.