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Independent learning program for GPs

Unit 488 November 2012

Biochemistry

The Royal Australian
College of General
Practitioners

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The five domains of general practice
Communication skills and the patient-doctor relationship
Applied professional knowledge and skills
Population health and the context of general practice
Professional and ethical role
Organisational and legal dimensions

The Royal Australian College of General Practitioners

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This unit of *check* looks at clinical scenarios in relation to some common or significant medical conditions encountered in general practice where it is important to know what biochemical tests to request and how to interpret the results. While a diagnosis is usually made on the basis of history and examination, the results of investigations can play an important role in confirming the diagnosis, excluding other diagnoses and assessing for potential complications. This unit focuses on considering differential diagnoses, formulating working diagnoses and selecting appropriate investigations. Informing patients about their diagnosis, communicating pathology results in a manner in which they can be understood and outlining treatment options are also pivotal roles of the GP.

The author brings a wealth of experience to this topic.

The author of this unit is:

- Ken Sikaris MBBS, FRCPA, FFSc, BSc(Hons), FAACB, GAICD, Director of Chemical Pathology at Melbourne Pathology and Associate Professor, Department of Pathology, The University of Melbourne. He has special interests in prostate-specific antigen (PSA) testing, analytical measurement uncertainty and the quality of reference intervals, as well as the clinical decision limits used in pathology.

The learning objectives of this unit are to:

- understand the differential diagnosis in patients who present with tiredness, request appropriate investigations and confidently interpret the results
- develop increased confidence in assessing patients who present with chest pain suggestive of cardiac ischaemia, including analysis of a high sensitivity troponin result (when requested in the appropriate setting)
- develop increased confidence in assessing patients who present with clinical manifestations of underlying biochemical or hormonal disturbances such as metabolic syndrome and polycystic ovarian syndrome
- demonstrate increased competence in the analysis of thyroid function tests in patients who present with symptoms that could suggest altered thyroid function, including those on thyroxine therapy
- understand the differential diagnosis in patients who present with back pain suggestive of a non-musculoskeletal cause, perform an appropriate clinical assessment, request relevant investigations and confidently interpret these results.

We hope that this unit of *check* will help you manage many of your patients in general practice.

Kind regards,

Catherine Dodgshun MBBS, DRANZCOG, FRACGP

Medical Editor, *check* Program

GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF *CHECK*

ECG	electrocardiograph	eGFR	estimated glomerular filtration rate	NAFLD	non-alcoholic fatty liver disease
ACTH	adrenocorticotropic hormone	ESR	erythrocyte sedimentation rate	OGTT	oral glucose tolerance test
ALP	alkaline phosphatase	fT3	free triiodothyronine	PCOS	polycystic ovarian syndrome
ALT	alanine transaminase	fT4	free thyroxine	PSA	prostate-specific antigen
AST	aspartate transaminase	FBE	full blood examination	PTH	parathyroid hormone
BGL	blood glucose level	FSH	follicle stimulating hormone	RDW	red cell distribution width
BMI	body mass index	GGT	gamma-glutamyl transferase	SHBG	sex hormone binding globulin
BP	blood pressure	HbA1c	glycated haemoglobin	SPIEP	serum protein immunoelectrophoresis
CBG	cortisol binding globulin	HDL-C	high density lipoprotein cholesterol	T3	triiodothyronine
cFT	calculated free testosterone	HRT	hormone replacement therapy	T4	thyroxine
CK	creatinine kinase	hs-TnT	high sensitivity troponin T	TFTs	thyroid function tests
CK-MB	creatinine kinase MB	LDL	low density lipoprotein	TSH	thyroid stimulating hormone
COCP	combined oral contraceptive pill	LDL-C	low density lipoprotein cholesterol	UEC	urea, electrolytes and creatinine
CRP	C-reactive protein	LFTs	liver function tests		
DHEAS	dehydroepiandrosterone sulphate	LH	luteinising hormone		

CASE 1

EVA IS CONSTANTLY TIRED

Eva, aged 23 years, is a receptionist at a car dealership who presents to you feeling exhausted. She says she has felt physically tired 'all the time' for the past 6 months and has also experienced appetite loss, nausea, vague abdominal pain and dizziness when changing position. She has felt so tired recently that she took the last 3 days off work. She is a lacto-ovo vegetarian and has 'regular periods', which aren't heavy, but she is on the combined oral contraceptive pill (COCP).

Eva says she has been 'stressed,' but her mood is normal. She sleeps well from about 10 pm–6 am on most nights of the week, and her weight has been stable. Symptom review reveals no other symptoms. She consumes 2 standard drinks of alcohol on Saturday nights and she does not smoke. Eva has no relevant past medical history. She has not travelled overseas recently. Eva's mother has 'an underactive thyroid' and has been on tablets for 15 years. She has been 'nagging' Eva to get a blood test done.

On examination Eva doesn't appear anaemic, she is afebrile, her pulse rate is 88 beats/minute, and her blood pressure is 112/70 mmHg standing and 99/70 mmHg lying. Eva's body mass index (BMI) is 23 kg/m^2. She has pigmentation of the skin, creases of her hands and of her buccal mucosa. She has no tremor and her reflexes are normal. Her abdominal examination reveals no abnormalities. Eva's chest is clear, her heart sounds are normal, and she has no cervical, axillary or groin lymphanenopathy.

QUESTION 1

What are the common causes of tiredness in a young woman? What serious conditions can cause tiredness?

QUESTION 2

What blood tests would you request for Eva?

FURTHER INFORMATION

You request blood tests. Eva says that she can get the blood tests done later that afternoon. Full blood examination (FBE), urea, electrolytes and creatinine (UEC), liver function tests (LFTs), C-reactive protein (CRP) and blood glucose level (BGL) are all within normal limits. The results of Eva's iron studies (*Table 1*), thyroid function tests (TFTs) (*Table 2*) and serum cortisol (*Table 3*) are available the following day.

Table 1. Eva's iron studies

	Result	Normal reference interval
Serum iron	5 µmol/L	5–30 µmol/L
Serum transferrin	4.0 g/L	2.0–3.6 g/L
Transferrin saturation	5%	10–45%
Ferritin	25 µg/L	30–120µg/L

Table 2. Eva's thyroid function tests

	Result	Normal reference interval
Thyroid stimulating hormone (TSH)	0.15 mIU/L	0.5–5.0mIU/L
Free thyroxine (fT4)	11.3 pmol/L	9.0–19.0pmol/L

Table 3. Eva's serum cortisol

	Result	Normal reference interval
Cortisol PM	220 nmol/L	150–350 nmol/L

QUESTION 3

How would you interpret Eva's iron studies?

QUESTION 4

How would you interpret Eva's TFTs?

QUESTION 5

How would you interpret Eva's serum cortisol?

QUESTION 6

What further blood tests are indicated in Eva?

FURTHER INFORMATION

You request a short Synacthen® test for Eva. The results are displayed below in *Table 4*.

Table 4. Eva's short Synacthen® test

	Result	Normal reference range
Basal cortisol	310 nmol/L	150–500 nmol/L
30-minute cortisol	450 nmol/L	>500 nmol/L

QUESTION 7

How would you interpret Eva's Synacthen® test?

QUESTION 8

What would your immediate management of Eva be given her Synacthen® test result?

CASE 1 ANSWERS

ANSWER 1

While tiredness is common, being tired all the time is not as common.[1] In general, tiredness can be due to environmental factors such as sleep deprivation, psychological causes such as depression or anxiety, or physical conditions. Physical conditions include iron deficiency, thyroid disorders, sleep disorders, post-infective fatigue, medical conditions such as kidney failure, inflammatory disorders, chronic infections and malignancy.

While psychological causes of tiredness should be considered, physical causes should be excluded first whenever possible. Iron deficiency is very common in young women, particularly if the patient is a vegetarian.[2] Both hypothyroidism and hyperthyroidism can also present with tiredness.[3,4]

One of the most serious, albeit rare, causes of tiredness in a young woman is adrenal insufficiency. Primary adrenocortical insufficiency is also known as Addison disease. In Eva's case, clinical features that suggest Addison disease include symptoms such as tiredness, anorexia, nausea and abdominal pain, and a possible family history of autoimmune disease. On examination, patients with Addison disease typically have evidence of hypotension (such as postural hypotension) and may have increased pigmentation of the skin or mucosal surfaces.

ANSWER 2

The blood tests that should be considered for Eva are:

- FBE and iron studies, looking for manifestations of iron deficiency[2]
- TSH, and if it is abnormal, the laboratory will usually perform fT4 and possibly free triiodothyronine (fT3)
- LFTs, looking for impairment of liver function
- CRP, looking for inflammation or infection
- UEC, looking for hyperkalaemia and hyponatremia, which are commonly seen in Addison disease, but may not always be present
- BGL, checking for hypoglycaemia, (which can occur in Addison disease) or evidence of diabetes
- vitamin B12 level, looking for B12 deficiency in the setting of vegetarianism
- a morning cortisol level. In general, this can be requested as a preliminary test in a patient with a low clinical likelihood of Addison disease. However, the test that should be requested to exclude Addison disease is a short Synacthen® test.[5,6]

ANSWER 3

Eva's serum iron level is at the lower limit of the reference interval. However, this may be due to normal diurnal variation, where low serum iron levels are often seen in afternoon samples (the nadir occurs about 4 pm). Eva's transferrin level may be elevated due to the effect of the oestrogen in the COCP or iron deficiency, as both can cause an increase in the level of this protein. Eva's low transferrin saturation is a mathematical consequence of her low serum iron and high transferrin, as these two values are used to calculate the saturation of transferrin.

There is only one possible cause of a low ferritin and that is iron depletion. Pathology laboratories currently vary in what they describe as a lower reference limit for ferritin. Some use a population description where – due to premenopausal women often having low ferritin levels – the reference limit down to 15 µg/L or even lower is considered 'normal'. Other laboratories use expert-derived reference limits based on studies of lethargy, sports physiology or the correlation between ferritin and haematological changes to determine a lower reference limit for ferritin of 30 µg/L.[7]

It is important to consider that a vegetarian patient might also have vitamin B12 depletion. The co-existence of iron and B12 deficiency can cause an anaemia where the average red cell size is normal. However, the presence of both microcytes and macrocytes increases variation in red cell size. This is generally reported as an elevated red cell distribution width (RDW) or 'anisocytosis'.

ANSWER 4

Eva's TSH level is low and her fT4 is in the low region of the reference interval.

While TSH levels in the afternoon are usually 30% lower,[8,9] this is not enough to explain Eva's TSH level of 0.15 mIU/L. Eva's low TSH is significant because a mildly low TSH could signal early hyperthyroidism. But if Eva had hyperthyroidism, her fT4 would be in the high region of the reference interval (eg.18.0pmol/L).

A suppressed TSH and a normal fT4 can also be seen in T3 toxicosis. In general, laboratories do not routinely perform fT3 unless the TSH is ≤ 0.10 mIU/L when T3 toxicosis is more likely to be present.

The finding of a low TSH and a fT4 in the lower region of the reference interval in Eva suggests either hypopituitarism, or changes that may be seen in the presence of severe non-thyroidal illness (also known as sick euthyroid syndrome). Sickness or stress can cause a particular pituitary response including increased adrenocorticotropic hormone (ACTH), growth hormone and prolactin,[10] while other

pituitary hormones such as the gonadotropins (follicle stimulating hormone and luteinising hormone) and TSH may decrease[11] or exhibit no change. It is difficult to assess if Eva has hypopituitarism as she has regular withdrawal bleeds on the COCP. Therefore, both non-thyroidal illness and hypopituitarism are possibilities.

ANSWER 5

Eva's afternoon cortisol level is in the normal reference interval. However, there are some factors to consider. Firstly, Eva is on the COCP, which usually increases cortisol binding globulin (CBG), and typically results in a cortisol level in the higher region of the normal reference interval or a clearly high cortisol level. Secondly, if Eva is 'stressed', we would also expect her cortisol level to also be in the higher region of the reference interval or increased. Therefore, Eva's cortisol level, which is in the normal reference interval, cannot exclude Addison disease or hypopituitarism.

ANSWER 6

Eva's apparently normal afternoon cortisol level is concerning. In primary adrenocortical insufficiency, the ACTH level is typically very high, representing the pituitary's attempt to increase cortisol production. An ACTH level should be requested for Eva.

Addison disease is most commonly due to autoimmunity. Adrenal antibodies are usually present, but they are not reliable in making a diagnosis or excluding the disease. Where there is a high likelihood of Addison disease, the test to exclude Addison disease is a short Synacthen® test. This consists of a blood test to determine the baseline cortisol level, followed by an intramuscular injection of a synthetic analogue of ACTH (tetracosactrin, also known as Synacthen®), then a blood test at 30 minutes. A blood test at 60 minutes is also commonly performed by most pathology services. The test should be performed in a facility equipped for resuscitation due to the rare possibility of anaphylaxis.

ANSWER 7

There are two criteria that must be met for a Synacthen® test to exclude adrenocortical insufficiency (*Table 5*).[12] These criteria are listed below in *Table 5*.

Table 5. Criteria for a Synacthen® test to exclude adrenocortical insufficiency

The 30-minute cortisol level rises to >500 nmol/L
There is a rise in cortisol of at least 200 nmol/L

However, the dose and route of Synacthen® administration, timing of the test and criteria for excluding adrenocortical insufficiency have been the subject of debate over the years, so it is best to discuss these details with the particular laboratory involved, especially as cortisol assays vary between laboratories.

Neither of the criteria in *Table 5* are satisfied in Eva's case, and it is suspected she has adrenocortical insufficiency. Given her possible family history of autoimmune thyroid disease, adrenal antibodies could also be requested to confirm the suspicion of Addison disease.

A flat Synacthen® test (ie. an absent or blunted cortisol response to Synacthen®) may also be seen in hypopituitarism and a 'long' Synacthen® test may be required. A long Synacthen® test consists of use of an oily depot injection of Synacthen,® which stimulates the adrenal gland for 3 days and may succeed in 'waking' the adrenal into action.

ANSWER 8

An immediate endocrinology referral is indicated. The diagnosis of Addison disease is a high risk situation as the patient could have an Addisonian crisis at any time, particularly during a stressful challenge. Dexamethasone should be prescribed to help prevent an Addisonian crisis. Use will not interfere with subsequent cortisol analysis.

It is important to note that if a patient presents in an Addisonian crisis, treatment should be instituted before definitive testing.

CASE 2

HENRY IS FEELING TIRED AND SHORT OF BREATH

Henry, aged 82 years, presents to the emergency department of the local regional hospital where you work shifts on the weekend roster. He presents with ongoing tiredness concerned that his heart is 'playing up' following a 'turn' 3 days ago. On further questioning, Henry says that he experienced chest tightness, which came on while mowing the lawn. It lasted at least a couple of hours and was accompanied by shortness of breath. Henry has had no further chest discomfort since, but has been tired and experienced shortness of breath on exertion.

Henry has a past history of reflux oesophagitis, for which he is on lansoprazole. He has had no other past medical problems.

On examination, Henry's pulse is 88 beats per minute (regular), blood pressure is 135/83 mmHg, respiratory rate is 16 breaths per minute and he is afebrile. His oxygen saturation is 96% in room air. There is no tenderness of his chest wall, both heart sounds are audible, there are no murmurs and his chest sounds clear. His jugular venous pressure is not elevated and he has no peripheral odema.

You arrange for an electrocardiograph (ECG), which is unchanged compared with his last ECG performed 6 months ago in the context of symptoms of heartburn and waterbrash.

QUESTION 1

What clinical features might indicate that Henry's chest tightness was due to coronary artery disease?

QUESTION 2

In general, what blood tests can be performed to investigate patients who present with chest pain suspected to be ischaemic in origin?

FURTHER INFORMATION

You request blood tests for Henry including troponin. Henry's troponin result is recorded in *Table 6* below.

Table 6. Henry's high sensitivity troponin T

	Result	Normal reference interval
High sensitivity troponin T (hs-TnT)	30 ng/L	<15 ng/L

QUESTION 3

How would you interpret Henry's hs-TnT result?

QUESTION 4

In a patient who presents with ischaemic-sounding chest pain on the same day as the pain, how soon after the first hs-TnT would you repeat the hs-TnT level? When would you repeat Harry's hs-TnT level?

CASE 2 ANSWERS

ANSWER 1

There are a number of clinical features that help predict chest pain due to coronary artery disease. They include:[13]

- whether the patient is at risk based on their age and history of known clinical vascular disease – such as coronary artery disease, cerebrovascular disease or peripheral vascular disease. An elderly man like Henry is considered at risk. However, his absence of previous clinical vascular disease is a factor in his favour
- the relationship of exercise to the pain. Chest pain brought on by exercise is a reliable indicator of ischaemic heart disease
- whether the pain is reproducible with palpation. The fact that Henry's chest pain could not be reproduced by palpation is significant
- whether the patient believes the pain is of cardiac origin. The fact that Henry believes the pain is cardiac in origin is an important consideration.

ANSWER 2

Cardiac markers that can be requested in cases of suspected ischaemic chest pain include troponin, creatinine kinase (CK) and creatinine kinase MB (CK-MB).

In all patients with chest pain suggestive of cardiac ischaemia where the pain is new, recurrent, increasingly frequent or prolonged, the presumptive diagnosis should be acute coronary syndrome (myocardial infarction or unstable angina).[14]

The preferred test for an acute coronary syndrome is a troponin test. Compared with CK and its isoenzyme CK-MB, troponin release is as fast as the release of CK-MB, and troponin is highly specific for cardiac injury. Furthermore, highly sensitive troponin assays that can detect the mildest cardiac injury exist. Unlike CK and its isoenzyme CK-MB, which are elevated for a couple of days following an ischaemic event, troponin is usually elevated for 7–10 days after the event[15] (see *Figure 1*).

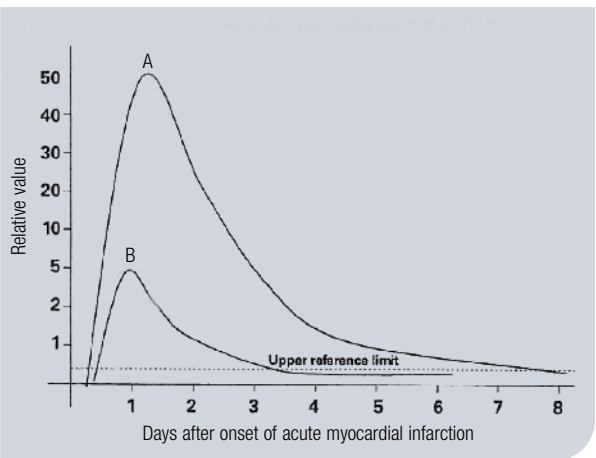

Figure 1. Timing of release of cardiac markers. A: troponin; B: creatine kinase-MB

ANSWER 3

Henry's hs-TnT result is clearly elevated compared to the upper reference limit of 14 ng/L for the cardio-healthy Australian population.[16] High sensitivity troponin levels below this level reflect the fact that healthy individuals have tiny, but detectable, levels of hs-TnT. Henry's elevated hs-TnT in combination with his clinical history is consistent with a possible cardiac event 3 days ago.

However, non-infarct causes of cardiac myocyte injury such as myocarditis, congestive cardiac failure and pulmonary embolus as well as renal impairment can also increase the troponin level. In addition, troponin levels are known to be often elevated in elderly patients.[17]

While there are many causes of an elevated troponin other than myocardial infarct, they are, nevertheless, each associated with increased risk of cardiovascular mortality. A patient with a hs-TnT above 14 ng/L has a 60% cardiovascular mortality risk over the next 10 years.[18] This risk may not be unexpected in an 82-year-old man, but would be very unusual in a young man.

It is relevant to note that Henry's ECG is unchanged compared to his previous ECG performed 6 months earlier. An ECG is unlikely to reveal changes in the presence of a small troponin rise such as in Henry.

ANSWER 4

A repeat hs-TnT 3 hours after the first is indicated when a patient presents acutely on the same day as chest pain.[19] In an acute coronary syndrome, a 50% rise is generally thought to signify an acute myocardial infarct,[19] but this will not be seen if patients present later when the level of hs-TnT is in the plateau phase.

However, in Henry it may be useful to repeat the hs-TnT in 1 week, when any elevation from an acute event is likely to have subsided. When interpreting hs-TnT over weeks, a 100% rise or 50% fall is considered to be a considerable change.[20] If Henry's next hs-TnT, at least 1 week after the first, is <15 ng/L or >60 ng/L, he can be considered to have had a significant improvement or worsening of his condition respectively.

CASE 3

CONNIE IS CONCERNED ABOUT HER INCREASING BODY HAIR

Connie, aged 16 years, says she has noticed increasing facial and body hair over the last 6 months. She wonders if there is 'something wrong with her hormones'.

On further questioning, Connie has irregular periods, which occur once every 2 or 3 months. This has occurred since menarche 4 years ago. Connie's last menstrual period was about 2 months ago and she has never been sexually active. She has no relevant past medical history and takes no medications.

On examination, Connie has hirsutism and acne. Her blood pressure is 112/75 mmHg and her BMI is 26 kg/m^2.

QUESTION 1

What is your working diagnosis?

QUESTION 2

What investigations would you request?

FURTHER INFORMATION

You request blood tests for Connie. The following table shows Connie's hormone results.

Table 7. Connie's hormone results

	Result	Normal reference interval
Follicle stimulating hormone (FSH)	4 IU/L	follicular phase 2.8–9.3 IU/L midcycle 3.0–19.2 IU/L luteal phase 1.7–7.7 IU/L
Luteinising hormone (LH)	8 IU/L	follicular phase 2.8–7.6 IU/L midcycle 10.5–8.5 IU/L luteal phase 1.0–11.4 IU/L
Total testosterone	1.8 nmol/L	<1.9 nmol/L
Sex hormone binding globulin (SHBG)	15 nmol/L	30–150 nmol/L
Calculated free testosterone (cFT)	45 pmol/L	3–37 pmol/L
Dehydroepiandrosterone sulphate (DHEAS)	17 µmol/L	3–15 µmol/L
17-hydroxyprogesterone	3.7 nmol/L	0.6–12.0 nmol/L

Connie's TSH and prolactin level are both normal.

Connie's fasting BGL is shown in *Table 8* below.

Table 8. Connie's fasting blood glucose level (BGL)

	Result	Normal reference interval
Fasting BGL	5.8 mmol/L	3.8–6.0 mmol/L

QUESTION 3

How would you interpret Connie's hormone levels?

QUESTION 4

How would you interpret Connie's fasting BGL?

CASE 3 ANSWERS

ANSWER 1

As Connie has evidence of hirsutism and oligomenorrhoea, a diagnosis of polycystic ovarian syndrome (PCOS) should be considered. Patients with PCOS can present with:

- menstrual disturbance such as oligomenorrhoea, amenorrhoea or anovulatory dysfunctional uterine bleeding
- symptoms or signs of androgen excess such as hirsutism or acne
- infertility
- obesity.

According to the Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group 2003, the diagnosis of PCOS requires that at least two out of the following three criteria be met for a diagnosis of PCOS:[21]

- oligo-ovulation and/or anovulation
- clinical and/or biochemical signs of hyperandrogenism
- polycystic ovaries on ultrasound (defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume greater than 10 ml).

It is also necessary that other aetiologies – such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing syndrome – be excluded in order to make the diagnosis of PCOS.

ANSWER 2

You could request the following tests (see *Answers 3* and *4*):

- investigations to confirm the diagnosis of PCOS
- investigations to exclude other diagnoses
- investigations to assess for complications of PCOS

ANSWER 3

While Connie's LH is higher than her FSH (ratio 2:1), a higher LH/FSH ratio (>2.5:1) is accepted as evidence for PCOS.[22] However, an altered LH/FSH ratio is not essential to make a diagnosis of PCOS.

Connie's total testosterone level is normal. This is a common finding in PCOS. Testosterone exists in two forms; in a free, bioavailable form or bound to SHBG. While total testosterone levels in PCOS are often normal, cFT levels are often elevated, as is the case in Connie. This probably explains her hirsutism. In PCOS, the cFT is often elevated as a consequence of a decrease in SHBG, which occurs due to hyperinsulinaemia in the setting of insulin resistance – a common finding in PCOS.

Connie's DHEAS level is slightly elevated, but this is not unusual around puberty. In general, total testosterone levels usually correlate with DHEAS levels.[23] Testosterone in women is produced by both the ovaries and adrenal glands, but ovarian testosterone also depends on DHEAS produced from the adrenal gland.

Blood tests that should be requested for Connie to exclude other endocrinopathies include TSH, prolactin, DHEAS (markedly elevated in adrenal tumours) and 17-hydroxyprogesterone (this is elevated in late onset congenital adrenal hyperplasia).[21] In patients where relevant, β human chorionic gonadotrophin should also be requested.

Ideally, blood tests for hyperandrogensim should occur in the follicular phase in women who are regularly menstruating.[24]

Ultrasound is generally not recommended first line in adolescents for diagnosis of PCOS given its lack of specificity.[24]

For patients where ultrasound is appropriate, an ultrasound should be performed by an experienced operator in a reputable facility. Ideally it should be performed in the early follicular phase (days 3–5 of the menstrual cycle if regularly menstruating). It should preferably be transvaginal, except in those who have never been sexually active. An ultrasound allows for confirmation of the diagnosis of PCOS, and also provides the opportunity to check for endometrial hyperplasia, which can be a complication of PCOS. The ultrasound diagnostic criteria for polycystic ovaries are listed in *Answer 1*. However, PCO seen on ultrasound in a woman in the absence of an ovulatory disorder or hyperandrogenism does not classify for a diagnosis of PCOS.[21]

ANSWER 4

Connie's fasting BGL is in the normal reference interval of 3.8–6.0 mmol/L. In Australia, impaired fasting glycaemia is defined as a glucose level between 6.1–6.9 mmol/L. However, many countries, including the USA, define impaired fasting glycaemia as fasting glucose levels between 5.6–6.9 mmol/L. In fact, current Australian guidelines suggest that an oral glucose tolerance test (OGTT) be performed for patients with fasting glucose levels between 5.6–6.9 mmol/L.[25]

Insulin resistance is commonly associated with PCOS. It is possible for a patient to have insulin resistance, but no evidence of impaired glucose tolerance because their insulin resistance is compensated by hyperinsulinism. While it is possible to measure insulin levels, it is not routinely recommended at present. In Connie's case it is not necessary as her low SHBG already demonstrates evidence of hyperinsulinism.

While glycated haemoglobin (HbA1c) is now accepted as a diagnostic test for diabetes in Australia,[26] it is not covered by the Medicare Benefits Schedule and there is no HbA1c level that has been accepted as a cut-off point for impaired glucose tolerance.

Some controversy still exists about what test to perform to screen for impaired glucose intolerance or diabetes in patients with PCOS.[27] However, the Jean Hailes Foundation for Women's Health on behalf of the PCOS Australian Alliance evidence-based guideline suggests an OGTT should be performed in all women with PCOS at diagnosis.[24]

Dyslipidaemia is also associated with PCOS. Lipid studies should also be requested.

CASE 4

ZARA IS EXPERIENCING HOT FLUSHES

Zara, aged 49 years, has a past history of hypothyroidism and has been on the same dose of thyroxine (100 µg a day) for 20 years. She consulted you 3 months ago with disabling hot flushes in the setting of irregular periods. At that stage you discussed her options for treatment of hot flushes. You also assessed her cardiovascular risk factors and discussed prevention of osteoporosis. Zara decided to start hormone replacement therapy (HRT).

Zara presents to you and says she is still experiencing hot flushes. She's not sure if the symptoms are menopausal, or whether they could be due to her thyroxine treatment. You request TFTs, the results are shown in *Table 9* below.

Table 9. Zara's thyroid function tests

	Result	Normal reference interval
TSH	3.0 mIU/L	0.5–5.0 mIU/L
fT4	21 pmol/L	9.0–19.0 pmol/L
fT3	4.0 pmol/L	3.5–5.5 pmol/L

QUESTION 1

How would you interpret Zara's TFTs?

CASE 4 ANSWER

ANSWER 1

The only abnormality in Zara's TFTs is a raised fT4.

When monitoring patients taking thyroxine (T4) therapy, it is more like therapeutic drug monitoring than assessing the thyroid gland. In patients taking thyroxine therapy, fT4 levels should be between 15–23 pmol/L, not between 9.0–19.0 pmol/L as suggested by the hormone reference interval.[28] Also, because Zara is taking T4 rather than T3 treatment, fT3 levels should be in the lower part of that reference interval.

For these reasons, TSH is actually the best indicator of T4 treatment. While there is considerable debate regarding ideal TSH levels,[29] the recommended target for patients taking thyroxine therapy is probably a TSH level between 0.3–1.0 mIU/L, (ie. in the lower part of the reference interval). This is because TSH production by the pituitary gland will be reduced by feedback inhibition.

Zara's TSH level of 3.0 mIU/L could be improved. Oestrogen treatment, like anti-convulsant medications, is metabolised by the liver, and is known to induce increased thyroxine catabolism. Therefore, thyroxine requirements may increase in patients taking oestrogen treatment. However, a good rule for thyroxine therapy is not to change what has been a reliable regimen of treatment on the basis of one result. Zara's symptoms are more likely to be related to her peri-menopausal status than to minor variations in thyroid hormones.

CASE 5

MATHIAS HAS ABNORMAL LIVER FUNCTION TEST RESULTS

Mathias, aged 40 years is an accountant. He consulted another doctor 2 weeks ago for an insurance medical examination. Abnormal LFTs were discovered and he was advised to see you for follow-up. Mathias has been well recently with no symptoms. He has no relevant past medical or surgical history, and takes no medication. He drinks a couple of glasses of wine or beer once a week. He has not travelled overseas recently, has a longterm partner and has no relevant family history.

On examination, Mathias' blood pressure is 140/90 mmHg. His BMI is 33 kg/m^2. His abdominal examination reveals no abnormalities, in particular, no hepatomegaly. He has no peripheral stigmata of liver disease.

Mathias' LFTs are shown below.

Table 10. Mathias' liver function tests

	Result	Normal reference interval
Bilirubin	35 µmol/L	3–20 µmol/L
Alkaline phosphatase (ALP)	97 U/L	30–110 U/L
Gamma-glutamyl transferase (GGT)	44 U/L	10–50 U/L
Alanine transaminase (ALT)	127 U/L	5–40 U/L
Aspartate transaminase (AST)	40 U/L	5–40 U/L
Total protein	77 g/L	64–79 g/L
Albumin	46 g/L	35–48 g/L

QUESTION 1

What is/are the most likely cause(s) of Mathias' abnormal LFTs?

QUESTION 2

What further investigations would you request for Mathias?

FURTHER INFORMATION

You request hepatitis B and C serology as well as fasting blood tests for iron studies, BGL and lipids. Hepatitis B and C serology as well as fasting iron studies and BGL are all within normal limits. Mathias' lipid studies are shown in *Table 11* below.

Table 11. Mathias' lipid studies

	Result	Normal reference interval
Total cholesterol	6.2 mmol/L	<5.5 mmol/L
High density lipoprotein cholesterol (HDL-C)	0.9 mmol/L	>1.0 mmol/L
Low density lipoprotein cholesterol (LDL-C)	4.2 mmol/L	<3.5 mmol/L
Triglyceride	2.4 mmol/L	<1.5 mmol/L
Total cholesterol/HDL-C ratio	6.9	<4.5

You also arrange for an ultrasound of the liver, which reveals changes consistent with non-alcoholic fatty liver disease (NALFD).

QUESTION 3

What does Mathias' lipid profile indicate?

CASE 5 ANSWERS

ANSWER 1

Mathias' bilirubin is elevated and his ALT is also elevated.

The most likely cause of Mathias' elevation in bilirubin is Gilbert syndrome. This is due to decreased conjugation of bilirubin and is present in up to 15% of the Australian population.[30] Laboratories vary in their upper reference limits for bilirubin between 18–25 µmol/L, and this can affect whether bilirubin is reported as abnormal or not.

Gilbert syndrome is usually of no clinical consequence. In fact, bilirubin is one of the main antioxidants in serum and its elevation in Gilbert syndrome is considered cardioprotective.[31] Unless bilirubin levels are above about 50 µmol/L there will be no clinical evidence of jaundice.[32,33]

An elevated bilirubin should be investigated if there is evidence of either biliary obstruction or anaemia. Mathias' ALP and GGT are normal, which suggests that biliary obstruction is not present, and there is no suggestion of haemolytic anaemia such as anaemia, dark urine or an increase in AST.

Mathias' elevation of ALT, which is specific for liver damage, needs an explanation. The most likely explanation of a raised ALT in our community is NAFLD. It is usually asymptomatic and diagnosed incidentally on the basis of abnormal LFTs or medical imaging.[34] It is closely associated with the metabolic syndrome.[34] The criteria for the diagnosis of metabolic syndrome according to the International Diabetes Federation are:[35]

- central obesity (defined as waist circumference ≥94 cm for European men and ≥80 cm for European women, with ethnicity specific values for other groups)

plus any two of the following four factors:

- raised TG (≥1.7 mmol/L) or on specific treatment for this
- reduced HDL-C (≤1.03 mmol/L in males and ≤1.29 mmol/L in females) or on specific treatment for this
- raised blood pressure: systolic BP≥130 mmHg or diastolic BP≥85 mmHg or on treatment for previously diagnosed hypertension
- raised fasting BGL (≥5.6 mmol/L) or previously diagnosed type 2 diabetes.

NAFLD can be characterised by inflammation or progress to fibrosis and cirrhosis. As AST is a short-lived enzyme in vivo, when it is elevated it suggests more active disease that could progress.

ANSWER 2

Mathias has no features on history that suggest viral hepatitis due to hepatitis A, B, C, Epstein Barr virus or cytolomegalovirus. However, viral hepatitis cannot be excluded without serology. Serology for hepatitis B and C should be requested. Haemochromatosis is not an uncommon cause of chronic hepatitis in a man of Mathias' age and fasting iron studies should be requested in the first instance.

Investigations for rarer causes of abnormal ALT such as autoimmune hepatitis, Wilson disease and alpha-1 antitrypsin deficiency should be requested in certain circumstances. Examples of these circumstances are where another explanation of the elevated ALT is not available, the condition progresses, or a family history suggestive of one of these causes is present.

ANSWER 3

Mathias' elevated TG and low HDL-C are criteria for the diagnosis of the metabolic syndrome. The cholesterol/HDL-C ratio is one of the most powerful predictors of cardiovascular risk, and the total cholesterol and HDL-C are used to assess risk in the Australian absolute cardiovascular risk calculator (see *Resources*) in combination with other factors.

It is also important to appreciate the reason why high TGs and low HDL-C are so important. The levels of these parameters predict that the low density lipoproteins (LDLs) in this patient are not only elevated, but very likely to be in the form of highly atherogenic small dense LDL particles.[36] While reducing the concentration of these particles with a statin may appear to be a reasonable approach, altering the nature of these particles by addressing the metabolic syndrome and insulin resistance may be more beneficial.

CASE 6

AMIR HAS A SORE BACK

Amir, aged 72 years, presents with 2 months of lumbosacral back pain. It was initially precipitated by activity such as walking, but is now occurring at rest and interfering with his sleep. He has tried paracetamol and diclofenac without effect. He also experiences some transient shortness of breath on climbing the hill in his street while walking the dog each day. Symptom review reveals that he gets up to go to the toilet twice each night, but has no other symptoms suggestive of prostate disease.

Amir has no history of falls or fractures. He has no relevant past history and takes no medication. He has no relevant family history. He is a non-smoker.

Examination reveals a thin man with normal vital signs. There is spinal tenderness at L3 and L5. He has no neurological signs in his lower limbs and his abdominal examination reveals no abnormalities. Digital rectal examination reveals a mildly enlarged prostate, which feels benign. Amir's chest is clear, his jugular venous pressure is not elevated and he has no peripheral oedema.

QUESTION 1

What is your differential diagnosis?

QUESTION 2

What investigations would you request?

FURTHER INFORMATION

Amir's FBE reveals a normochromic normocytic anaemia.

Amir's ESR result is shown below in *Table 12*.

Table 12. Amir's erythrocyte sedimentation rate

	Result	Normal reference interval
Erythrocyte sedimentation rate (ESR)	88 mm/hour	2–14 mm/hour

Amir's PSA result is shown in *Table 13*.

Table 13. Amir's prostate-specific antigen

	Result	Normal reference interval
Prostate-specific antigen (PSA)	8.5 µg/L	0.3–6.5 µg/L

Amir's UEC results are shown in *Table 14*.

Table 14. Amir's urea, electrolytes and creatinine

	Result	Normal reference interval
Sodium	142 mmol/L	135–145 mmol/L
Potassium	4.2 mmol/L	3.5–5.2 mmol/L
Chloride	101 mmol/L	95–110 mmol/L
Bicarbonate	25 mmol/L	22–30 mmol/L
Urea	9.6 mmol/L	3.5–8.5 mmol/L
Creatinine	125 µmol/L	60–110 µmol/L
Estimated glomerular filtration rate (eGFR)	49 ml/min/1.73m^2	>60 ml/min/1.73m^2

Amir's calcium-related tests are shown in *Table 15*.

Table 15. Amir's 'calcium-related' tests

	Result	Normal reference interval
Calcium	2.50 mmol/L	2.15–2.55 mmol/L
Total protein	82 g/L	64–83 g/L
Albumin	36 g/L	35–45 g/L
Corrected calcium	2.64 mmol/L	2.15–2.55 mmol/L
25-hydroxycholecalciferol (25-OH Vit D)	42 nmol/L	>50 nmol/L
Parathyroid hormone (PTH)	0.6 pmol/L	1.0–7.0 pmol/L

Amir's serum protein immunoelectrophoresis (SPIEP) results are shown in *Table 16*.

Table 16. Amir's serum protein immunoelectrophoresis results

	Result	Normal reference interval
Total protein	82 g/L	63–80 g/L
Albumin	36 g/L	38–51 g/L
Alpha 1 band	5.7 g/L	2.2–4.1 g/L
Alpha 2 band	10.3 g/L	4.9–8.7 g/L
Beta 1 band	5.0 g/L	3.4–5.8 g/L
Beta 2 band	19.0 g/L	2.1–4.9 g/L
Gamma band	5.3 g/L	6.0–16.0 g/L
An IgA kappa paraprotein band of 18 g/L is detected in the beta 2 region and is associated with immune paresis.		

Amir's LFTs are within normal limits.

Amir's chest X-ray (CXR) is normal.

QUESTION 3

How would you interpret Amir's PSA result?

QUESTION 4

How would you interpret Amir's UEC?

QUESTION 5

How would you interpret Amir's calcium-related tests?

QUESTION 6

How would you interpret Amir's SPIEP?

CASE 6 ANSWERS

ANSWER 1

Your differential diagnoses include:

- osteoarthritis
- soft tissue injury
- prostate cancer with bony metastases
- lung cancer with bony metastases
- multiple myeloma
- osteoporosis with a crush fracture
- Paget disease.

The fact that the pain is persistent, worsening, not responding to usual analgesics and is associated with focal spinal tenderness suggests a serious cause.

ANSWER 2

The following investigations could be requested for Amir:

- FBE, looking for anaemia
- ESR, looking for an elevated ESR, which occurs in multiple myeloma and can occur in carcinoma
- CRP, checking for evidence of recent inflammation or infection, which helps in the interpretation of an elevated ESR
- PSA test, after appropriate counselling regarding the limitations of the test
- UEC, checking for renal impairment
- LFTs, looking for an elevated ALP that can occur in the presence of bony metastases or Paget disease
- calcium, PTH level and vitamin D
- SPIEP, looking for evidence of a paraprotein
- lumbosacral X-rays, looking for osteolytic lesions of multiple myeloma or bony metastases
- CXR, looking for a cause of shortness of breath such as lung carcinoma
- bone densitometry, looking for evidence of osteoporosis, could also be requested depending on the results of the above investigations.

ANSWER 3

Amir's PSA level is elevated compared to the age-specific reference limit. Although there is a 30% chance of prostate cancer with such an elevation it is very unlikely that any cancer would have spread to bone. He should be informed that this is not likely to be the cause of his back pain.[37,38] While Amir seems relatively active and healthy for his age, the immediate concern is his back pain and discussion of further PSA monitoring should be deferred until the cause of his back pain is evident.

ANSWER 4

Amir has significant renal impairment with both elevated urea and creatinine, and reduced eGFR calculated according to his age and gender. Although he appears more active than most 72-year-old men, it is unlikely that he has significant variation in muscle mass from the average 72-year-old precluding the use of the eGFR as a reliable indicator of renal function. Therefore, a 24-hour urine collection for creatinine clearance is unlikely to add significant information.

As prostate disease is unlikely to be the cause of Amir's renal impairment, further investigation is needed. A urine albumin level to assess for the presence of renal damage may be useful.

ANSWER 5

While Amir's corrected calcium (ie. calcium level that has been corrected for his low albumin level) is borderline-high, his vitamin D and PTH levels do not provide an explanation for this. If his PTH level were elevated, it would be clinically significant. But it is not usually elevated unless vitamin D is much lower (< 30 nmol/L).[39] Furthermore, we might expect the PTH level to be elevated in a man who has renal impairment, so this rules out hyperparathyroidism.

The most concerning aspect of Amir's results are that his total protein level is borderline-high and his albumin level is borderline-low, which means that his globulin level (82 g/L minus 36 g/L equals 46 g/L) is elevated (usual reference limits 24–39 g/L).

ANSWER 6

The increase in serum protein (globulins) is likely to be due to an abnormal paraprotein characterised as an IgA kappa band. There is a small increase in alpha 1 and alpha 2 globulins, suggestive of mild inflammation in the last few weeks. The gamma region is also lacking its usual levels of gamma globulins and this suggests that the plasma cells, which are producing the paraprotein, may be taking over Amir's bone marrow.

Other features that support a diagnosis of multiple myeloma are the presence of a normochromic normocytic anaemia of chronic disease, an elevated ESR, hypercalcaemia (not due to hyperparathyroidism) and renal impairment, (which is more likely with kappa light chains).[40]

Further investigation could include urinalysis looking for Bence Jones protein. An excess production of light chains (in this case kappa light chains) indicates an imbalance of heavy and light chain production, which is more typical of malignant plasma cells. This historical test is gradually being superceded by the measurement of light chains in serum because serum free light chains are more sensitive studies than urine studies.

The results are highly suggestive of multiple myeloma, which bone X-rays with or without a nuclear bone scan would usually identify. Amir's myeloma-associated hypercalcaemia, usually due to PTH-related protein production by the myeloma, may cause polyuria and polydipsia due to the nephrogenic diabetes insipidus in the short-term and generalised reabsorption of bone in the long-term.[41]

1. Flecknoe-Brown S. Tired all the time. Common sense pathology 2010;August:1–5.
2. Working Group of the Royal Australian College of Physicians. Chronic fatigue syndrome: Clinical practice guidelines. Med J Aust 2002;176(Suppl.):S23–56.
3. So M, MacIsaac RJ, Grossman M. Hypothyroidism – investigation and management. Aust Fam Physician 2012;41(8):557–562.
4. Campbell K, Doogue M. Evaluating and managing patients with thyrotoxicosis. Aust Fam Physician 2012;41(8):557–562.
5. Wallace I, Cunningham S, Lindsay J. The diagnosis and investigation of adrenal insufficiency in adults. Ann Clin Biochem 2009; 46: 351–367.
6. Bird S. Failure to diagnose: Addison Disease. Aust Family Physician 2007;36(10):859–861.
7. Sikaris KA. Combining clinical biochemistry and haematology databases to define predictive values for ferritin. Clin Biochem Rev 1997;18:81.
8. Patel YC, Alford FP, Burger HG. The 24-hour plasma thyrotropin profile. Clin Sci 1972;43:71–7.
9. Russell W, Harrison RF, Smith N, Darzy K, Shalet S, Weetman AP, et al. Free triiodothyronine has a distinct circadian rhythm that is delayed but parallels thyrotropin levels. J Clin Endocrinol Metab 2008;93:2300–6.
10. Hargreaves KM. Neuroendocrine markers of stress. Anesth Prog 1990;37:99–105.
11. Mebis L, Van den Berghe G. Thyroid axis function and dysfunction in critical illness. Best Pract Res Clin Endocrinol Metab 2011;25:745–57.
12. Novartis Synacthen®product indformation. Available at www.novartis.com.au/Downloadfile.aspx?t=p&f=syn.pdf [accessed 20 October 2012].
13. Bösner S, Haasenritter J, Becker A, Karatolios K, Vaucher P, Gencer B, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. Can Med Assoc J 2010;182:1295–300.
14. Cardiovascular Expert Group. Therapeutic guidelines: cardiovascular. Version 5. Melbourne: Therapeutic Guidelines Limited, 2008.
15. Lewandrowski K, Chen A, Januzzi J. Cardiac markers for myocardial infarction. Am J Clin Pathol 2002;118(Suppl.):S93–9.
16. Koerbin G, Tate JR, Hickman PE. Analytical characteristics of the Roche highly sensitive troponin T assay and its application to a cardio-healthy population. Ann Clin Biochem 2010;47:524–8.
17. Vasikaran SD, Bima A, Botros M, Sikaris KA. Cardiac troponin testing in the acute care setting: ordering, reporting, and high sensitivity assays-an update from the Canadian society of clinical chemists; the case for age related acute myocardial infarction cut-offs. Clin Biochem 2012 Apr;45(6):513–4.
18. Alehagen U, Dahlström U, Rehfeld JF, Goetz JP. Prognostic assessment of elderly patients with symptoms of heart failure by combining high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide measurements. Clin Chem. 2010;56:1718–24.
19. Chew DP, Aroney CN, Aylward PE, Kelly AM, White HD, Tideman PA, et al. 2011 addendum to the National Heart Foundation of Australia/ Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. Heart Lung Circ 2011;20:487–502.
20. Frankenstein L, Wu AH, Hallermayer K, Wians FH JR, Giannitis E, Katus HA. Biological variation and reference change value of high-sensitivity troponin T in healthy individuals during short and intermediate follow-up periods. Clin Chem. 2011;57:1068–71.
21. ESHRE/ASRM-sponsored PCOS Consensus Working Group. Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovarian syndrome. Available at www.pcos.gr/gr/files/ESHR_ASRM_PCOS.pdf [accessed 22 September 2012.]
22. Battaglia C, Regnani G, Mancini F, Iughetti L, Venturoli S, Flamigni C. Polycystic ovaries in childhood: a common finding in daughters of PCOS patients. A pilot study. Hum Reprod 2002;17:771–6.
23. Davison SL, Bell R, Montalto JG, Sikaris K, Donath S, Stanczyk FZ, et al. Measurement of total testosterone in women: comparison of a direct radioimmunoassay versus radioimmunoassay after organic solvent extraction and celite column partition chromatography. Fertil Steril. 2005 Dec;84(6):1698–704.
24. Jean Hailes Foundation for Women's Health on behalf of the PCOS Australian Alliance. Evidence-based guideline for the assessment and management of polycystic ovarian syndrome. Melbourne: 2011. Available at www.managingpcos.org.au/ [accessed 22 September 2012.]
25. Colagiuri S, Davies D, Girgis S, Colagiuri R. National evidence based guideline for case detection and diagnosis of type 2 diabetes. Canberra: Diabetes Australia and the NHMRC, 2009.
26. d'Emden MC, Shaw JE, Colman PG, Colagiuri S, Twigg SM, Jones GR, et al. The role of HbA1c in the diagnosis of diabetes mellitus in Australia. Med J Aust 2012;197(4): 220–221.
27. Boyle J, Teede HJ. Polycystic ovarian syndrome: an update. Aust Fam Physician 2012;41(10):752–756.
28. Burnett JR, Cooke R, Crooke MJ, Feek CM. A study of L-thyroxine replacement. N Z Med J. 1992;105:105–6.
29. Phillips PJ. Thyroid Therapy – Tips and traps. Aust Fam Physician 2012;41(8):589–91.
30. Gürtler V, Parkin JD, Mayall BC. Use of double gradient denaturing gradient gel electrophoresis to detect (AT)n polymorphisms in the UDP-glucuronosyltransferase 1 gene promoter associated with Gilbert's syndrome. Electrophoresis 1999;20:2841–3.
31. Lin JP, Schwaiger JP, Cupples LA, O'Donnell CJ, Zheng G, Schoenborn V, et al. Conditional linkage and genome-wide association studies identify UGT1A1 as a major gene for anti-atherogenic serum bilirubin levels-the Framingham Heart Study. Atherosclerosis 2009;206:228–33.
32. Roche SP, Kobos R. Jaundice in the adult patient. Am Fam Physician. 2004 15;69(2):299–304.
33. Coates P, Liver Function Tests. Common sense pathology 2009;June:1–8.
34. Chin Hee K, Zobair MY. Nonalcoholic fatty liver disease: A manifestation of the metabolic syndrome. Cleveland Clinic Journal of Medicine 2008: 75(10):721–728.
35. International Diabetes Federation. International Diabetes Federation worldwide definition of the metabolic syndrome. Available at www.idf.org/metabolic-syndrome [accessed 22 September 2012.]
36. St-Pierre AC, Cantin B, Dagenais GR, Mauriége P, Després JP, Lamarche B. The triglyceride/high-density lipoprotein cholesterol ratio, the small dense low-density lipoprotein phenotype, and ischemic heart disease risk. Metab Syndr Relat Disord. 2004;2:57–64.
37. Sikaris K. Prostate cancer screening. Pathology. 2012;44:99–109.
38. Lam QT, Frydenberg M. Strategies for detecting prostate cancer. Common Sense Pathology 2009;March:1–8.
39. Chen JS, Sambrook PN, March L, Cameron ID, Cumming RG, Simpson JM, et al. Hypovitaminosis D and parathyroid hormone response in the elderly: effects on bone turnover and mortality. Clin Endocrinol (Oxf) 2008; 68:290–8.
40. Mollee P. Current trends in the diagnosis, therapy and monitoring of the monocloncal gammopathies. Clin Biochem Rev. 2009; 30: 93–103.
41. Zajac J, Ebeling P. Biochemical measurements in osteoporosis. Common Sense Pathology 2003;April:1–10.

RESOURCES FOR DOCTORS

- The Royal College of Pathologists of Australasia (RCPA) produces a manual on the use and interpretation of pathology tests, which is available at www.rcpamanual.edu.au/ – it provides a search facility by clinical problem and pathology test as well as pathology decision support tools for testing patients who present with particular symptoms. The RCPA also publishes *Common sense pathology*, which is a regular case-based series on practical topics for GPs. It is available at www.rcpa.edu.au/Publications/CommonSensePathology.htm
- Information on requesting and interpreting troponin is outlined in the journal article. The 2011 addendum to the guidelines for 'the management of acute coronary syndromes 2006', available at www.heartfoundation.org.au/sitecollectiondocuments/2011-ACS-addendum-article-in-press.pdf
- Australian absolute cardiovascular disease risk calculator is available at www.cvdcheck.org.au
- Jean Hailes Foundation for Women's Health provides a wide range of information for GPs on PCOS including a summary on diagnosis and management. This information is available at www.managingpcos.org.au/
- The following publication clarifies what test to request to assist in the diagnosis of certain endocrine conditions and also explains interpretation of tests such as TFTs: Endocrinology Expert Group. Therapeutic guidelines: endocrinology. Version 4. Melbourne: Therapeutic Guidelines Limited, 2009
- *Australian Family Physician* 'test and results' series for 2011 provides information on various biochemistry investigations such as LFTs and the OGTT. It is available at www.racgp.org.au/afp
- *Australian Prescriber* provides information on interpretation of various tests such as TFTs. It is available at www.australianprescriber.com/

RESOURCES FOR PATIENTS

- The Victorian Government Department of Health's 'Better Health Channel' provides information on a wide variety of medical conditions including fatigue, Addison disease, cardiovascular risk factors and cardiovascular disease, PCOS, thyroid disorders and NAFLD. It is available at www.betterhealth.vic.gov.au
- Jean Hailes Foundation for Women's Health provides patient information on PCOS at www.managingpcos.org.au/health-professionals/patient-information
- The Gastroenterological Society of Australia produces a fact sheet for patients on NAFLD. It is available at www.gesa.org.au/
- Cancer Council Victoria is available at www.cancervic.org.au/ and provides patient information on cancers such as multiple myeloma

Biochemistry

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at www.gplearning.com.au, and
- log onto the *gplearning* website at www.gplearning.com.au and answer the following 10 multiple choice questions (MCQs) online, and
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at www.gplearning.com.au

If you have any queries or technical issues accessing the test online, please contact the *gplearning* helpdesk on 1800 284 789.

FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3.

QUESTION 1

Samantha, aged 28 years, presents with 4 months of tiredness. After obtaining further history and examining her, you request blood tests including an FBE, iron studies, CRP, TSH, UEC and LFTs. Which of the following is true in relation to interpretation of her iron studies?

A. Serum iron levels are not affected by diurnal variation.

B. The COCP typically results in a low transferrin level.

C. Transferrin saturation is calculated based on the serum ferritin and transferrin.

D. A high ferritin is always due to iron overload.

E. A low ferritin is a reliable indicator of iron depletion.

QUESTION 2

You receive a letter from an endocrinologist regarding Lucy, aged 32 years, who has been diagnosed with primary adrenocortical insufficiency. Which of the following is correct in relation to the interpretation of blood tests performed for suspected primary adrenocortical insufficiency?

A. A normal serum cortisol level usually excludes the diagnosis.

B. COCP use typically results in a cortisol level in the lower region of the normal reference interval.

C. 'Stress' often results in a cortisol level in the lower region of the normal reference interval.

D. The ACTH level is typically low in primary adrenocortical insufficiency.

E. An appropriate rise of cortisol level, to a specified level, during a short Synacthen® test usually excludes primary adrenocortical insufficiency.

QUESTION 3

Takaska, aged 68 years, presents with a suspected acute coronary syndrome to the emergency department of the local rural hospital where you work. An ECG reveals a left bundle branch block, and you have no previous ECG for comparison. You request blood tests, including troponin, CK and CK-MB. Which of the following is true regarding troponin in Takaska?

A. It is released more slowly than CK-MB.

B. It can be increased in the presence of non-infarct causes of cardiac myocyte damage.

C. It usually returns to a normal level 2 days after a cardiac event.

D. It should be repeated 1 hour after the first level is indicated.

E. It does not help predict cardiovascular mortality.

QUESTION 4

Ella, aged 25 years, presents with amenorrhoea. After obtaining further history and examining Ella, you consider that it is likely she has PCOS. You consider the Rotterdam PCOS consensus workshop group 2003 criteria for the diagnosis of PCOS. Which of the following is essential (ie. must be present) to make a diagnosis of PCOS?

A. Evidence of anovulation

B. The presence of polycystic ovaries on pelvic ultrasound

C. Clinical signs of hyperandrogenism

D. Obesity

E. Exclusion of other aetiologies of her symptoms.

QUESTION 5

Ella subsequently mentions that she had noticed hair growth on her upper lip, but thought nothing of it as her mother and sister also have upper lip hair growth. You decide to request blood tests for Ella. Which of the following is true regarding biochemical tests in PCOS?

A. An altered LH/FSH ratio is necessary for the diagnosis.

B. Total testosterone levels are invariably increased.

C. A reduction in SHBG can lead to an increase in calculated free testosterone.

D. DHEAS levels correlate poorly with total testosterone levels.

E. SHBG elevation commonly occurs in the presence of hyperinsulinaemia.

QUESTION 6

You arrange for Ella to have a pelvic ultrasound. In general, when requesting a pelvic ultrasound to assist in the diagnosis of PCOS:

A. it should ideally be performed transabdominally

B. it should ideally be performed in the luteal phase of the cycle

C. two or more follicles in each ovary seen on pelvic ultrasound are sufficient to label the ovaries as polycystic

D. it may reveal polycystic ovaries in normal women who do not have PCOS

E. the same ultrasound definition of polycystic ovaries applies to those taking the COCP.

QUESTION 7

Mae, aged 50 years, is on long-term thyroxine therapy for hypothyroidism. She presents with increasing tiredness over the past 3 months. You assess her clinically and wonder if her thyroid treatment could be inadequate and if this could be contributing to her tiredness. Which of the following is the best test for monitoring of thyroxine therapy?

A. TSH

B. fT4

C. fT3

D. thyroxine levels

E. thyroid autoantibodies.

QUESTION 8

Emilio, aged 56 years, says that his brother has just been diagnosed with NAFLD. He would like to know more about the condition. You inform him that NAFLD is:

A. uncommon in the developed world

B. commonly produces symptoms such as upper abdominal discomfort

C. closely associated with metabolic syndrome

D. commonly characterised by the biochemical finding of an isolated elevation in total bilirubin

E. usually of no clinical significance.

QUESTION 9

Tony, aged 45 years, presents with extensive onychomycosis. Prior to treatment with oral terbinafine, you request LFTs, which are abnormal. You obtain further history and examine Tony. You suspect NAFLD as the cause of his abnormal LFTs. Which of the following is true regarding the investigations you would request for Tony?

A. Hepatitis B and C serology and iron studies should be performed to help exclude other diagnoses.

B. Fasting lipid studies and blood glucose level should be performed to check for conditions that can be associated with NAFLD.

C. Rarer causes of abnormal LFTs should be investigated in certain circumstances, for example, if there is a family history of one of these causes.

D. Medical imaging, such as an ultrasound of the liver, may provide evidence to support the diagnosis.

E. All of the above.

QUESTION 10

Basil, aged 78 years, presents with bone pain in the ribs and lumbar spine, associated with tiredness and weight loss. Haematology testing reveals a normochromic, normocytic anaemia and a markedly elevated ESR. You then review his biochemistry results. Of the options below, which of the following would be MOST consistent with a diagnosis of multiple myeloma?

A. Bence Jones protein seen on serum protein immunoelectrophoresis

B. Reduced serum total protein

C. Hypocalcaemia

D. Renal impairment

E. Hypokalaemia.