best tests

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SCREENING TESTS:
Tumour Markers
PSA Screening
Bowel Cancer Screening

QUIZ FEEDBACK:
Investigating the gut

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The use of SCREENING TESTS

Key messages:

- It is important for health professionals to understand and provide advice for patients on the role of individual screening tests
- Although screening has the potential to improve quality of life, it also has the potential to cause harm
- Screening should be based on good quality evidence that can demonstrate more good than harm

GPs frequently perform tests for screening purposes, whether for formal screening programmes, such as cervical screening, or less formalised opportunistic screening such as cardiovascular risk assessment. Table 1 shows the organised and opportunistic screening currently occurring in New Zealand.[1]

GPs may be aware of the potential benefits of screening (usually perceived as the earlier detection of a pathological process whilst still treatable), however it is also important to consider the limitations of screening tests and the potential for harm associated with these tests.

Recommended criteria for screening

Although, intuitively it may appear to be a good idea to identify people early in the course of a potential disease process, screening is in fact a complex process, which requires careful consideration of a number of issues.

Formal screening programmes involve planning and co-ordination of all activities along the screening pathway, with funding to allow this to occur. Formal screening programmes involve screening entire populations, or a large easily identifiable group within the population. This is usually achieved by systematically identifying (for example, through a population register) and inviting the target population to undertake screening.

Recommended criteria for the assessment of a screening programme:[1]

- The condition is a suitable candidate for screening
- There is a suitable test available
- There is an effective and accessible treatment or intervention for the condition identified through early detection
- There is high quality evidence that a screening programme is effective in reducing mortality or morbidity
- The potential benefit of the screening test should outweigh potential harm
- The health sector should be capable of supporting diagnosis, follow-up and programme evaluation
- There is consideration of social and ethical issues
- There is consideration of cost-benefit issues

Table 1: Organised and opportunistic screening in New Zealand[1]

Type of Screening	Current Examples
Screening programmes	▪ Breast cancer screening (BreastScreen Aotearoa/BSA) ▪ Cervical screening (National Cervical Screening Programme/NCSP) ▪ Newborn baby metabolic screening for phenylketonuria, maple syrup urine disease, galactosaemia, biotinidase deficiency, congenital adrenal hyperplasia, congenital hypothyroidism, cystic fibrosis ▪ Adult Hepatitis B screening

Opportunistic screening	▪ Screening for hearing impairment at school entry
	▪ Antenatal screening:
	  ▪ anaemia
	  ▪ rhesus incompatibility (to avoid newborn haemolytic disease)
	  ▪ gestational diabetes
	  ▪ serology for syphilis, rubella, hepatitis B
	  ▪ ultrasound screening for anatomical abnormalities e.g., neural tube defects
	  ▪ risk factors for HIV
	  ▪ chromosomal abnormalities e.g., Down syndrome (nuchal translucency +/- maternal serum screening)
	▪ Newborn physical examination to screen for congenital hip dislocation, undescended testes, cardiac abnormalities, etc
	▪ Well Child screening for developmental delays
	▪ Screening for complications of diabetes (retinal, foot and kidney)
	▪ Screening for breast cancer with clinical breast examination
	▪ Mammographic breast screening outside of BSA
	▪ Diabetes screening
	▪ Colorectal cancer screening
	▪ Prostate cancer screening
	▪ Cardiovascular disease risk factor screening (smoking, serum cholesterol, hypertension)
	▪ Screening for alcohol and drug misuse among adolescents and adults
	▪ Osteoporosis risk factor screening (which may include bone mineral density scanning)
	▪ Screening for congenital hearing impairment
	▪ Chlamydia screening in young adults

Opportunistic screening has generally evolved over time in response to emerging evidence, but generally with no formal assessment, monitoring or evaluation of quality processes. Opportunistic screening may be organised to a greater or lesser degree, for example: hearing testing at school entry, and performing cardiovascular risk assessment in general practice.

Opportunistic screening is undertaken with varying evidence to support it. In some cases there may be conclusive evidence from randomised controlled trials, while some screening may be done despite inconclusive evidence of benefit. In some cases there may be practical reasons why a programme is not implemented.

Screening defined

Screening is defined by the National Health Committee (NHC) as "A health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are not affected by a disease or its complications, are asked a question or offered a test in the hope of identifying those individuals who are more likely to be helped than harmed by further tests or treatments to reduce the risk of disease or its complications."[1]

Table 2: Benefits and disadvantages of screening[1]

Benefits	Disadvantages
Improved prognosis for some cases detected by screening	Longer morbidity for cases whose prognosis is unaltered
Earlier treatment (cheaper, less radical, cures some early cases with improved quality of life)	Over-treatment of questionable abnormalities
Potential resource savings Reassurance for those with true negative test results	Resource costs False reassurance for those with false-negative results and possibility of later treatment with worse prognosis May legitimise "unhealthy lifestyle"
Wider "public good" benefits in the case of infectious diseases, due to reduced transmission Knowledge of their situation for people with true positive test results Opportunity for counselling on lifestyle	Anxiety, lingering doubts and sometimes morbidity for those with false-positive results Screening procedures are often accompanied by some discomfort, anxiety, and inconvenience for asymptomatic individuals Anxiety and risks associated with further investigations, which may be unnecessary for those with false-positive results Exacerbation of inequalities if there is unequal access to screening Costs and inconvenience incurred during investigations and treatment Hazards due to screening test, e.g. radiation

Informed consent

"There is a responsibility to ensure that those who accept (an invitation to screening) do so on the basis of informed choice, and appreciate that in accepting an invitation or participating in a programme to reduce their risk of a disease, there is a risk of an adverse outcome."[1]

In practice, it is not always easy to achieve the standard required for informed consent. The provision of information, discussion and reflection, may take considerable effort, time and skill, and many GPs are not able to easily fit this into the usual 15 minute consultation. This is where the provision of written information about testing in the form of patient information leaflets can be invaluable (e.g. pamphlets discussing the benefits and harms of PSA testing).

"For health care professionals to merely encourage patients to decide for themselves about screening tests is abjuring their duty. "[2]

Benefits and harms of screening

Although screening has the potential to improve quality of life, it also has the potential to cause harm. For this reason screening should be based on sufficient evidence that the test demonstrates more good than harm.

It is important that all people in the target population have equal access to a screening programme so that health inequalities are not exacerbated by being less accessible to groups with poorer health status. Screening providers should ensure all barriers to participation are minimised.

Limitations when interpreting screening tests

When using screening tests that are not part of formal screening programmes, it is important to consider the following concepts that may influence interpretation and subsequent treatment.

Does everyone with the disease need to be detected?

Any screening programme has the potential for over-detection and over-treatment,[3] because there is a risk that screening will detect clinically irrelevant disease e.g. many older men are shown to have low grade prostate cancer on autopsy but are unlikely to have ever been affected by it. Generally, the harder you look, the more you find.

Does screening benefit the whole population?

Screening is often more biased towards individuals who are frequently more health conscious, have less co-morbidities and comply with follow-up. As a result of this screening bias, apparent improved outcomes from screening programmes may not necessarily reflect the efficacy of screening and early treatment, but rather a healthier subset of the population.[2]

Does screening mean people live longer?

Screening may be able to detect a condition at an earlier stage than had they not been screened. Therefore a person has a longer time living with the condition. Due to this studies may report longer survival times as a result of the screening, also known as lead time bias. In reality the patient may not have an extended life, but rather their survival time was measured from an earlier starting point.[2]

What is the screening test actually detecting?

Length bias occurs because of the varying nature of diseases. For example, an indolent case of a cancer has a longer asymptomatic period than an aggressive case. Therefore, the indolent case is more susceptible to detection by screening whereas aggressive malignancies are more likely to progress from asymptomatic to being clinically symptomatic during the interval between screening tests and are therefore diagnosed upon presentation. For this reason malignancies identified during screening are less likely to be aggressive with a better prognosis.

Other screening terms

- **Prevalence:** the number of individuals in a population with the target condition
- **Sensitivity:** The sensitivity of a test is a measure of how good it is at correctly identifying people who actually have the disease
- **Specificity:** The specificity of a test is a measure of how good it is at correctly identifying people who do not have the disease
- **False positive:** Refers to a positive result in an individual who does not have the condition that the test is for
- **False negative:** Refers to a negative result in an individual who does have the condition that the test is for

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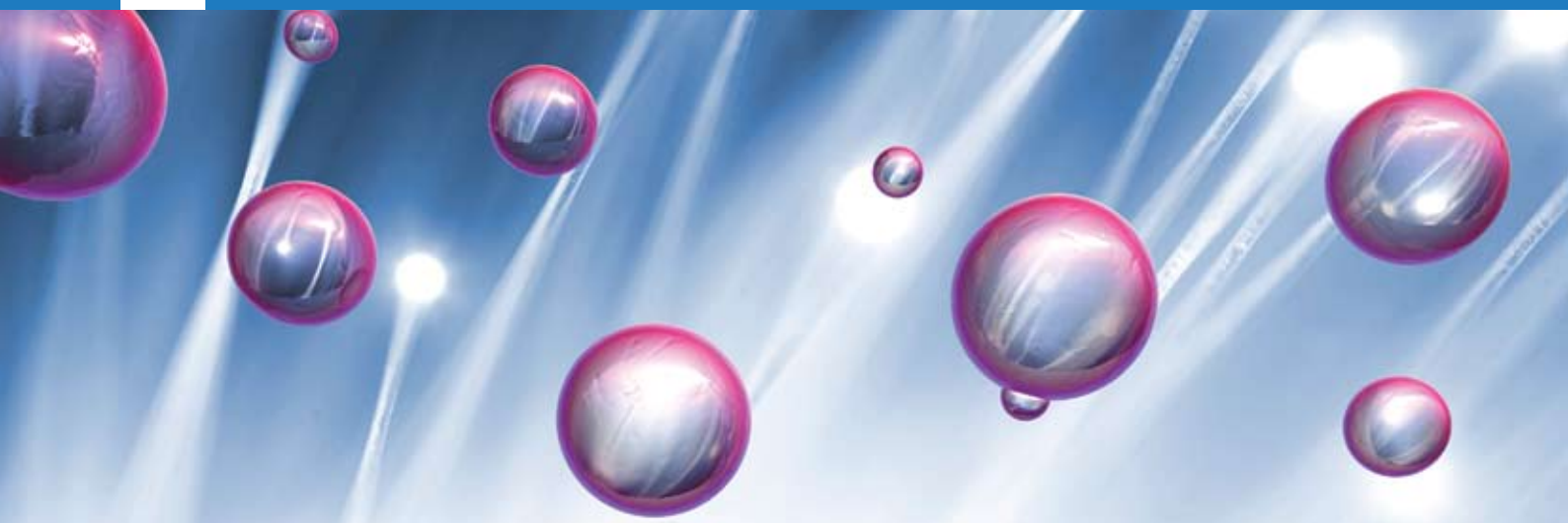


Appropriate use of **tumour markers**

www.bpac.org.nz keyword: tumour-markers

Key messages:

- Tumour markers have a limited role in primary care
- For tumour markers to provide useful information, it is important that they are requested appropriately
- Tumour markers are not indicated as screening tests in primary care
- The key role for individual tumour markers is in the management of patients with established malignancy

The term "tumour marker" embraces a spectrum of molecules with widely divergent characteristics sharing an association with the clinical detection, management, and prognosis of cancer patients.[1]

In most cases, the key role for individual tumour markers is in the management of patients with established malignancy. Nearly all markers show some correlation with the clinical course of disease, with marker elevation in any stage declining to normal after a curative intervention.

The ideal tumour marker would be a "test for cancer" that was easily and reproducibly measured, in which a positive result would occur only in patients with malignancy and quantitative levels would correlate with stage and response to treatment. Unfortunately, no tumour marker currently available meets this ideal.

Table 1 provides an overview of commonly requested tumour markers.

Table 1: Common tumour markers (adapted from[2])

Tumour Marker	Description
Alpha-fetoprotein (AFP)	May be raised in various cancers (liver, germ cell testicular cancers, bowel, stomach, lung, breast, lymphoma) as well as non-cancerous conditions (e.g. chronic hepatitis, cirrhosis)
Beta-human chorionic gonadotropin (ß-HCG)	Is produced during pregnancy but also occurs in cancers originating in the placenta (trophoblastic disease), germ cell tumours of the ovary and in men with germ cell testicular cancer.
Carbohydrate antigen 125 (CA 125)	May be raised in a variety of gynaecological conditions (e.g. menstruation, pregnancy, benign ovarian cysts, endometriosis) as well as ovarian cancer.
Carbohydrate antigen 19-9 (CA 19-9)	May be raised in cancers of the digestive tract (stomach and bowel), and particularly in pancreatic cancer.
Carbohydrate antigen 15-3 (CA 15-3)	May be raised in people with breast cancer but also in non-cancerous condition (e.g. cirrhosis, benign diseases of ovaries and breast)
Carcinoembryonic antigen (CEA)	May be raised with cancer of the colon but also in patients with other cancers (lung, breast, liver, pancreas, thyroid, stomach and ovary) or non-cancerous conditions (e.g. ulcerative colitis, smoking)
Lactate dehydrogenase (LD)	Levels can be raised for a variety of reasons where cellular destruction is present (e.g. lymphoma, pancreatitis, liver and kidney disease)

Tumour markers make poor screening tests

Tumour markers are not recommended for screening asymptomatic patients for malignancy because they generally:

- Lack specificity – many patients may have an elevated result due to benign disease
- Lack sensitivity – many patients with malignancy will have a normal result

An inappropriately ordered test that returns an elevated result, can lead to a cascade of unnecessary investigations, whereas a negative result may give false reassurance.

There is evidence that tumour markers are not always requested appropriately.[3] A 12 month study of tumour marker requesting,[4] found that in the majority of instances, tumour markers were being inappropriately requested as screening or diagnostic tests. In addition, approximately 20% of all requests for CA 125 and CA 15-3 (both usually indicated only in women) were requested in men.

Tumour markers in ovarian cancer

In New Zealand, ovarian cancer is the fourth highest cause of cancer death in women. In 2004, the death rate was 5.4 per 100,000 of the female population. The mortality rate for Māori women was estimated at 8.5 per 100,000.[5]

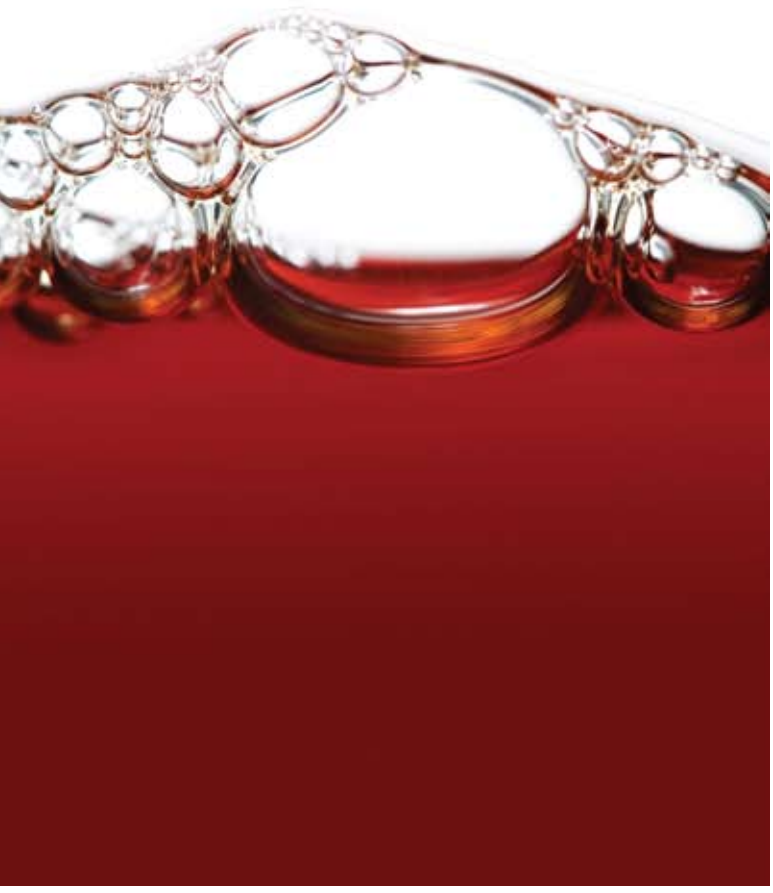
Although CA 125 is frequently requested when investigating suspected ovarian cancer, its main role is for the management of ovarian cancer in secondary care. Because CA 125 is not recommended for screening or diagnosis its role in primary care is limited.

The most common ovarian cancer is serous epithelial cancer but CA 125 is not a useful screening test for this type of cancer because it has poor sensitivity, particularly in early stage disease. Although CA 125 is usually positive

CA 125 may be elevated by a range of other conditions[6]

CA 125 is nonspecific, meaning it may be elevated for a wide range of conditions other than ovarian cancer. Because these conditions occur more frequently than ovarian cancer, a raised CA 125 is more likely to be the result of one of these conditions than ovarian cancer:

- Menstruation
- First-trimester pregnancy
- Benign ovarian cysts
- PID and salpingitis
- Cirrhosis, ascites
- Peritoneal inflammation of any cause
- Pleuritis/pericarditis
- Renal failure
- Endometriosis



at late stages, it will not be elevated in at least 20% of patients with advanced disease.

In addition, most women under 40 years of age with ovarian cancer, have a non-serous type, which does not typically produce CA 125.[6] Therefore a "normal" result can be falsely reassuring.

In rare situations, CA 125 may be used to help distinguish benign from malignant disease, particularly in post-menopausal women, presenting with pelvic masses or in women from families where hereditary ovarian cancer exists. In these situations, it is recommended that CA 125 be performed in conjunction with transvaginal ultrasound.

CA 125 is best used in the monitoring of patients undertaking a course of chemotherapy for epithelial serous ovarian cancer. Serial CA 125 levels have the potential to detect recurrent disease earlier and more cost effectively than radiological procedures. CA 125 levels after chemotherapy are one of the strongest available indicators of disease outcome. Testing frequency will normally be determined by secondary care, with the first sample usually taken within 2 weeks prior to treatment. Patients are frequently monitored every 3–4 months for a number of years.

Tumour markers other than CA 125: New ovarian cancer markers offer promise, however, their contribution to the current standard of care is presently limited and further investigations in large properly designed clinical trials are needed.

Tumour Markers in Colorectal Cancer

In New Zealand, cancer of the colorectum and anus are the most frequently diagnosed cancers, and the third highest cause of cancer death.[5]

Carcinoembryonic antigen (CEA) is the tumour marker most commonly used in management of colorectal cancer. Production of CEA commences during foetal development and it is found in low levels in healthy adults. Colorectal cancer may increase CEA levels, however it is non-specific for this condition and may often be elevated in individuals with gastric, pancreatic, lung, breast and medullar thyroid cancer. In addition it may be elevated in a number of non-cancerous conditions including ulcerative colitis, pancreatitis and cirrhosis, and in people who smoke.

CEA is not recommended as a screening or diagnostic test for colorectal cancer due to its poor sensitivity and specificity, as well as the low prevalence of colorectal cancer in asymptomatic people.[7]

In general, the main application of CEA is for monitoring patients with previously diagnosed colorectal cancer. Testing frequency will normally be determined by secondary care and monitoring may be continued for at least 3 years after diagnosis. CEA may give independent prognostic information that may help with surgical management and provide a baseline level for subsequent determinations.

Tumour markers in testicular cancer

Testicular cancer is one of the more common cancers in young male patients although as a proportion of all cancer types it is relatively uncommon, representing about 1.7% of all cancer registrations. Testicular cancer is two to three times more likely to affect men aged 15–35 years, than it is to affect older men.[5]

Although large numbers of serum markers have been studied, only HCG, alpha fetoprotein (AFP) and lactate dehydrogenase (LD) have been shown to provide independent diagnostic and prognostic value.

About 95% of testicular cancers originate in primordial germ cells and rarely from extra-gonadal sites. Germ cell tumours are classified as seminomas (40%), non-seminoma tumours (40%) and "mixed" germ cell tumours (20%).[8]

Most non-seminomatous tumours have elevated levels of one or more of AFP, HCG and LD, while only hCG and LD are useful markers in seminoma.

Diagnosis of testicular cancer is usually made on clinical signs and symptoms. Investigations include ultrasound and CT scan. Although it is recommended that all patients have AFP, HCG and LD determined prior to the initiation of any therapy.[8]

If AFP or HCG is elevated before therapy, the rate of marker decline reflects the response to therapy. Persistent elevation after chemotherapy indicates residual disease, the need for further therapy and is associated with an adverse prognosis.

CA 19-9 and CA 15-3

CA19-9 is a tumour marker elevated in about 30% of cases of gastric and colon cancer and approximately 80% of cases of pancreatic cancer. It has been proposed as a way to differentiate benign from malignant pancreatic disease, but this capability remains to be established.[9] It has no value for population screening for malignancy and should not be requested for this; the only recognised use is for monitoring known malignancy.

CA 15-3 may be elevated in patients with breast cancer but lacks sensitivity for early disease and has no role in screening or diagnosis. Besides breast cancer, other non-cancerous conditions (e.g. cirrhosis, benign diseases of ovaries and breast) are known to cause elevated levels.[10] CA 15-3 may have a role in monitoring for recurrence or for checking effectiveness of treatment in patients with metastatic disease but there is no high quality evidence of usefulness and it should not be used alone for these purposes.

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Case report

How tumour marker tests can be non-specific

Hypothyroidism mimicking intra-abdominal malignancy[11]

A 74 year old woman was admitted as an emergency with suspected pelvic malignancy.

The presenting features included cachexia, anorexia and ascites. Vital signs were normal. Examination revealed bilateral pleural effusions but no abdominal masses were palpable. Diagnostic and therapeutic paracentesis revealed an exudate (protein 37 g/L) however there were no malignant cells present.

Investigations showed an extremely elevated serum CA 125 level of 1059 U/mL (< 37). CA 19-9, CA 15-3, CEA, and AFP were all normal. At this stage the patient was strongly suspected to have ovarian carcinoma or disseminated peritoneal metastases from an unknown primary tumour.

CT of the abdomen showed extensive ascites but no obvious abdominal or pelvic mass. A diagnostic laparoscopy showed no evidence of intraperitoneal malignancy. Mammography and oral gastroduodenoscopy also gave normal results.

Although the patient was not clinically overtly hypothyroid, thyroid function tests were performed because of hoarse voice and dry skin. These revealed severe primary hypothyroidism with a serum thyroid stimulating hormone level of 73 mU/L (0.2 to 5.7). Over the next 8 weeks, the patient's condition gradually improved with restoration of the euthyroid state.

Discussion

Ascites is a well known but uncommon feature of hypothyroidism and occurs in about 4% of patients. It is thought that the extremely high CA 125 concentrations in myxoedema ascites are due to peritoneal irritation caused by the presence of ascitic fluid. Others have reported that patients with ascites who have benign conditions such as nephrotic syndrome, cirrhosis, tuberculous peritonitis, renal failure, and pancreatitis may sometimes have CA 125 concentrations as high as those seen in ovarian carcinoma. In addition, mildly increased CA 125 concentrations have been reported in women with hypothyroidism.

This case report demonstrates that although a CA 125 test was not an inappropriate test in a 74 year old lady with cachexia and ascites (as this is a high risk group of ovarian cancer) that the focus should not solely be on ovarian cancer as the only possible cause due to the low specificity of the CA 125 test. In this case, the CA 125 was elevated for reasons other than ovarian cancer.

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PSA screening in asymptomatic men

– the debate continues

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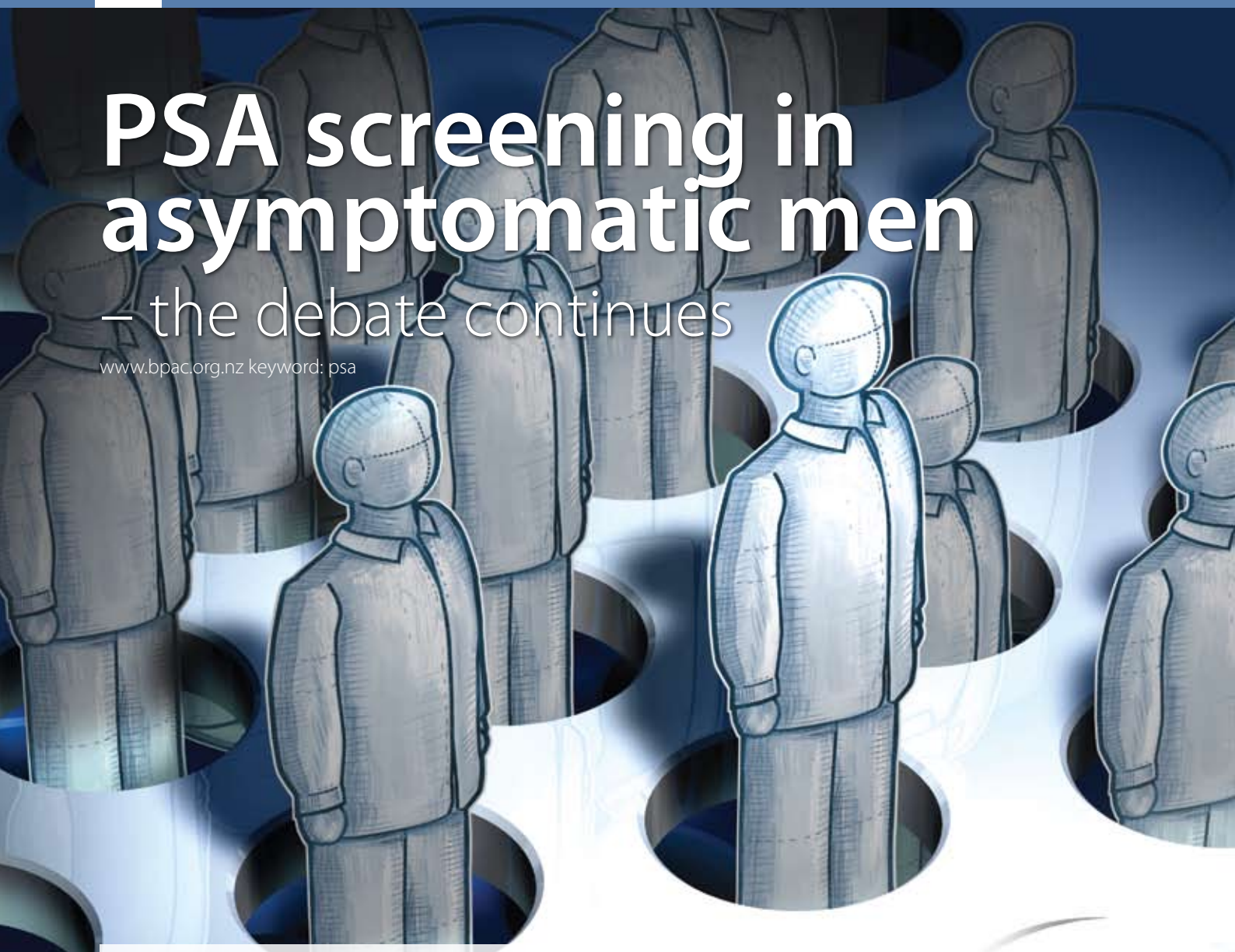

Key messages:

- PSA is present in the benign and malignant prostate
- There is currently no national screening programme for prostate cancer in New Zealand
- It is recommended that every man has the right to decide for himself whether or not to be tested, guided by health professionals providing adequate information
- There is no PSA level below which a man can be completely reassured he does not have prostate cancer. A significant number of men with prostate cancer will have a normal PSA
- The use of the PSA test for screening asymptomatic men for prostate cancer remains controversial

Prostate specific antigen (PSA) is a glycoprotein produced by the prostate gland, responsible for liquefying seminal fluid. PSA is usually present in small quantities in serum. Changes to the prostate from normal and non-cancerous conditions as well as prostate cancer, can lead to increased levels of PSA in the blood stream (see sidebar: "Non-cancerous causes of elevated PSA", over page).

Prostate cancer is the most commonly diagnosed cancer in New Zealand men, and is the third highest cause of male cancer deaths. The lifetime risk of death from prostate cancer is about 3%.[1] Approximately 2,500 new cases of prostate cancer are detected each year, and almost 600 men die per year of prostate cancer (this is similar to the number of deaths due to breast cancer in women). The registration rate for prostate cancer for Māori males is lower than for the non-Māori population, but the mortality rate for Māori males is higher.[2]

PSA testing in New Zealand

PSA testing has been available in New Zealand since 1991. The number of PSA tests performed has increased almost 50% over the last five years (Figure 1). Not surprisingly prostate cancer registrations in New Zealand increased dramatically, over this time, in line with many other developed countries. However, the number of registrations has declined over recent years. The New Zealand mortality rate, due to prostate cancer, has remained static for approximately 50 years (Figure 2).[3]

The GPs role

GPs are the "gate-keepers" for PSA testing – they influence who does and doesn't get tested. It is currently recommended by NZGG[4] that every man has the right to decide for himself whether or not to be tested. This decision making is to be guided by doctors and other practitioners who have a duty under the *Code for Health and Disability Services Consumers' Rights Regulations 1996*,[5] to provide good, balanced information on prostate cancer and the possible benefits and harms of testing and treatment.[4]

Screening for prostate cancer

Prostate cancer screening in asymptomatic men is a controversial public health issue generating much debate with polarised views around the appropriate use of PSA, both internationally and within New Zealand.

Currently in New Zealand, a national screening programme has not been recommended, as there is a lack of consensus as to whether the benefit of screening outweighs the harms. The issue of prostate cancer screening is currently being considered by a Parliamentary Health Select Committee.[6]

Despite New Zealand not having a formal screening programme for prostate cancer, PSA testing is already widely used in primary care. In 2009, for example, GPs performed on average 74 PSA tests each per year.[7]

Approaches to testing

At present, NZGG does not support population screening with PSA for asymptomatic men, but they do recommend

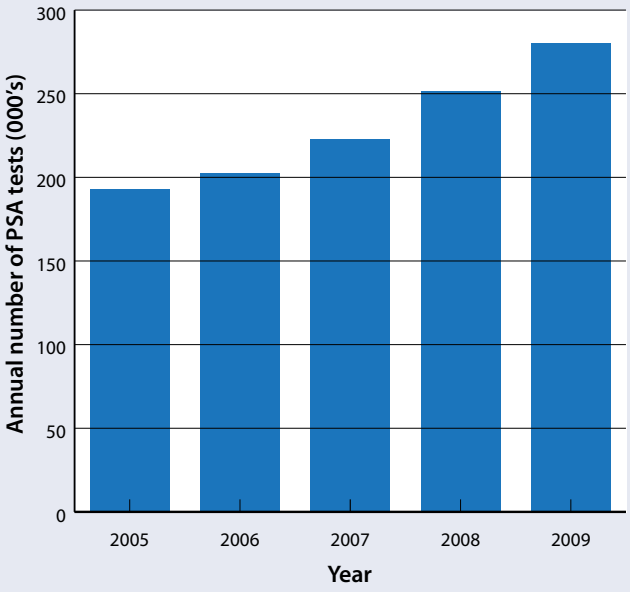

Figure 1: Annual totals for PSA tests requested by GPs in New Zealand[7]

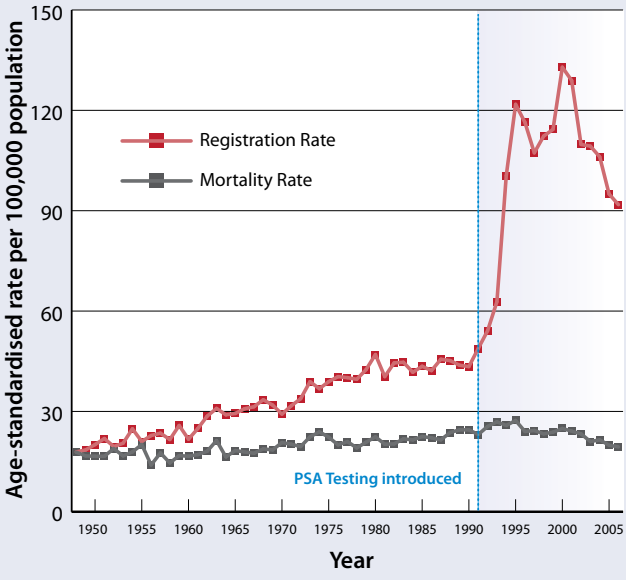

Figure 2: New Zealand prostate cancer registration and mortality rates[3]

GPs advise patients of the risks and benefits of testing, as well as the likelihood of them developing prostate cancer.

The Urological Society of Australia and New Zealand (USANZ)[8] however, encourages all men who are interested in their prostate health to have a single PSA test and digital rectal exam (DRE) performed at, or beyond, age 40 years.

What is the risk of developing prostate cancer[4]

Age

Risk of prostate cancer increases with age.

What is the chance of diagnosis/death for prostate cancer?		
	Diagnosis	**Death**
For a man in his 40s	1 in 500 men	< 1 in 1000 men
For a man in his 50s	1 in 50 men	1 in 1000 men
For a man in his 60s	1 in 14 men	1 in 67 men
For a man in his 70s	1 in 9 men	1 in 43 men

Family history

Risk of diagnosis increases with a positive family history. The risk is higher if a close relative is diagnosed before 65 years, or more than one close relative is affected.

ONE relative (father, brother) diagnosed	Risk is about 2 and a half times higher
TWO relatives (father, brothers) diagnosed	Risk is about 4 to 5 times higher

Interpreting PSA results

Results and laboratory terms

PSA results: Normal levels usually range from 0 to 4 µg/L, although age-specific values (upper limit of normal) are frequently reported as follows:

- 40 – 49 years 2.5 µg/L
- 50 – 59 years 3.5 µg/L
- 60 – 69 years 4.5 µg/L
- 70 – 79 years 6.5 µg/L

PSA results between 4 and 10 µg/L are considered mildly to moderately elevated, while levels over 10 are considered high.

The higher the PSA, the more likely the presence of prostate cancer. However, there is no PSA level that below which a man can be reassured he definitely does not have prostate cancer.

As there are a number of non-cancerous contributors to an increased PSA (see side bar), it is generally prudent to repeat any initial high result. Care should be taken when interpreting trends, particularly being careful not to over interpret small changes.[9]

Effect of ejaculation and DRE have historically been thought to increase the PSA level temporarily. This effect is variable and in most patients insignificant (about 5% rise over several days for DRE). While PSA can usually be performed after DRE, it is probably better, if practical, to either collect the PSA sample beforehand or delay collection for up to a week.[1]

If there is concern at the current level of PSA, or an increase of the PSA level, referral to a specialist is recommended.[1,10]

Non-cancerous causes of elevated PSA[1,9]

- Daily biological/ laboratory variability of PSA
- Benign prostatic enlargement
- Urinary infection
- Urinary retention
- Prostatitis or sub-clinical prostate inflammation
- Ejaculation
- DRE
- Prostatic massage

More good than harm?

There has been much controversy around prostate screening both in New Zealand and internationally. There remains a lack of consensus as to whether the benefits of detecting early disease by screening asymptomatic men outweigh the potential harms.

Recent trial data

It was anticipated that the long awaited results from two randomised trials (see sidebar opposite) would tell us, once and for all, whether PSA screening is beneficial. Unfortunately, there is lack of agreement on the interpretation of the results, leading to continued debate about the use of PSA testing for screening.

Both studies have been criticised for a number of reasons:

Significant contamination of the control group: The PLCO trial was performed in the USA, which has a high level of PSA testing performed by GPs in usual day-to-day practice. As a result about 38% of the control patients had PSA testing and 44% had been tested before entry into the study. Therefore, it could be considered this was not a trial of screening versus no screening, but rather screening versus some screening. There was also some contamination of the ERSPC trial, but it was less than the PLCO trial and the trial was designed to cope with a contamination rate of 20%.

Short follow-up time: Prostate cancer is usually a slowly progressing condition, therefore the effect on the mortality rate may not be clear for several more years. At this stage, some believe the reported reduction in mortality is negligible, while others are surprised it is so high already, considering prostate cancer predominantly progresses slowly.[13]

Over-detection and over-treatment

One of the arguments against PSA screening is that it leads to over-diagnosis of prostate cancer (i.e. would not have been detected, was it not for screening). It is suggested that over-diagnosis leads to over-treatment. It has been estimated that at age 55 years, PSA testing results in an over detection rate of 27%, by age 75, this is estimated to be 56%.[1]

Most men with an elevated PSA will proceed to biopsy. One in four prostate biopsies will find prostate cancer,[1] while the risk of significant bleeding or infection is 1 to 4% of patients. For those diagnosed with prostate cancer, approximately 90% will elect to have some sort of intervention. This includes surgery, radiation therapy, or androgen deprivation. All of these treatments may be associated with adverse effects, such as urinary, bowel and erectile dysfunction.

Many patients may consider the adverse effects to be acceptable trade-offs for a procedure they regard as "life saving". There is also the argument, that any morbidity associated with intervention, is better than the morbidity from metastasised prostate cancer.

Others argue that up to 50% of the prostate cancers detected would not have caused illness in the man's lifetime.[14] Therefore, for 50% of men any adverse effects from any intervention can be considered a harm.

The European Randomised Study of Screening for Prostate cancer (ERSPC),[11] was designed to evaluate the effect of screening with PSA on mortality from prostate cancer. The study took place between 1997 and 2006, and involved 162,387 men, aged 55 – 69 years. Men were randomly assigned either 4 yearly screening or not offered PSA testing. During a mean follow-up of 9 years, fewer prostate cancer–related deaths occurred in the screened group than in the control group

The Prostate, Lung, Colon and Ovary trial (PLCO)[12] was also designed to evaluate the effect of annual PSA and DRE on mortality rate from prostate cancer. This study included 76,693 men (aged 55 to 74 years). Men were randomly assigned to either annual screening (annual PSA for 6 years and annual DRE for 4 years) or usual care (from GP). During 10 years of follow-up, researchers found no difference in prostate cancer–related deaths (roughly 85 in each group).

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Bowel cancer screening in New Zealand

Many developed countries including Australia, the United Kingdom, France, Italy, Canada, Japan and Israel are either currently running or piloting bowel cancer screening programmes. It has been estimated that bowel cancer screening in New Zealand could save up to 270 lives per year.

A Bowel Cancer Taskforce has been formed, to provide advice and recommendations to the Minister of Health on bowel cancer screening. This taskforce is required to provide guidance on the establishment of a bowel cancer programme, including implementation, ensuring people with increased risk are screened, ensuring access to treatment and diagnostic services for all people. They will also be required to monitor and evaluate any programme, and provide any other advice as required.

In addition, a Māori Equity Advisory Group (MEAG) has been formed, to provide advice and recommendations on reducing inequalities in treatment and outcomes for people with bowel cancer. The key objective of MEAG is to ensure a Bowel Cancer Screening programme actively and intentionally reduces bowel cancer for Māori.

A National bowel cancer screening pilot has recently been announced by the Ministry of Health. It is anticipated that a pilot programme will begin in one or two regions of New Zealand in 2011, and will run for four years. It will aim to screen people aged 50–74 years, by mailing them a screening kit for faecal occult blood, which can be returned and analysed in the laboratory. Patients with a positive faecal occult blood result will be then offered a colonoscopy, while those with negative results will be re-screened after two years. A decision on whether New Zealand then adopts a national bowel cancer screening programme will be made following the evaluation of this pilot programme.

To ensure the success of the screening programme there are a number of components that will need to be developed, including:

- Agreement on the screening and diagnostic tests and any subsequent treatment
- Ability to manage invitation, recall and tracking of participants
- Assurance of sufficient capacity for colonoscopy and care of people diagnosed with bowel cancer
- Laboratory capacity for faecal occult blood testing and colonoscopy biopsies
- Quality standards and evaluation framework

In the meantime, until a national screening programme is confirmed, the Ministry of Health is focusing on:

- Increasing colonoscopy capacity in District Health Boards (DHBs)
- Providing additional training for colonoscopists
- Developing guidelines for people with suspected bowel cancer
- Developing a New Zealand Familial Gastrointestinal registry and national surveillance programme for high risk populations.

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QUIZ FEEDBACK

Investigating the Gut

www.bpac.org.nz keyword: gut-quiz

Introduction

This quiz feedback provides an opportunity to revisit the March, 2010 "Best Tests" document and accompanying quiz which focused on the role of laboratory testing when investigating the gut. All general practitioners who responded to this quiz, will receive personalised online feedback and CME points.

1.	Which of the following is true about the use of a lactose free diet when investigating lactose intolerance?	Your peers	Preferred
☐	Can be diagnostic if symptoms resolve, then return following reintroduction of lactose	98%	✓
☐	If dietary challenge is inconclusive, it is useful to consider faecal pH test	1%	✗
☐	Food labels must be carefully studied during the trial, to avoid "hidden" sources of lactose	86%	✓
☐	It is useful to use both trial of diet and laboratory tests to diagnose lactose intolerance	3%	✗

Comment:

The role of laboratory tests in diagnosing lactose intolerance in primary care is limited. In most cases the diagnosis can be made on clinical grounds. The American Academy of Paediatrics recommends that when lactose intolerance is suspected, a lactose free diet should be trialled for two weeks. However, during the trial ,it is important that all sources of lactose are eliminated and food labelling should be closely studied. If symptoms resolve over this trial period and then return with subsequent reintroduction of lactose containing foods, then lactose intolerance can be diagnosed. This diagnosis can be made by a GP and further investigation is rarely needed.

2.	Which of the following is true about faecal calprotectin?	Your peers	Preferred
☐	Can provide a definite diagnosis of inflammatory bowel disease	11%	✗
☐	Is appropriate for routine use by GPs	1%	✗
☐	It is expensive and not widely available	97%	✓
☐	The antibody tests pANCA, ASCA, Anti-CBir1, Anti-Omp C, Anti-I-2 provide the same information as faecal calprotectin	4%	✗

Comment:

Faecal calprotectin may be useful to differentiate between irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), in symptomatic patients with only slightly raised CRP, but is not helpful in determining the cause of inflammation.

Although there is no charge to the patients it is expensive for the laboratory. As the test is not currently widely available, most gastroenterologists will instead proceed directly to colonoscopy and biopsy if there are symptoms suggestive of IBD.

3.	Which of the following tests are most useful for diagnosing lactose intolerance in primary care?		
		Your peers	Preferred
☐	Trial of lactose-free diet/reintroduction of lactose	98%	✓
☐	Small bowel disaccharidases	1%	✗
☐	Lactose tolerance test	<1%	✗
☐	Hydrogen breath test	2%	✗
☐	Faecal pH test	1%	✗
☐	Faecal reducing substances	1%	✗

Comment:
A trial of lactose-free diet/reintroduction is usually sufficient for diagnosis however there are a number of laboratory investigations that are available, but these are most often reserved for use in secondary care.

Small bowel disaccharide testing remains a very good test for lactose intolerance, but it is invasive requiring a small bowel biopsy. It can not differentiate between primary and secondary lactase deficiency.

Lactose tolerance test is rarely performed, due to poor sensitivity (about 75%), and may also cause unpleasant symptoms such as diarrhoea and abdominal pain.

Hydrogen breath test is an alternative to the lactose tolerance test. Although it is preferable to the lactose tolerance test in children, it is not widely available.

Faecal pH test is of limited value and no longer recommended.

Faecal reducing substances is unreliable and not recommended.

4.	Why is faecal fat no longer favoured?		
		Your peers	Preferred
☐	Because it is both unpleasant for patients to collect and for laboratory staff to process	83%	✓
☐	Because the diagnosis of steatorrhoea can usually be made on patient history	76%	✓
☐	Faecal fat has low sensitivity for pancreatic insufficiency	84%	✓
☐	Other tests can provide more useful information	71%	✓

Comment:
The faecal fat test is no longer recommended because it has low sensitivity for pancreatic insufficiency, as well as being a very unpleasant test. The diagnosis of steatorrhoea can usually be made on patient history. The hallmark of steatorrhoea is the passage of pale, bulky and malodorous faeces, which often float and are difficult to flush.

The faecal elastase test is a more sensitive test for pancreatic insufficiency. Measurement of fat soluble vitamins would not normally be indicated in the first instance but may be recommended later.

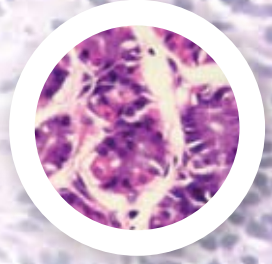
5.	Which of the following is true about pernicious anaemia?		
		Your peers	Preferred
☐	Lifelong B12 treatment will be required	97%	✓
☐	It is associated with other autoimmune endocrinopathies, particularly thyroid disease and diabetes	95%	✓
☐	Parietal cell antibodies may be positive in 20-30% of first degree relatives of patients with pernicious anaemia	92%	✓
☐	Schilling test is still frequently used	1%	✗

Comment:
The diagnosis of pernicious anaemia identifies the need for lifelong B12 treatment and may be associated with other autoimmune endocrinopathies, particularly thyroid disease and diabetes. There is also a small increased incidence of associated stomach cancer.

Partial cell and intrinsic factor antibody tests should be requested for a patient with low vitamin B12, and signs/symptoms consistent with pernicious anaemia. Both tests should be ordered, as there are some limitations with each:

Intrinsic factor antibodies: Are very specific and virtually diagnostic for pernicious anaemia but sensitivity is low, meaning a negative result does not rule out a diagnosis of pernicious anaemia

Parietal cell antibodies: Has high sensitivity, which means most patients with pernicious anaemia will have positive parietal cell antibodies, but low specificity, means high number of false positives. For example, the incidence in healthy individuals rises from 2.5% of those in their twenties, to 10% of those in their seventies. The test may also be positive in 20–30% of first degree relatives of patients with pernicious anaemia and also in some patients with other autoimmune endocrine disorders.



6.	Which of the following is true about the prevalence of *Helicobacter pylori* infection?		
		Your peers	Preferred
☐	Overall infection rates are becoming less in New Zealand as living conditions have improved	84%	✓
☐	Where prevalence is >30%, serology testing should be used for detecting *H. pylori* infection	92%	✓
☐	Māori and Pacific people have higher rates of *H. pylori* infection than European New Zealanders	96%	✓
☐	Prevalence is lowest amongst Europeans living in the South Island	85%	✓

Comment:
H. pylori infection is usually acquired in early childhood, and does not resolve spontaneously. There is a higher risk of infection with lower socioeconomic living conditions. As living conditions have improved in New Zealand, *H. pylori* infection rates have decreased. As a result *H. pylori* infection is more common in older people, due to a higher prevalence when they were children.

There is incomplete data on *H. pylori* infection rates throughout New Zealand, however it is known that rates are significantly higher in Māori and Pacific people compared to European New Zealanders.

The NZGG Dyspepsia Guideline contains the following statements about *H. pylori* infection rates:

- Rates in the South Island are well below 30%
- Rates tend to be >30% in adult Māori and Pacific peoples, and those with lower socio-economic status
- Rates in adults living in Auckland have generally been found to be greater than 30%

When testing for *H. Pylori*, serology tests and stool antigen tests are the most frequently used tests. Although both tests do have some limitations, the "rule-of-thumb" is to use serology tests where the prevalence of *H. pylori* infection is greater than 30%, and use stool antigen tests where prevalence of *H. pylori* infection is less than 30%.

7.	Which of the following is true about testing for coeliac disease?		
		Your peers	Preferred
☐	People should abstain from eating gluten prior to testing	5%	✗
☐	A negative result always excludes coeliac disease	2%	✗
☐	IgA TTG is the preferred initial test	98%	✓
☐	Population screening for coeliac disease is likely in the future	1%	✗

Comment:
IgA tissue transglutaminase (TTG) Is the preferred initial test for detecting coeliac disease. Testing is recommended for all symptomatic children and adults as well as asymptomatic people at increased risk. People must have consumed adequate amounts of gluten (equivalent to four slices of bread daily) for 4–6 weeks prior to testing. Negative results can not exclude coeliac disease if the patient has had a significantly reduced gluten intake.

People at increased risk include:

- Siblings of any index case (because the test may be unreliable, it may be preferable to avoid using it until the child is 2–3 years of age, unless there are symptoms)
- Those with Type I diabetes and other systemic autoimmune disorders
- Patients with IgA deficiency
- Children with Down syndrome

8.	Which of the following is true about a low vitamin B12?		
		Your peers	Preferred
☐	May be the result of drug therapy	93%	✓
☐	A negative intrinsic factor antibody in a person with low B12 excludes pernicious anaemia	8%	✗
☐	Pernicious anaemia is an unlikely cause of the low B12 in people younger than 30 years	85%	✓
☐	Positive intrinsic factor antibodies and positive parietal cell antibodies confirm pernicious anaemia as the cause of the low vitamin B12.	90%	✓

Comment:
There are number of causes of low vitamin B12 levels but pernicious anaemia is among the most important to identify. Pernicious anaemia is rare in people under 30 years.

Other possible causes of low vitamin B12 include:

- Nutritional deficiency – main dietary sources are meat and dairy products therefore elderly patients with "tea and toast"diets, chronic alcoholics and strict vegans are especially at risk
- Gastric causes e.g. gastrectomy
- Intestinal causes e.g. ileal disease/resection
- Severe pancreatic insufficiency
- Medications e.g. oral contraceptives, metformin, long term proton pump inhibitor therapy

Partial cell and intrinsic factor antibody tests should be requested for a patient with low vitamin B12, and signs/symptoms consistent with pernicious anaemia. Approximately 90% of people with pernicious anaemia will test positive for one or both of these tests. Intrinsic factor antibodies have low sensitivity (approximately 60%); therefore a negative result does not rule out a diagnosis of pernicious anaemia.

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