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PATHOLOGY *focus*

Medical Newsletter

SEASON'S GREETINGS

and Happy New Year!

Thank you from everyone at Clinical Labs

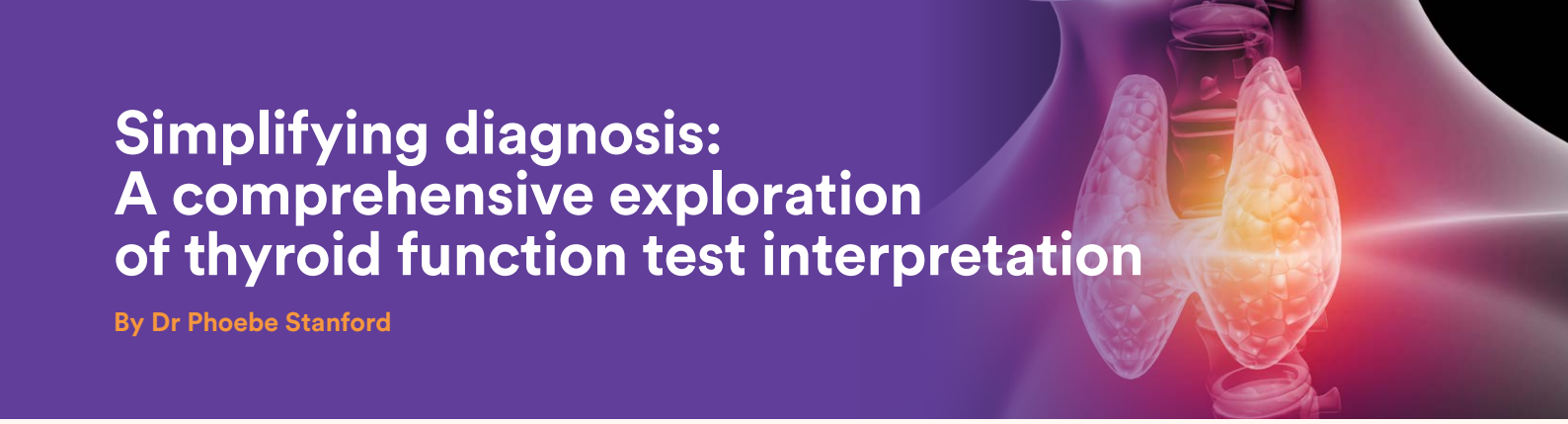
As we approach the end of another busy year in Australian healthcare, we would like to express our gratitude for your ongoing partnership with Clinical Labs and the trust you place in us to provide the pathology services required to complement your patient management and care.

We hope that the 2023 editions of Pathology Focus, covering topics such Long COVID, Antimicrobial Resistance, and the Medicare Rebate for Genetic Carrier Screening, have provided valuable insights for your practice. We are excited to share more relevant and beneficial content with you next year.

Wishing you, along with your dedicated practice teams, a wonderful festive season filled with celebration, well-deserved rest, relaxation, and quality time spent with loved ones. We look forward to working with you again in 2024.

Simplifying diagnosis: A comprehensive exploration of thyroid function test interpretation

By Dr Phoebe Stanford



Thyroid function tests commonly refer to measurements of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3). These are measured by immunoassays, which involve antibodies targeting a particular part of the hormone. These assays are not standardised, and differences in assay design and in the nature of the antibodies used may cause slight differences in results between different methods. There may also be method-specific interferences in some cases.

Who to test?

While there is insufficient evidence to support routine population screening, targeted testing in high-risk groups is recommended (see Table 1) (Garber J, 2012). As the symptoms of thyroid disease are often non-specific, thyroid function testing may have utility in the investigation of a number of clinical presentations and some biochemical changes (see Table 2).

Table 1. High-risk groups that warrant thyroid function testing in asymptomatic individuals:

- Autoimmune diseases (type 1 diabetes, Addison's disease, pernicious anaemia)
- Family history of thyroid disease
- Down syndrome
- Turner syndrome
- History of neck radiation
- Iodine deficiency or high iodine load
- Medications that may cause thyroid dysfunction:
  - Lithium
  - Amiodarone
  - Immune checkpoint inhibitors

(Royal College of Pathologists of Australasia, 2017)

Table 2. Features of thyroid dysfunction

HYPOTHYROIDISM	HYPERTHYROIDISM
Biochemical abnormalities	**Biochemical abnormalities**
• Hypercholesterolaemia • Hyperprolactinaemia (primary hypothyroidism) • Hyponatraemia • Mild anaemia	• Low cholesterol • Abnormal liver enzymes • Increased ALP of bone origin • Hypercalcaemia
Clinical features	**Clinical features**
• General effects - Fatigue - Weight gain - Cold intolerance - Hair loss • Skin and connective tissue - Dry skin, brittle nails - Non-pitting oedema • Gastrointestinal - Constipation • Cardiovascular - Bradycardia - Pericardial effusion • Musculoskeletal - Myopathy - Arthralgia • Neurological/psychiatric - Depression - Impaired memory/cognitive decline - Neuropathy (Carpal tunnel syndrome) • Respiratory - Sleep apnoea - Pleural effusion • Reproductive system - Impaired fertility - Menorrhagia - Oligo-amenorrhoea	• General effects - Fatigue - Weight loss - Heat intolerance - Sweating, tremor • Ocular - Lid retraction - Opthalmopathy (Graves' disease) • Gastrointestinal - Increased stool frequency • Cardiovascular - Tachycardia - Atrial fibrillation - Heart failure • Musculoskeletal - Proximal myopathy - Osteoporosis • Neurological/psychiatric - Anxiety - Depression - Insomnia • Reproductive system - Oligo-amenorrhoea

Thyroid function testing should not be performed during acute illness unless there is a high index of suspicion, as acute illness alone can affect thyroid function test results, making these difficult to interpret.

What to test?

In most circumstances, screening with TSH alone is sufficient:

- with FT4 to be tested if TSH is elevated,
- and FT4 and FT3 if TSH is low.

For this cascade testing to be performed automatically under current MBS requirements, TFT should be requested rather than TSH.

The rationale for this approach is that the relationship between FT4 and TSH is not linear, with a greater change in TSH for a given change in FT4, making the TSH measurement a sensitive marker for thyroid dysfunction.

> ***"As the symptoms of thyroid disease are often non-specific, thyroid function testing may have utility in the investigation of a number of clinical presentations and some biochemical changes."***

There are certain scenarios where this approach is not valid, including when secondary (central) hypothyroidism due to hypothalamic/pituitary disease is suspected. Secondary hypothyroidism will result in a low or inappropriately normal TSH, along with a low FT4. If this is suspected, initial testing with TSH and FT4 is recommended.

Thyroid antibodies

Thyroid antibodies, including TPO and Tg antibodies, are present in most cases of autoimmune lymphocytic "Hashimoto's" thyroiditis, the most common cause of hypothyroidism in iodine-sufficient areas, including Australia.

TPO antibodies are more sensitive and specific than Tg antibodies for diagnosing thyroid dysfunction in autoimmune thyroiditis (O'Leary PC, 2006; Ralli M, 2020). Therefore, measuring TPO antibodies is generally sufficient for investigating hypothyroidism. TPO antibodies do not need to be repeated once positive, as there is no value in serial monitoring of TPO antibody levels.

Antithyrogloblin antibodies are recommended when measuring thyroglobulin is required for the follow-up of patients with thyroid cancer because their presence can falsely lower the thyroglobulin result due to analytical interference.

TSH receptor antibodies (TRAb) or TSH receptor stimulating immunoglobulin (TSI) are useful in investigating hyperthyroidism, whether it's subclinical or overt. A positive TRAb or TSI is consistent with Grave's disease. The presence of TRAb or TSI is also crucial during pregnancy, as they may cross the placenta and affect the foetal thyroid.

UNDERSTANDING THE IMPACT OF BIOTIN INTERFERENCE IN IMMUNOASSAYS FOR THYROID FUNCTION TESTING

Biotin may interfere in immunoassays that use biotin-streptavidin interaction as part of the assay methodology. In such assays, high doses of biotin may result in falsely high FT4 and FT3 and/or falsely low TSH, mimicking hyperthyroidism. There are numerous cases of patients being inappropriately investigated and treated for hyperthyroidism due to this (Kummer A, 2016; Elston MS, 2016). As such, it is important to consider the clinical presentation when interpreting test results and question the results if they are out of keeping with the clinical picture.

Biotin interference is not a concern with standard multivitamin doses. However, doses of 5-10 mg or more, which may be present in over-the-counter hair and skin supplements, have been shown to affect some assays (Haslam S, 2019). Since the effect of biotin is assay-specific, if a patient is taking biotin, it is best to check with the laboratory as to whether the method is affected. To avoid interference, stopping biotin for 3 days before testing is generally sufficient, although a longer period may be required in the case of very high doses.

Interpretation of thyroid function tests

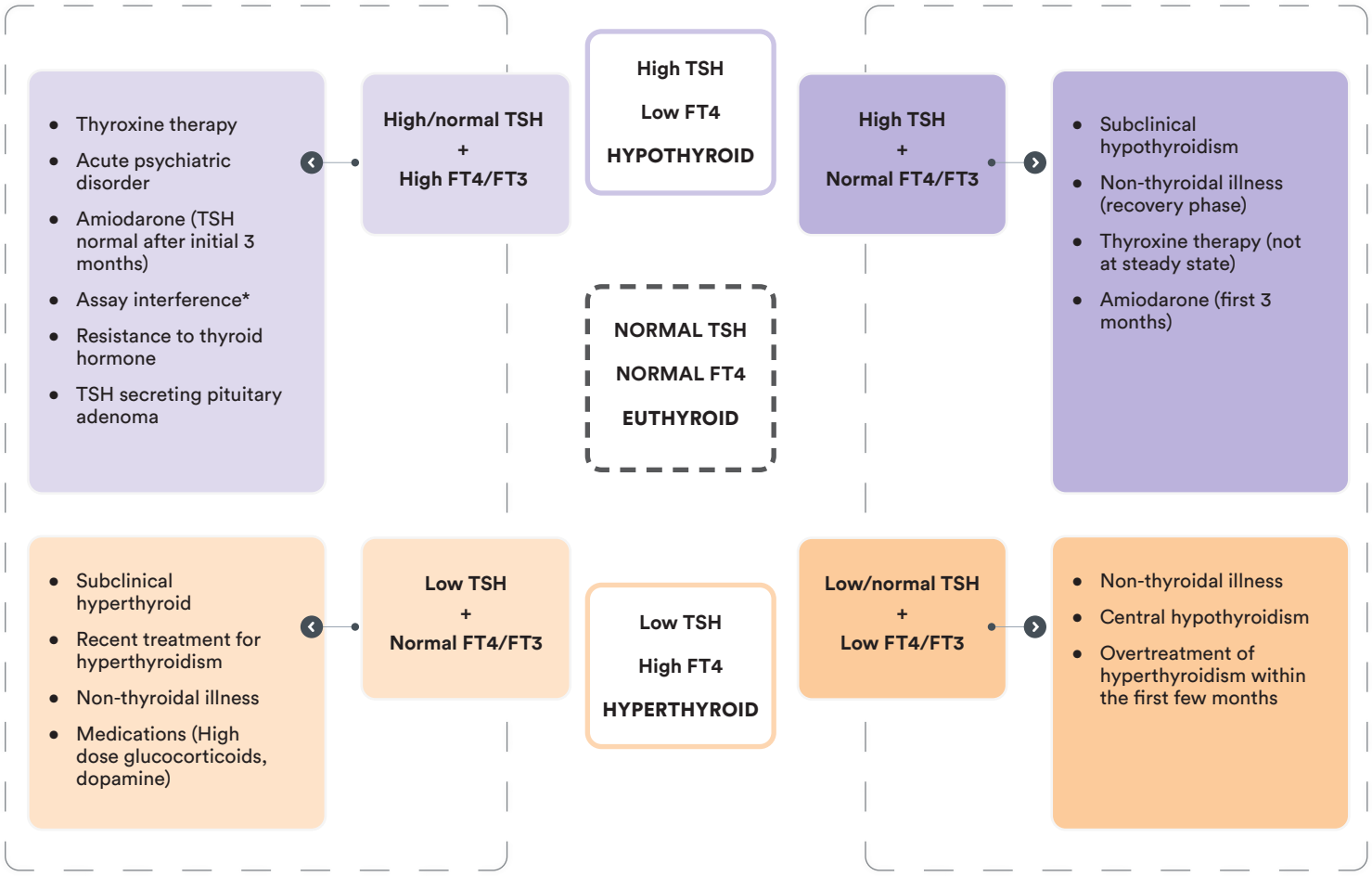
Reference intervals are dependent on method and age

As TSH and thyroid hormone assays are not standardised, there will be slight differences in the reference intervals between methods, particularly for FT4 and FT3. Variations in reference intervals between laboratories using the same methods may also occur, depending on the characteristics of the population used to define those reference intervals.

Several studies have found that the upper limit of the reference interval for TSH is increased in the elderly. Large US-based population studies have identified a shift in the entire TSH distribution curve towards higher TSH for ages 70-89 compared to the 20-39 age group, with the TSH upper reference limit increasing to 7.5 mIU/L in those over 80 years (Surks M, 2007).

Patterns of thyroid function tests

Figure 1 – Interpreting thyroid function test results at-a-glance



**Assay interference may result in artefactually low or high TSH, FT4, and/or FT3, which may result in any of the above patterns. If results do not fit with the clinical picture, and assay interference is suspected, contact the laboratory.*

High TSH with low or normal FT4 and FT3:

The biochemical picture of an elevated TSH with a low FT4 is consistent with overt primary hypothyroidism. A more common finding is an elevated TSH with FT4 within the normal range. This may be due to subclinical hypothyroidism; however, this may also be a transient effect reflecting recovery from non-thyroidal illness, and may also be seen during the first few months of treatment with amiodarone. Moreover, a mildly elevated TSH (< 7 mIU/L) in patients >65 years may be considered a normal manifestation of ageing (Garber J, 2012).

A significant proportion of individuals with a mildly increased TSH (< 10mIU/L) with normal FT4 will revert to normal without treatment (Meyerovitch J, 2007). Therefore, such results should be confirmed with repeat testing of TSH together with FT4 and TPO antibodies after 6-8 weeks.

Low TSH with elevated FT4 and/or FT3:

A suppressed TSH (generally undetectable) with elevated FT4 and/or FT3 is consistent with a diagnosis of thyrotoxicosis. This may be due to increased production of thyroid hormones (hyperthyroidism), commonly due to Grave's disease, toxic multinodular goiter, or toxic adenoma, or due to release of pre-formed thyroid hormone due to destructive thyroiditis (subacute, silent, or lymphocytic). It is important to establish the cause, as the treatment approach differs. Thyrotoxicosis may also be factitious, due to excess use of exogenous thyroid hormones, which may be deliberate or unintentional (potentially included in natural therapies or weight loss supplements bought overseas), or due to excess iodine intake.

Testing of TSH receptor antibodies (TRAb or TSI) is recommended as a first-line diagnostic test. A positive TRAB or TSI is consistent with Grave's disease. If TRAb/TSI is negative, a nuclear medicine study of the thyroid may be considered.

Low TSH with normal FT4 and FT3:

A low TSH with normal FT4/FT3 may occur transiently with non-thyroidal illness or represent mild, subclinical hyperthyroidism, so repeat testing should be performed after 6-8 weeks for confirmation.

Subclinical hyperthyroidism may be caused by the same pathology as overt hyperthyroidism. The approach to

management depends on the risk for adverse outcomes and the degree of TSH suppression. Asymptomatic patients under age 65 with no history of cardiac disease or osteoporosis and with mildly suppressed TSH (0.1-0.4 mIU/L) may be monitored every 6-12 months. Treatment may be beneficial for older patients or those with a history of, or risk factors for heart disease or osteoporosis and is recommended if TSH is persistently < 0.1 mIU/L (Ross D, 2016). Specialist endocrine referral is recommended where treatment is being considered.

Low or normal TSH with low FT4/FT3:

A low TSH with low FT4/FT3 may be due to severe non-thyroidal illness. If the patient has no obvious systemic illness, central hypothyroidism due to hypothalamic or pituitary disease should be considered. This is important not to miss, as there may be potentially life-threatening concomitant adrenal insufficiency which may be precipitated by treatment for hypothyroidism before commencing glucocorticoid replacement.

If central hypothyroidism is suspected, pituitary hormone testing (morning cortisol, LH, FSH, sex steroids, IGF-1 and prolactin) and endocrine referral is recommended.

Unexpected results - High TSH with elevated FT4 and/or FT3:

An elevated TSH with a high FT4 (or FT3) may occur transiently due to non-thyroidal illness, amiodarone therapy, acute psychiatric illness, or during treatment for hypothyroidism where a steady state has not yet been achieved, possibly due to intermittent adherence to thyroxine therapy. Depending on the clinical presentation, a repeat test in 6-8 weeks may be a reasonable approach.

This pattern of thyroid function may also be due to an antibody interference in the test method. If this is suspected, discussion with the laboratory is recommended.

Rarely, an elevated TSH with high FT4 may be due to Resistance to thyroid hormone (RTH), a genetic condition inherited in an autosomal dominant fashion, or a TSH-producing pituitary tumour (TSHoma). If assay interference has been excluded, and this is suspected, specialist referral is recommended.

References

Elston MS, S. S. (2016). Factitious Graves' Disease Due to Biotin Immunoassay Interference- A Case and Review of the Literature. *101: 3251-3255*.

Garber J, C. R. (2012). Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the AmericanThyroid Association. *Endocrine Practice, 18*(6), 988-1028.

Haslam S, O. J. (2019). A comparison of biotin interference in routine immunoassays on the Roche Cobas 8000, Beckman Coulter DXi and Siemens Advia Centaur XPT immunoassay platforms. *57*(11:e287-e290).

Kummer A, H. D. (2016). Biotin Treatment Mimicking Graves' Disease. *375*(7: 704-706).

Meyerovitch J, R.-P. P. (2007). Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. *Arch Intern Med., 167*(14), 1533-1538.

O'Leary PC, F. P. (2006). Investigations of thyroid hormones and antibodies based on a community health survey: the Busselton thyroid study. *64: 97-104.*

Ralli M, A. D. (2020). Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic T protocols, therapeutic strategies, and potential malignant transformation. *Autoimmunity Reviews, 19*(10), 1568-9972.

Ross D, B. H. (2016). 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid, 26*(10), 1343-1421.

Royal College of Pathologists of Australasia. (2017, July). *Position Statement: Thyroid function testing for adult diagnosis and monitoring*. Retrieved June 2023, from https://www.rcpa.edu.au/getattachment/8d6639b7-af88-403c-a9ab-c5fe729757c1/Thyroid-Function-Testing-for-Adult-Diagnosis-and-M.aspx

Surks M, H. J. (2007). Age-Specific Distribution of Serum Thyrotropin and Antithyroid Antibodies in the U.S. Population: Implications for the Prevalence of Subclinical Hypothyroidism. *The Journal of Clinical Endocrinology & Metabolism, 92*(12), 4575-4582.

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Dr Stanford graduated from the University of New South Wales in 2005. She completed Basic Physician Training, followed by Advanced Training in Chemical Pathology and Endocrinology. This included undertaking a year with a focus on bone disease at St Vincent's hospital (Sydney), followed by a year of general clinical endocrine training at Prince of Wales Hospital. Dr Stanford then completed her joint training based at the Prince of Wales and Royal North Shore Hospital Laboratories. In 2019, she was awarded fellowship of both the Royal Australasian College of Physicians and The Royal College of Pathologists of Australasia. Dr Stanford then worked at Tan Tock Seng hospital laboratory in Singapore before returning to Australia to take up a Chemical Pathologist position at Australian Clinical Labs.

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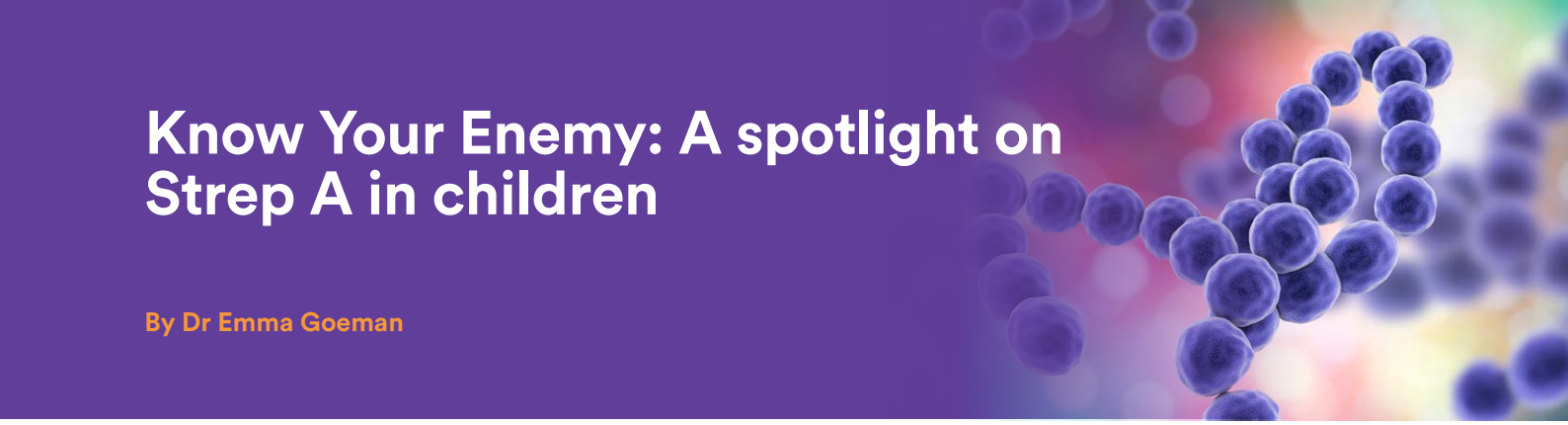
Dr Tony Mak is a chemical pathologist who graduated from the medical school of the Chinese University of Hong Kong. Before migrating to Australia, Tony worked as a consultant chemical pathologist at Princess Margaret Hospital – a major acute district general hospital in Hong Kong. Tony founded, developed, and operated the highest level clinical toxicology laboratory in Hong Kong. He led his team to develop numerous useful analyses to solve many difficult clinical toxicology problems with public health implications, including Chinese medicine related poisoning, plant-related poisoning, novel psychoactive substances, slimming agents and related problems, drug adulteration and counterfeit drugs. Tony held numerous management roles in Hong Kong including Head of the Department of Pathology, Service Director (Quality and Safety) and Deputy Hospital Chief Executive. He has published more than 100 articles in international peer-reviewed academic journals and a number of books. We are excited to announce Tony's new role as Clinical Director, Chemical Pathology for Clinical Labs in WA.

Know Your Enemy: A spotlight on Strep A in children



By Dr Emma Goeman

The rising threat of Strep A in children

Streptococcus pyogenes, also known as Group A streptococcus or Strep A, is an increasingly common cause of life-threatening disease, termed invasive group A streptococcal infection (iGAS), especially in children. A spike in iGAS cases in Australia, including some with devastating outcomes, has received media coverage in the past 9-12 months.[1,2,3,4] iGAS is now a notifiable condition in all Australian states and territories, and jurisdictions commenced reporting at different times throughout 2021 and 2022. Even taking into account changes to reporting, recent high incidence rates in Australia are causing considerable concern.

Recent trends in iGAS infections

Pre-pandemic, rises in iGAS occurred in several high-income countries. However, rates dropped substantially in 2020-2021, likely due to measures implemented to reduce the spread of COVID-19. Data from the Paediatric Active Enhanced Disease Surveillance (PAEDS) Network showed that in Australian children aged 0 – 17 years, iGAS rates in 2022 sharply rose to 5.2 per 100,000 children in the third quarter and remained unseasonably high in the fourth quarter. Aboriginal and Torres Strait Islander children experienced incidence rates 1.8 times higher than non-Indigenous children during 2018 - 2022. Pneumonia and bacteraemia were the most common clinical syndromes. 32% of cases were severe and there were 3 deaths (1%).[5] Mortality rates are substantially higher in adults, particularly in the presence of necrotizing fasciitis, also known as “flesh-eating disease”. Data from the National Communicable Diseases Surveillance Dashboard shows that high iGAS case numbers are showing no signs of slowing down in 2023.[6]

Diverse clinical manifestations of Strep A infections

Strep A may live harmlessly in the throat and is transmitted via respiratory droplets and direct contact with infected skin sores. Common clinical syndromes include tonsillitis and impetigo (see Figure 1), which are generally mild, as well as scarlet fever. More severe disease manifestations include sepsis, meningitis, pneumonia, bone, joint, and deep tissue infections, toxic shock syndrome, and necrotizing fasciitis.

Strep A is also the cause of acute post-streptococcal glomerulonephritis and acute rheumatic heart disease, which can lead to chronic kidney damage and rheumatic heart disease. Aboriginal and Torres Strait Islander Australians have long borne the brunt of some of the highest rates in the world.

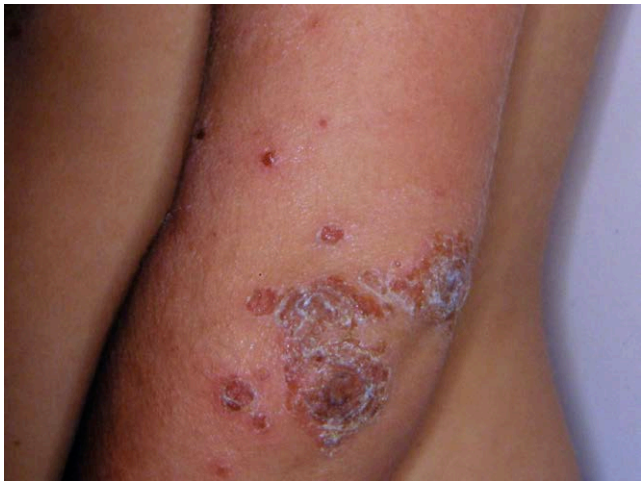


Figure 1 – Image shows an impetigo skin infection, also known as school sores.

Recognising sepsis

Where minor Strep A infections may progress into an emergency can be challenging to discern clinically. Therefore, it always helps to consider, “Could this be sepsis?”[15]

Sepsis is defined as a life-threatening condition that develops when the body’s response to an infection injures its own tissues and organs. When shock ensues, it can be rapidly fatal.[7]

Signs of sepsis in young children may include:[8]

- An altered conscious state (characterised by lethargy, irritability, floppiness, or a weak cry).
- An unwell appearance or high level of parental concern.
- A rash (which in the case of Strep A often resembles sunburn and may feel like sandpaper).
- Features of impaired circulation, such as reduced peripheral perfusion, pale, cool, or mottled skin, tachycardia, or decreased urine output.
- Tachypnea or grunting.
- Unexplained pain.
- Fever or hypothermia.

Toxin-mediated disease may be heralded by fever, vomiting, diarrhoea (which can be mistaken for gastroenteritis), myalgia, conjunctival injection, confusion, collapse, and a widespread erythematous rash.[8]

If sepsis is suspected, blood cultures should ideally be collected prior to the commencement of antibiotics as part of a bundle of care with initial resuscitation. However, collection should not cause a delay in antibiotic administration.[9]

Optimising blood culture collection

The most important factor in optimising the diagnostic yield of a blood culture is the volume of blood; more blood equals better sensitivity.

- The minimum acceptable volume of blood in a paediatric blood culture bottle is **0.5 mL**, but ideally, at least **1 mL** should be collected, even from newborns.
- For most preschool-aged children over the age of 12 months, the target volume is **4 mL**.
- Adult aerobic and anaerobic blood culture bottles can be used for school-aged children and adolescents, with volumes of **5 - 10 mL** per bottle.
- For adults, a recommended total collection is **40 – 60 mL** (2 - 3 sets of aerobic and anaerobic bottles, approximately 4 - 6 bottles, each containing 10 mL of blood inoculated) for adequate sensitivity.

Blood culture bottles should not be overfilled. Collection should be performed using strict aseptic technique via peripheral venipuncture to minimise the risk of contamination.

Laboratory detection of Strep A

Strep A is easily cultured and recognised in the laboratory on routine clinical samples. Throat swabs will pick up Strep A, causing pharyngitis and tonsillitis, as well as asymptomatic colonisation. Skin swabs from sores and open wounds will detect Strep A, causing impetigo, abscesses, and cellulitis. Culture of body fluids and tissues will aid in the diagnosis of invasive, deeper infections. Growth of Strep A in a child's urine usually reflects localised skin infection around the genital area, especially vulvovaginitis in pre-pubertal females, but may rarely reflect bloodstream infection with spillover into the urine.

Blood cultures are continuously monitored by an automated instrument in the laboratory for 5 days. The vast majority of significant pathogens will be detected within the first 48 hours of incubation. Treating clinicians will be notified of a positive blood culture result immediately. Initially, only the Gram stain characteristics of the organism will be known, such as Gram-positive cocci (see Figure 2) resembling streptococci. Further organism identification and susceptibility testing requires growth on solid media (agar plates) and takes a further 24- 48 hours.

Antibody tests (anti-streptolysin O titre, or ASOT, and anti-DNase B antibodies) are used to detect recent past Strep A infection, to aid in the diagnosis of complications such as acute post-streptococcal glomerulonephritis and acute rheumatic fever. It is preferred to collect two samples 2-4 weeks apart to detect rising antibody levels. Strep A can also complicate viral infections such as varicella, influenza, and COVID-19, as well as other respiratory viruses for which PCR tests are available.

> ***"Where minor Strep A infections may progress into an emergency can be challenging to discern clinically. Therefore, it always helps to consider, could this be sepsis?"***

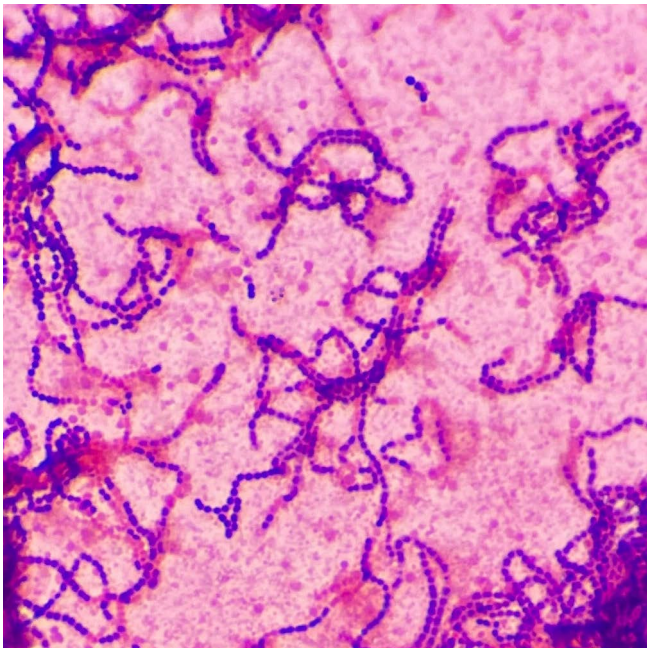


Figure 2 – Image shows Gram-positive cocci in chains.

Antibiotic resistance and treatment options

Strep A is universally susceptible to penicillin, and therefore, to amoxicillin, ampicillin, cephalexin, and flucloxacillin. Penicillins are the mainstay of treatment. However, resistance to other agents is increasing, with resistance rates to erythromycin, clindamycin, and tetracycline reaching 8.7%, 7.1%, and 18.7%, respectively, in Australia-wide data from 2019[10].

Cotrimoxazole is a useful alternative agent in certain settings, such as in patients with immediate severe or delayed severe penicillin allergy and clindamycin resistance. This is also the case when there is co-infection with Staphylococcus aureus, particularly MRSA. In remote settings, cotrimoxazole is preferred due to its low cost, twice-daily dosing, and good tolerability, especially in children.[11,12]

In a hospital setting, clindamycin is often added to benzylpenicillin for its anti-toxin effects, and intravenous immunoglobulin is given as an adjunctive treatment in severely septic individuals.

Preventative strategies and the search for vaccines

At a population level, preventative strategies for strep A infections include improving the social determinants of health, which involves improving skin health, including controlling scabies infections, particularly in remote communities in Northern Australia. Additionally, the race is on to find the best vaccine among a selection of candidate vaccines.[13] The promotion of respiratory and hand hygiene practices may also interrupt transmission.

On a more individual and community level, some jurisdictions recommend preventative antibiotics for household contacts of individuals with iGAS, similar to the model of care for meningococcal disease. This is because the risk of secondary cases of iGAS in this group is 2,000 times higher than that in the general population in the 30 days following exposure.[14]

References

1. https://www.theguardian.com/australia-news/2023/aug/23/cases-of-flesh-eating-invasive-strep-a-bacteria-surge-in-australian-children#:~:text=The%20paper%20included%20nationally%20invasive,was%201%2C185%2C%20the%20paper%20said.
2. https://www.mcri.edu.au/news-stories/australia-experiences-intense-surge-in-strep-a-cases-similar-to-northern-hemisphere-wave
3. https://www.medicalrepublic.com.au/child-dies-as-strep-a-spreads/87141
4. https://www.theage.com.au/national/victoria/two-children-die-amid-marked-increase-in-invasive-strep-a-infections-20230103-p5ca0e.html
5. Abo, Yara-Natalie et al. Increase in invasive group A streptococcal disease among Australian children coinciding with northern hemisphere surges. The Lancet Regional Health – Western Pacific, Volume 0, Issue 0, 100873
6. Hla TK, Cannon JW, Bowen AC, Wyber R. Getting to grips with invasive group A streptococcal infection surveillance in Australia: are we experiencing an epidemic? Medical Journal of Australia 2023, volume 219, issue 6, pp. 242-245
7. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287. PMID: 26903338; PMCID: PMC4968574.
8. The Royal Children's Hospital, Melbourne, Australia, Clinical Practice Guideline on Sepsis – Assessment and Management [Internet, last updated March 2020; cited 8/10/2023], Available from: https://www.rch.org.au/clinicalguide/guideline_index/SEPSIS_assessment_and_management/
9. Weiss, S.L., Peters, M.J., Alhazzani, W. et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 46 (Suppl 1), 10–67 (2020). https://doi.org/10.1007/s00134-019-05878-6
10. Australian Commission on Safety and Quality in Health Care. AURA 2021: fourth Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2021.
11. Bowen AC, Lilliebridge RA, Tong SY, Baird RW, Ward P, McDonald MI, Currie BJ, Carapetis JR. Is Streptococcus pyogenes resistant or susceptible to trimethoprim-sulfamethoxazole? J Clin Microbiol. 2012 Dec;50(12):4067-72. doi: 10.1128/JCM.02195-12. Epub 2012 Oct 10. PMID: 23052313; PMCID: PMC3502963.
12. Bowen AC, Carapetis JR, Currie BJ, Fowler V Jr, Chambers HF, Tong SYC. Sulfamethoxazole-Trimethoprim (Cotrimoxazole) for Skin and Soft Tissue Infections Including Impetigo, Cellulitis, and Abscess. Open Forum Infect Dis. 2017 Nov 2;4(4):ofx232. doi: 10.1093/ofid/ofx232. PMID: 29255730; PMCID: PMC5730933.
13. Walkinshaw, D.R., Wright, M.E.E., Mullin, A.E. et al. The Streptococcus pyogenes vaccine landscape. npj Vaccines 8, 16 (2023). https://doi.org/10.1038/s41541-023-00609-x
14. Carapetis JR, Jacoby P, Carville K, Ang SJ, Curtis N, Andrews R. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. Clin Infect Dis. 2014 Aug 1;59(3):358-65. doi: 10.1093/cid/ciu304. Epub 2014 Apr 29. PMID: 24785239.
15. Australian Commission on Safety and Quality in Healthcare (ACSQHC) Quality Statement 1 - Could it be sepsis? https://www.safetyandquality.gov.au/standards/clinical-care-standards/sepsis-clinical-care-standard/quality-statements/quality-statement-1-could-it-be-sepsis Accessed 15/11/23.

Figure 1. Reproduced with permission from ©DermNet www.dermnetnz.org 2023.

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Dr Sudha Pottumarthy-Boddu comes to us from Houston, Texas, where she was Assistant Professor in the Department of Pathology and Laboratory Medicine at the University of Texas, School of Medicine. She was also the Technical Director of the Clinical Laboratory Services at the Houston Department of Health and Human Services. After graduating from medical school in India, Dr Pottumarthy-Boddu migrated to New Zealand and completed her Pathology/Microbiology Fellowship training with the Royal College of Pathologists of Australasia. She is a recipient of various awards and scholarships, including the Neil Prentice Memorial Prize of RCPA. She is also a Diplomate of the American Board of Medical Microbiology. Over the last 10 years she gained experience in various hospital, research, and public health laboratories in the US, publishing over 30 articles in peer-reviewed journals and presenting at various national and international conferences. Detection of the first USA isolate of Enterobacter spp. with NmcAcarbapenem hydrolyzing enzyme and establishing clinical significance of Nocardia verterana are noteworthy. Dr Pottumarthy-Boddu's main research interests are antimicrobial susceptibility trends and molecular methods in the diagnosis of infectious diseases.

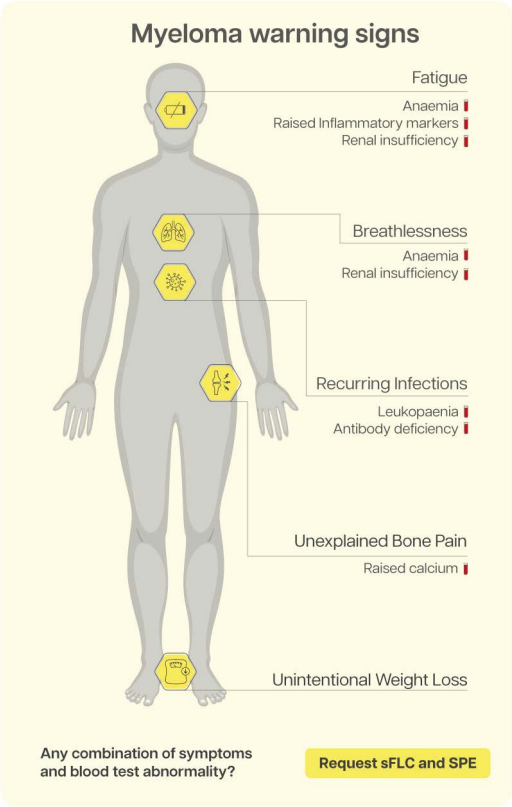
Signs & symptoms of multiple myeloma – Which tests to order for a timely diagnosis and to avoid complications

What is multiple myeloma?

Multiple myeloma is a blood cancer arising from plasma cells in the bone marrow. In Australia, it is estimated that 2,625 new cases of multiple myeloma were diagnosed in 2022, accounting for 1.6% of all new cancer cases diagnosed that year[1]. The incidence rate for multiple myeloma increases with age and is highest for those aged 85–89 years[1]; however, it is also diagnosed in younger people.

Signs and symptoms of multiple myeloma

Multiple myeloma symptoms are non-specific and may mimic the ageing process or more common conditions encountered in primary care, such as diabetes, hypertension, and cardiac disease[2]. Patients often present in primary care feeling generally unwell, with unexplained and persistent bone pain, back pain, and body aches[2]. As multiple myeloma progresses, advanced presentations are associated with end-organ damage. These are referred to as **CRAB** events of multiple myeloma and include hyper**C**alcaemia, **R**enal impairment, **A**naemia, and **B**one lesions.



sFLC - serum Free Light Chain SPE - Serum Protein Electrophoresis

Consequences of a delay in diagnosis and why a timely diagnosis is important

More than 50% of multiple myeloma patients experience a delay in diagnosis of over 6 months when diagnosed in primary care settings[3]. Over 70% of patients experience additional symptoms and complications due to a delayed diagnosis, such as fractures, spinal cord compression, and renal failure[4]. In particular, the number of patients experiencing renal disease is 2.6 times higher when the diagnosis is made after 6 months compared to when the diagnosis is made in under 3 months[3]. Timely diagnosis and subsequent management of multiple myeloma avoids complications that impact patients' quality of life. Earlier diagnosis and, therefore, the commencement of treatment have been shown to significantly improve 5-year survival rates of patients[5]. Specifically, more than 8 in 10 (84%) myeloma patients will survive for more than 5 years when diagnosis is made early, compared with fewer than 3 in 10 (26%) when diagnosed at a later stage[5]. It is also important to consider that if the patient develops too many complications, or the severity of the complications is too great, the haematologist may decide to limit patient treatment due to frailty. Primary care providers play a key role in recognising and ruling out multiple myeloma at the earlier stages of the disease.

Request correct blood tests to rule out multiple myeloma

A number of blood tests are recommended to rule out multiple myeloma, as highlighted in the publication by Dr Joseph Mikhael, MD, and Chief Medical Officer, International Myeloma Foundation. This includes, although not limited to, the following[2]:

- Complete Blood Count - to check for anaemia and raised Erythrocyte Sedimentation Rate (ESR).
- Serum Biochemistry Panel - to check for raised calcium, raised creatinine, and low albumin.
- Serum Protein Studies - to check for a monoclonal protein using serum free light chain (sFLC) and serum protein electrophoresis (SPE) tests.

The testing combination of sFLC + SPE has been shown to identify >99% of multiple myeloma patients[6]. This is why current expert guidelines, such as those from the International Myeloma Working Group (IMWG)[7] and the local ANZ Medical Scientific Advisory Group (MSAG) to Myeloma Australia, recommend this testing combination for initial screening and diagnosis of multiple myeloma.

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Significant deviation from these guidelines may cause diagnosis to be delayed or missed altogether due to the use of less sensitive testing panels. Data shows that 1 in 8 multiple myeloma patients may be missed when SPE alone is ordered[8].

Refer to haematology

When the patient's symptoms and basic laboratory findings are suggestive of multiple myeloma, an assessment of serum protein studies will help to rule out multiple myeloma[2]. The survival rate for multiple myeloma patients increases by over 1.5 times when the diagnosis is achieved through the primary care referral pathway rather than the emergency route[9]. Requesting the best test combination to rule out multiple myeloma earlier allows for a timelier referral pathway to haematology.

References

1. Government A. Multiple myeloma in Australia statistics. 2022;
2. Mikhael J, *et al.* Multiple Myeloma for the Primary Care Provider: A Practical Review to Promote Earlier Diagnosis Among Diverse Populations. *Am J Med* 2023; 136:33-41
3. Kariyawasan CC, *et al*. Multiple myeloma: causes and consequences of delay in diagnosis. *QJM* 2007; 100:635-640
4. Europe MP. MYELOMA DIAGNOSIS ACROSS EUROPE. 2022; 1-56
5. Bloodwise. The Current State of Blood Cancer Diagnosis in England. 2019; 1-22
6. Katzmann JA. Screening panels for monoclonal gammopathies: time to change. *Clin Biochem Rev* 2009; 30:105-111
7. Genzen JR, *et al*. Screening and Diagnosis of Monoclonal Gammopathies: An International Survey of Laboratory Practice. *Arch Pathol Lab Med* 2018; 142:507-515
8. Katzmann JA, *et al.* Screening panels for detection of monoclonal gammopathies. *Clin Chem* 2009; 55:1517-1522
9. Elliss-Brookes L, *et al*. Routes to diagnosis for cancer - determining the patient journey using multiple routine data sets. *Br J Cancer* 2012; 107:1220-6

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Dr Jenner began training in Chemical Pathology in 2001 and obtained Fellowship from the Colleges of Medicine of South Africa in 2004, as well as a Master's degree in Chemical Pathology from the University of Pretoria in 2005. He has worked as a senior registrar in Clinical Biochemistry at the Royal Infirmary of Edinburgh, as a consultant clinical biochemist at the NHS Borders Hospital (Scotland), and as a consultant chemical pathologist in private practice in South Africa. In 2012, Dr Jenner relocated to Australia and worked as a senior registrar at the Royal Brisbane and Women's Hospital. He obtained his Fellowship from the Royal College of Pathologists of Australasia in 2013 and joined Australian Clinical Labs in early 2014.

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New MBS Items for PSA tests

From NOVEMBER 1st 2023

By Dr David Deam

Effective from 1st November 2023, the MBS requirements for prostate-specific antigen (PSA) testing have changed.

The new items better align with the NHMRC-endorsed guidelines put forward by the Prostate Cancer Foundation of Australia and the Cancer Council of Australia in 2016.[1]

The general recommendation is for those men who decide to have PSA tests to assist in the early detection of prostate cancer to have a PSA blood test every two years from age 50 to 69 years.

PSA testing may also be useful in other situations, such as prostatitis and in the follow-up of patients with known prostate disease.

The importance of having a significant family history of prostate cancer is also recognised in the guidelines.

The percentage Free PSA can also be helpful in evaluating a raised PSA and in the management of known prostate disease.

The new items descriptors for PSA are:

Item No	Description	Time Restriction
	PSA	
66655	PSA quantitation	Not more than one in 23 months
66654	PSA quantitation in the monitoring of high-risk patients	Not more than one in 11 months
66656	PSA quantitation in the monitoring of previously diagnosed prostatic disease (including prostate cancer, prostatitis or a premalignant condition such as atypical small acinar proliferation)	None
	Free PSA Percentage	
66659	in the follow up of a PSA result under item 66654 or 66655 that lies at: (a) more than 2.0 ug/L but less than or equal to 5.5 ug/L for patients with a family history of prostate cancer; or (b) more than 3.0 ug/L but less than or equal to 5.5 ug/L for patients who are at least 50 years of age but under 70 years of age; or (c) more than 5.5 ug/L but less than or equal to 10.0 ug/L for patients who are at least 70 years of age	Not more than one in 11 months
66660	the monitoring of previously diagnosed prostatic disease, if the current PSA level lies at: (a) more than 2.0 ug/L but less than or equal to 5.5 ug/L for patients with a family history of prostate cancer; or (b) more than 3.0 ug/L but less than or equal to 5.5 ug/L for patients who are at least 50 years of age but under 70 years of age; or (c) more than 5.5 ug/L but less than or equal to 10.0 ug/L for patients who are at least 70 years of age	Not more than 4 times in 11 months

New MBS Items for PSA tests

How to order

Request "PSA" on our general Clinical Labs request form.

It is important that the laboratory knows if the patient is at increased risk for prostate cancer (such as with a strong family history or previous high PSA levels) or has known prostate disease so that they can be billed correctly under the new Medicare item numbers.

If the clinical information is not provided, or the patient is not eligible under these item numbers, then a private bill may be generated.

References

[1] See 'PSA-Testing-Guidelines.pdf' (pcfa.org.au): https://www.pcfa.org.au/media/612113/PSA-Testing-Guidelines.pdf

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Earn **30** CPD hours per year!

Annual Criteria for Qualification
- 20 Cervical Screening Tests recommended
- Reflection activity completed

5 HOURS Reviewing Performance • 5 HOURS Educational Activites • 20 HOURS Measuring Outcomes

5hrs	5hrs	12.5hrs	12.5hrs	15hrs
Reviewing Performance	Measuring Outcomes	Educational Activities (Knowledge and Skills)	Any Activity Type	Reviewing Performance and/or Measuring Outcomes

Scan the QR code to register for 2024.

Diabetes Clinical Evaluation Program

A CPD clinical audit designed to help you easily manage and provide clinical care for your patients living with diabetes.

Earn **20** CPD hours per year!

Annual Criteria for Qualification
- 40 HbA1c tests recommended
- 4 program login/views recommended
- Reflection activity completed

10 HOURS Reviewing Performance • 10 HOURS Measuring Outcomes

5hrs	5hrs	12.5hrs	12.5hrs	15hrs
Reviewing Performance	Measuring Outcomes	Educational Activities (Knowledge and Skills)	Any Activity Type	Reviewing Performance and/or Measuring Outcomes

Scan the QR code to register for 2024.

Skin Excision Evaluation Program

A CPD clinical audit that delivers a truly educational experience by analysing your diagnostic skill for identification of high-risk lesions.

Earn **27.5** CPD hours per year!

Annual Criteria for Qualification
- 40 histological samples recommended (submitted on specific audit request forms)
- Reflection activity completed

5 HOURS Reviewing Performance • 2.5 HOURS Educational Activites • 20 HOURS Measuring Outcomes

5hrs	5hrs	12.5hrs	12.5hrs	15hrs
Reviewing Performance	Measuring Outcomes	Educational Activities (Knowledge and Skills)	Any Activity Type	Reviewing Performance and/or Measuring Outcomes

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