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Medical Newsletter

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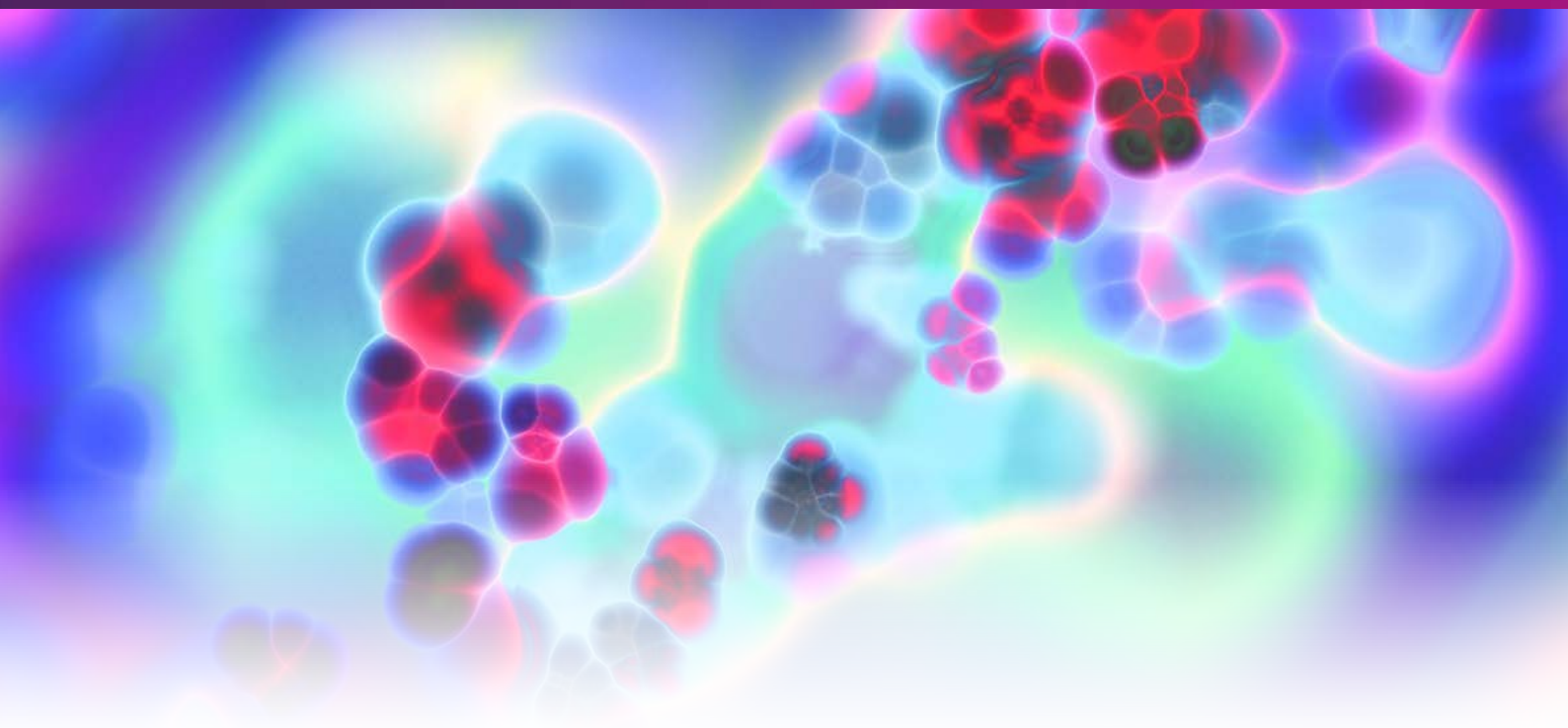


Accurate diagnosis of basal and squamous cell carcinomas in general practice

By Dr Gabriel Scripcaru and Dr Predrag Nikolic

Recognising the defining clinical features of various types of skin cancer, and an appropriate approach to the biopsy, are essential for their diagnosis and management. The importance of a timely diagnosis cannot be overemphasised, in view of achieving the best possible outcome and minimising the complications.

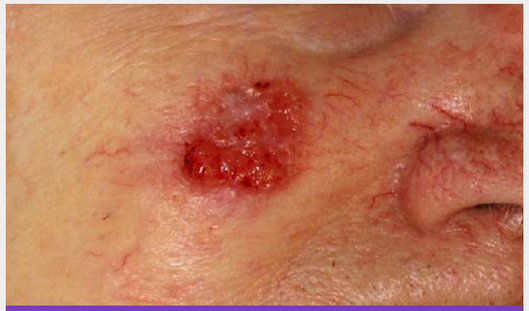
This article aims to discuss squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), two of the most common cancers in Australia.

Patient skin history

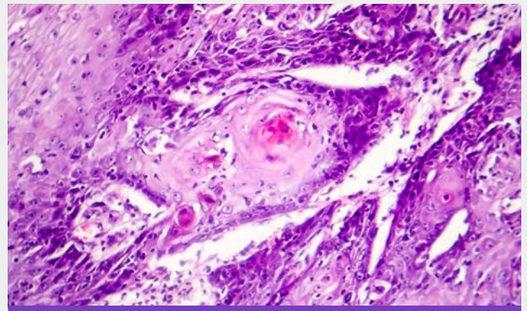
It is important to record the relevant patient skin history prior to completing a full body skin check or examining a particularly concerning new or changing lesion, including:

- Family history of skin cancers
- Previous skin cancers
- Previous excisions
- Occupation
- Past UV exposure/sunburn including use of solariums
- Frequency of sun protection

Squamous cell carcinoma (SCC)



Clinical Features



Histology

SCC is a malignant epithelial tumour of keratinocytes arising most commonly in sun-damaged skin. The vast majority of cases are associated with pre-existing actinic (solar) keratosis, squamous cell carcinoma in situ, or both. SCCs account for nearly 30% of non-melanoma skin cancers.

Some SCCs may be associated with human papillomavirus, chronic inflammation or radiation therapy.

From a histological point of view, these lesions may be well differentiated, moderately differentiated or poorly differentiated. The degree of differentiation is an essential marker of progression, risk of metastasis and prognosis. Many lesions display areas of varying degrees of differentiation, however, the worst area is to be considered when finally grading the lesion. It is the least differentiated area that ultimately determines the management and prognosis.

SCC with focal basaloid differentiation or basosquamous carcinoma, is regarded as a moderately differentiated lesion. Poorly differentiated SCCs are characterised by the absence of keratinisation. SCC may be slow or fast growing. In some cases, significant clinical changes may be evident within months, or even weeks.

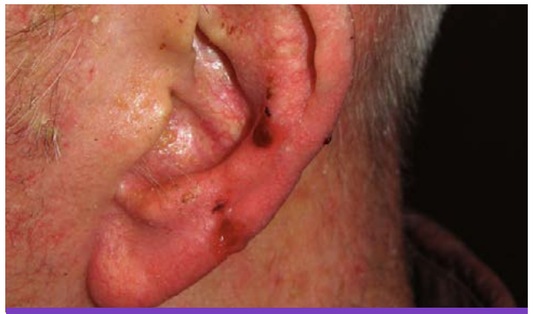
Clinical features

- Thickened red, scaly spot
- Slowly or rapidly growing papule or nodule
- Non-healing ulcers or recurrently bleeding
- May be tender to touch
- May be pigmented, raising the clinical suspicion of a pigmented lesion

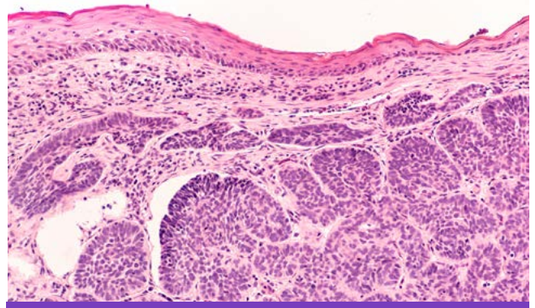
High-risk features

- SCCs found on the head and neck are considered high-risk
- Occurrence in immunosuppressed patients or at sites of previous pathology or trauma (e.g. burn scars, radiation scars, chronic ulcers/sinuses)
- The tumour growth is rapid, has a diameter >20 mm, poorly defined margins, field change, fixed to underlying structures, located over important structures or numerous tumours
- The patient experiences symptoms that suggest perineural invasion (e.g. tingling, pain, paraesthesia, formication, dysesthesia or impaired motor function)
- Where a biopsy has been performed, high-risk histopathological features include: tumour thickness >6 mm, invasion beyond the subcutis, lymphovascular invasion or high-risk pattern of perineural invasion, poorly differentiated tumours and/or aggressive subtypes (e.g. infiltrative/desmoplastic, sarcomatoid)

Basal cell carcinoma (BCC)



Clinical Features



Histology

Basal cell carcinoma (BCC) is a slow-growing locally invasive tumour, arising most commonly in sun-damaged skin from the basal layer of the epidermis. Progression of disease usually takes the form of local tissue destruction, but rarely progresses to metastases.

Histologically, tumours display several architectural patterns: nodular, superficial (which may represent an early phase of a nodular pattern), superficial multifocal, infiltrative, micronodular, morphoeic and metatypical (i.e. squamous or sebaceous differentiation). Often, a mixed pattern is observed in the same lesion.

Patient-related factors and the presence of high-risk features determine the course of treatment. BCC is the most common cancer in humans and accounts for nearly 70% of non-melanoma skin cancers.

Clinical features

- Pearly, translucent papule, plaque or nodule
- Scaly, dry area, shiny and pale or bright pink in colour
- Recurrent bleeding or ulceration
- May be pigmented, raising the clinical suspicion of a pigmented lesion

High-risk features

- Head and neck BCCs >10 mm are considered to be high-risk tumours
- Trunk and extremities BCCs >20 mm are considered to be high-risk tumours
- Aggressive histologic subtypes (e.g. micronodular, infiltrative, morphoeic or basosquamous/metatypical)
- Symptoms indicating perineural invasion (e.g. tingling, pain, paraesthesia, formication, dysesthesia impaired motor function)
- Fixation to underlying structures
- Genetic disposition of the patient (e.g. Gorlin syndrome or Xeroderma pigmentosum) and use of immunosuppressants

Steps prior to removing SCC/BCC

Prior to the excision of the tumour, the diameter should be measured and recorded. Tumour measurement after excision is not accurate due to tissue shrinkage, which occurs after excision and during specimen fixing and processing. The plane of section examined histologically is relevant to the distance from the tumour to the nearest margin, hence, it does not necessarily represent the greatest tumour dimension.

Confirming the diagnosis and notes on the histology report

In the first instance, the surgical options include a shave or punch biopsy for diagnostic purposes, or complete curative excision without prior tissue diagnosis. Primary curative excision is usually undertaken in cases of high clinical suspicion or at the patient's request.

A punch biopsy has the advantage of including the deeper aspect of the lesion and is easily processed with a lower risk of tissue artefacts.

Depending on its size, a shave biopsy may better reveal the architectural pattern and it may include a larger portion of the lesion, however, it may not include the deeper aspect of the tumour and it may be prone to artefacts, if it is too thin. A thicker shave is preferred to avoid folding or fragmentation which could significantly impair the histological assessment. A thicker shave biopsy also provides better insight into the tumour depth and architecture. It is important to note that margins cannot be accurately assessed in a punch or shave biopsy, although small lesions may be often completely excised employing one of these biopsy types. The presence of clear edges may be mentioned in such cases in the histological report, however clinical correlation is essential when determining the need for further excision.

Surgical excision is the treatment of choice for both SCC and BCC

There is no clear evidence-based recommendation regarding the minimum excision margin. Factors such as risk status of the tumour, surgical accessibility, patient age, co-morbidities and wound-healing capacity should be considered when deciding on the excision margin.

Clinical guidelines are regularly communicated and updated in publications and at conferences. Regardless of the guidelines followed by the clinician, it is important to note, that due to tissue shrinkage, the reported histological margins may be as little as half of the clinical margin measured at the time of surgery.

The histological report indicates the clearance of margins in the planes of section examined rather than representing an absolute guarantee of complete excision of the tumour. Re-excision, with the same recommended clinical margins as in the initial excision, should be attempted when involved margins are reported.

In approximately 50% of cases where a tumour was present at the edges of the biopsy, or at the margins of the excision in the initial specimen, there will be no further residual tumour in the re-excised specimen. This is explained by the fact that a minimal amount of residual tumour at the edge of the initial biopsy has been eradicated by the immune response and the regenerative process leading to repair and scarring following the initial surgical intervention.

Additional aspects of management

In cases of SCC with perineural invasion (PNI) or lymphovascular invasion (LVI), the patient should be referred to a specialist (radiation oncologist or hospital skin cancer unit). In cases of LVI, further investigations in view of staging may be indicated, while in cases of PNI, adjuvant therapy, such as radiation therapy may be employed.

Non-surgical options for BCC

Unlike in cases of SCCs, non-surgical options exist for a subset of BCCs. Cryotherapy, curettage and cautery can be used in combination in patients who cannot tolerate surgery. BCC rarely presents with LVI. Those cases should be treated like a moderately differentiated SCC with LVI. PNI is a more frequent occurrence in high-risk BCC. Radiation therapy may be indicated in these cases and the patient should therefore be referred to a specialist (radiation oncologist or hospital skin cancer unit) for further staging and management. Superficial BCC can be managed using a non-surgical approach.

Other treatment options, reserved for superficial BCC, include topical therapy such as Imiquimod (Aldara) cream and topical photodynamic therapy. These methods are generally not suitable for cases of BCC with high-risk features.

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Dr Gabriel Scripcaru studied medicine at the University of Medicine and Pharmacy “Gr.T.Popa”, Iasi Romania. After graduation he commenced training in neurosurgery working in Cluj, Romania and Newcastle, England. He subsequently became a member of the Royal College of Surgeons of Edinburgh upon completion of the required examinations. Gabriel’s clinical experience prior to anatomical pathology also included working in emergency medicine, intensive care and surgery both in Australia and Scotland. His training in anatomical pathology comprised rotations at the The Royal Melbourne Hospital, The Royal Women’s and Royal Children’s Hospitals in Melbourne. Before joining Australian Clinical Labs, Dr Scripcaru worked at Southern Sun Pathology in Sydney where he gained experience in dermatopathology.

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Dr Nikolic is a consultant histopathologist with an interest in lung pathology, breast pathology, dermatopathology and molecular diagnostics. Dr Nikolic completed his undergraduate medical degree and his masters degree (immunopathology) in Belgrade, Serbia and subsequently moved to New Zealand where he obtained a PhD degree at the University of Auckland, working on purinergic signaling and programmed cell death. He worked as a lecturer and as a medical officer in Auckland and moved to Australia to train in anatomical pathology. He received his pathology training at Monash Medical Centre and at Healthscope (now Australian Clinical Labs) and obtained his FRCPA in 2011. On completion of his training he stayed at Australian Clinical Labs as a consultant.

GP Connect: IRON STUDIES

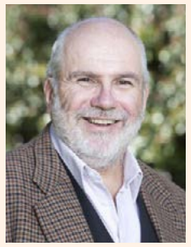
GP Connect is an initiative to facilitate a broader understanding of laboratory testing by focusing on common enquires between General Practitioners and Pathologists at Australian Clinical Laboratories. In this edition, Clinical Labs haematologist/ pathologist Associate Professor Chris Barnes responds to questions asked by general practitioner Dr Jon Barrell about the topic of iron deficiency and fatigue in patients.

A/Prof Chris Barnes

(Pathologist)

MBBS, FRACP, FRCPA

A/Prof Chris Barnes is a clinical and laboratory trained haematologist and the National Director of Haematology at Australian Clinical Labs. He also works as director of the Haemophilia Treatment Centre at the Royal Children’s Hospital, Melbourne. A/Prof Barnes has an active clinical research interest and is also director of Melbourne Haematology (Clinical) and Melbourne Paediatric Specialists.



Dr Jon Barrell

(General Practitioner)

MBBS, DRACOG, FRACGP

Dr Jon Barrell is founding principal of Springs Medical and works full-time between the Daylesford and Trentham clinics. He is also Conjoint Senior Clinical Lecturer in the School of Medicine, Faculty of Health at Deakin University. Dr Barrell enjoys teaching medical students and GP Registrars, and has been a FRACGP Examiner and Vice Chairman of the Ballarat and District Division of General Practice.

In the 2014 ABS Census, over 20% of randomly selected Australian adults had iron deficiency, usually undiagnosed. Diving deeper into the statistics, 34% of Australian women of child bearing age have iron deficiency, and 70% of pregnant women in their third trimester were affected. Determining a patient’s iron levels is essential for prompt diagnosis of iron deficiency or overloading, with an undiagnosed condition being a high risk to patient safety, potentially leading to more serious conditions, including colorectal cancer.

Dr Jon Barrell (General Practitioner)

One of my female patients in her late 30s presents with being tired. What tests should I order to see if she is iron deficient?

A/Prof Chris Barnes (Pathologist)

Iron deficiency is a common cause for fatigue and up to 1 in 6 females in the reproductive age range has iron deficiency and this may be even higher in certain ethnic groups. A complete assessment of iron studies is recommended, by a number of groups, as an important first step in the investigation of patients with lethargy.

Dr Jon Barrell (General Practitioner)

Should I order iron studies or just ferritin?

A/Prof Chris Barnes (Pathologist)

This is somewhat controversial. A serum ferritin is adequate if the patient is otherwise well, however it’s known to be an acute phase reactant, and may be artificially increased in both acute and chronic inflammation. Serum ferritin may be increased in fatty liver, raised BMI or in the setting of OCP use. A number of authorities suggest that additional laboratory markers may be helpful in the assessment of patients for iron deficiency. Iron studies can certainly offer more information regarding iron deficiency with a low transferrin saturation (<20%) supporting the diagnosis of iron deficiency in patients with concomitant inflammation or systemic illnesses (even in the presence of a normal serum ferritin). You may avoid the need for the patient to have another test done, if you order iron studies instead of just serum ferritin.

Dr Jon Barrell (General Practitioner)

I find interpreting complete iron studies results confusing - can you please break it down for me?

A/Prof Chris Barnes (Pathologist)

Trying to keep it simple, I first look at the serum ferritin and the transferrin saturation. If both are low, the patient is iron deficient. If the serum ferritin is normal (or low normal) and the transferrin saturation is also low, then I would be suspicious that the patient is also low in iron and act accordingly (e.g. consider excluding sources of blood loss, review dietary history, consider a trial of iron supplementation with close review).

Dr Jon Barrell (General Practitioner)

Are there other tests that help?

A/Prof Chris Barnes (Pathologist)

An assessment of inflammatory markers can be helpful if you are concerned the patient has inflammation present. CRP / ESR can be helpful in this scenario, but needs to be guided by the clinical situation. More sophisticated tests, like soluble transferrin receptor can be done, but are a non medicare rebatable item and the patient may incur out-of-pocket fees.

Dr Jon Barrell (General Practitioner)

There seems to be some variability in normal ranges for ferritin & age & gender. And some Cardiologists (heart failure) & surgeons / anaesthetists (Pre-op) advocate ferritin > 100. What are your views on this? Should one consider ferritin < 100 as suboptimal in some circumstances and consider possible underlying causes and interventions in some cases?

A/Prof Chris Barnes (Pathologist)

Reference ranges for laboratory tests are most commonly established using large numbers of samples (e.g. 10,000) from a "normal" population. We need to show our accrediting bodies that our reference ranges are established using robust science. From a practical point of view, particularly when dealing with complex patients that may have more than one pathological process, a general rule-of-thumb is that if the patient has a serum ferritin above 100ng/ml, they are generally not likely to have any significant iron deficit. I think surgeons are quite keen on this to ensure that there is adequate iron in the setting of potential blood loss. I am not sure I would intervene and expose the patient to potential side effects of iron supplementation if they have very "normal" iron stores as assessed by iron studies, but I would be reaching out to the patient / surgeon in order to discuss relevant risks and benefits.

Dr Jon Barrell (General Practitioner)

When considering oral iron supplement, is there evidence to advocate one preparation over another?

A/Prof Chris Barnes (Pathologist)

Oral iron therapy is typically associated with a high incidence of gastrointestinal side effects such as nausea and constipation. This may occur in up to 40% of patients treated with therapeutic iron supplementation. Many of the manufacturers claim their preparation is associated with a low incidence of side effects, but in my experience these claims cannot be substantiated. If a iron preparation is not causing any side effects, it is often because there is very little iron. Iron in supplements is measured as equivalent to elemental iron. Recommended supplements to treat iron deficiency and improve iron stores contain 75 – 100mg per day of elemental iron. Some medications proposing to provide iron supplements contain as little 5mg per day of elemental iron and will therefore, be an inadequate supplement.

Patients' vitamin D levels drop significantly during winter

By Dr David Deam

Vitamin D levels fluctuate significantly depending on the season, especially in the Southern states of Australia. At the end of winter, approximately 36% of Australians are vitamin D deficient, in comparison to 14% at the end of summer. Therefore, making the end of winter the best time to test patients for vitamin D deficiency.

The below diagrams indicate the percentage of Australians with a vitamin D deficiency in summer (diagram 1) versus winter (diagram 2).

Diagram 1 - Vitamin D deficiency in summer by state (2011-2012)

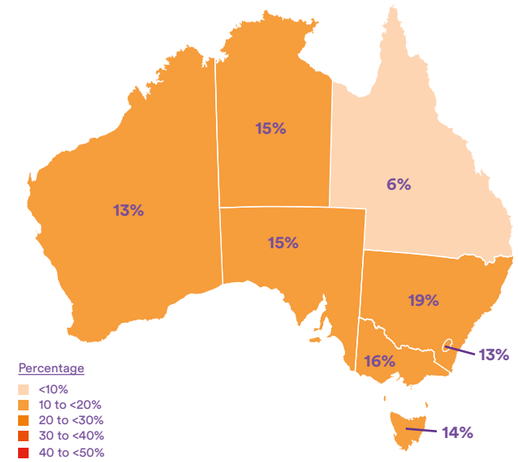
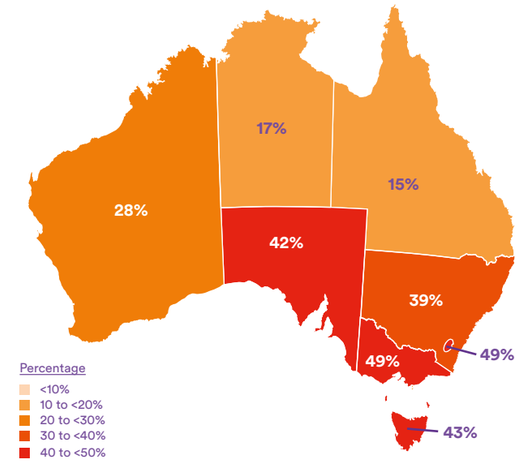


Diagram 2 - Vitamin D deficiency in winter by state (2011-2012)



Source: Australian Health Survey: Biomedical Results for Nutrients

Health implications of vitamin D deficiency

Vitamin D deficiency is of concern as it can lead to a variety of health conditions including the loss of bone density, which can contribute to osteoporosis and fractures in adults and rickets in infants and children. Low levels of vitamin D have also been found in association with other health conditions, such as cardiovascular disease, diabetes, immune system diseases, microbial and respiratory diseases, cognitive impairment in older adults, mental health and cancer.

Target vitamin D levels

The international recommendations for adequate vitamin D levels vary, but based on a review of current literature and recently published recommendations [1,2] Clinical Labs suggests that adequate vitamin D status is a serum level equal to, or greater than, 50 nmol/L at the end of winter. This level should be 10-20 nmol/L higher at the end of summer to allow for seasonal decrease.

This figure is based on the level below which parathyroid hormone concentrations begin to rise and the risk of fractures increases.

As for all tests, Australian Clinical Labs' pathologists and scientists will continue to evaluate current literature and our target range may change as new evidence emerges.

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Please tick one of the below:

- ◯ General Practitioner
- ◯ Specialist
- ◯ Medical Centre / Practice Manager

Thank you

Who to test

Vitamin D testing should be ordered for patients at risk of vitamin D deficiency, including:

- Housebound people - including the sick and disabled
- Elderly in high care
- People with darker skin
- People who cover their skin due to religious or cultural reasons
- People who regularly avoid the sun
- People who work indoors

Also patients with:

- Signs, symptoms and/or planned treatment of osteoporosis or osteomalacia
- Increased alkaline phosphatase with otherwise normal LFTs
- Hyperparathyroidism, hypo- or hypercalcaemia or hypophosphataemia
- Malabsorption (i.e. CF, IBD, coeliac, etc)
- Medications known to decrease vitamin D levels (i.e. anticonvulsants)
- CRF and transplant recipients

Vitamin D testing

Vitamin D testing at Clinical Labs measures the concentration of total 25-hydroxyvitamin D (25-OHD) in a patient's serum. The report will also include previous test results, for comparison (if applicable), and suggested cut points to define sufficient, deficient and severely deficient vitamin D levels.

Further testing

When ordering a vitamin D test for a patient, also ordering a serum calcium assessment and parathyroid hormone (PTH) test, will assist in placing the vitamin D level within the context of overall calcium homeostasis. If Osteoporosis is present, fasting blood crosslaps (CTX) will provide a way of monitoring bone turnover in response to therapy.

Treatment

To ensure adequate levels of vitamin D are maintained throughout the year, the following sun exposure times (mins per day) are recommended for 1/3MED for moderate fair skin, at either 10am or 2pm daily [3].

	December-January	July-August
Perth	5-6 mins	20-28 mins
Adelaide	5-7 mins	25-38 mins
Melbourne	6-8 mins	32-52 mins
Hobart	7-9 mins	40-47 mins
Sydney	6-8 mins	26-28 mins
Brisbane	6-7 mins	5-19 mins
Cairns	6-7 mins	9-12 mins

If patients are unable, for a variety of reasons, to gain the required amount of sun exposure for vitamin D production, supplementation may be required.

A maintenance dose of up to 1000 IU/day may be adequate, however some individuals will require higher doses. Severe vitamin D deficiency (serum level <20 nmol/L) may require 3000-5000 IU/day for 6-12 weeks.

Supplements should be vitamin D3. Adequate dietary calcium is also required, at least 1g/day and up to 1.3g/day, for older adults. Many patients will require supplementation to achieve this amount.

Note: Calcium supplements are best taken before sleep to ensure maximum absorption and suppression of peak bone turnover which usually occurs between approximately 2am and 3am.

Serum 25-OHD should be retested no earlier than 3 months following commencement of supplementation with vitamin D or a change in dose. Once a desirable target has been achieved, especially at the end of winter, no further testing is required unless risk factors change [2].

References

1. Vitamin D and health in adults in Australia and New Zealand: a position statement. MJA 196(11), 18 June 2012.
2. RCPA Position Statement: Use and Interpretation of Vitamin D testing. The Royal College of Pathologists of Australasia, May 2013.
3. Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. Vitamin D and adult bone health in Australia and New Zealand: a position statement. MJA 2005; 182: 281–28.

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