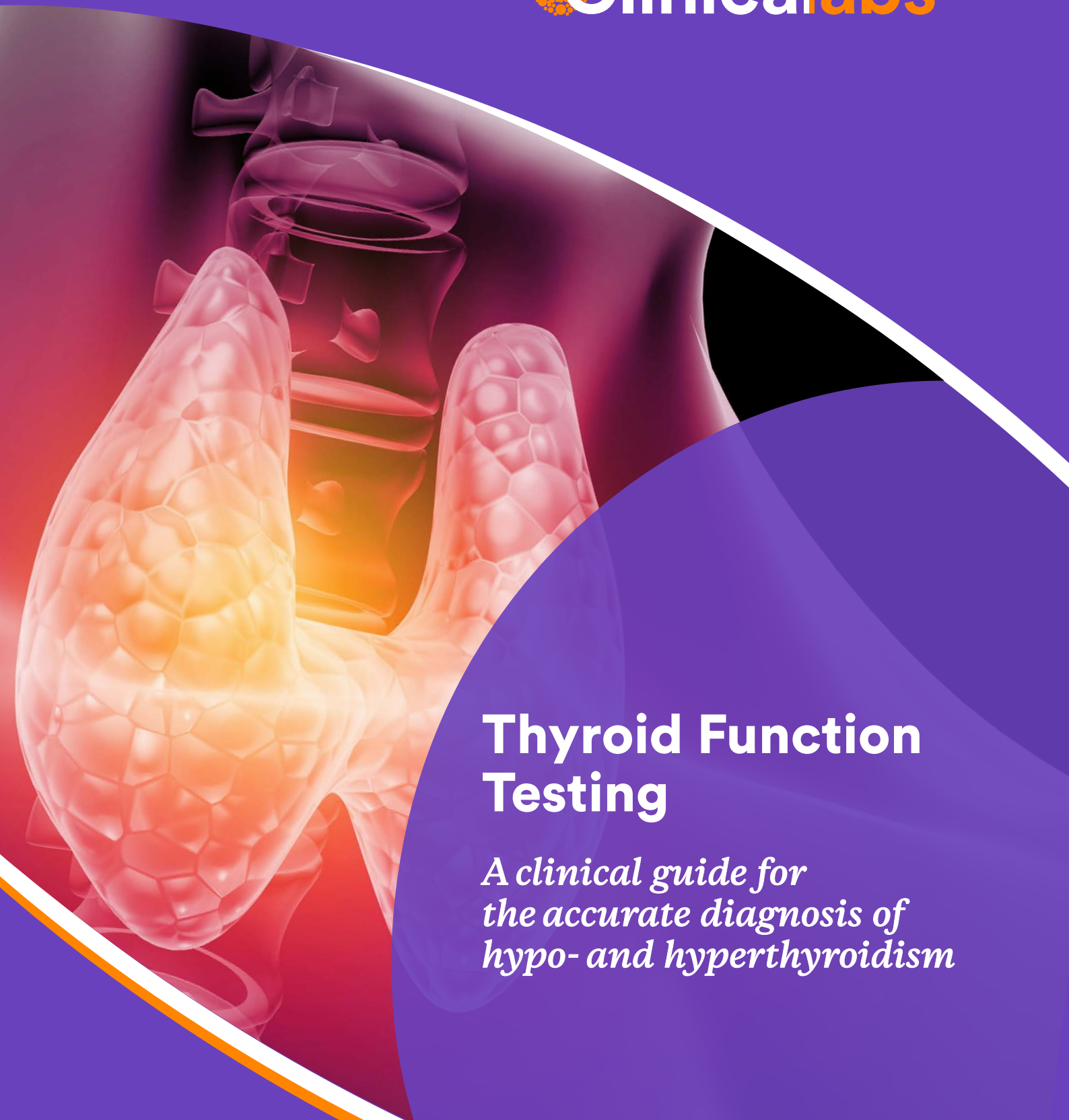
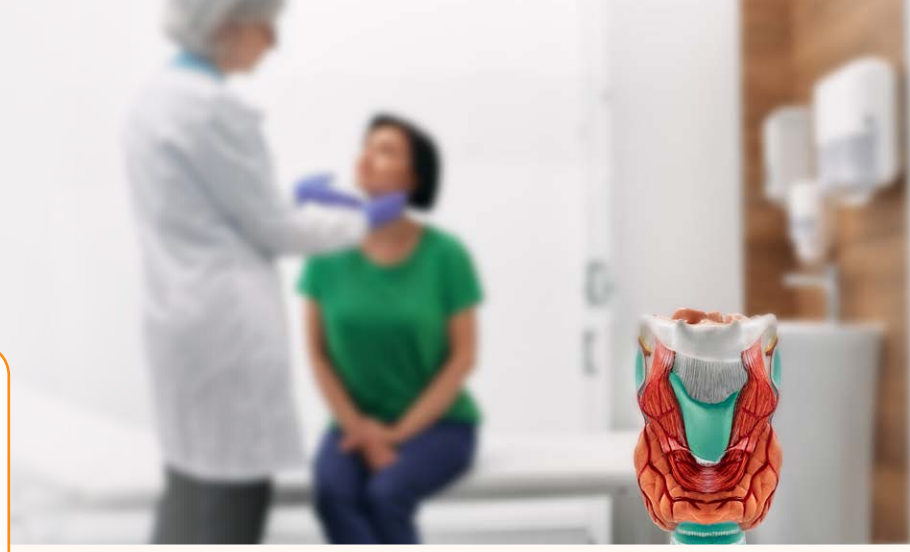
AUSTRALIAN Clinicallabs



Thyroid Function Testing

A clinical guide for the accurate diagnosis of hypo- and hyperthyroidism

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.



"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."

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

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.

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.

Please Note: 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.

Thyroid antibodies

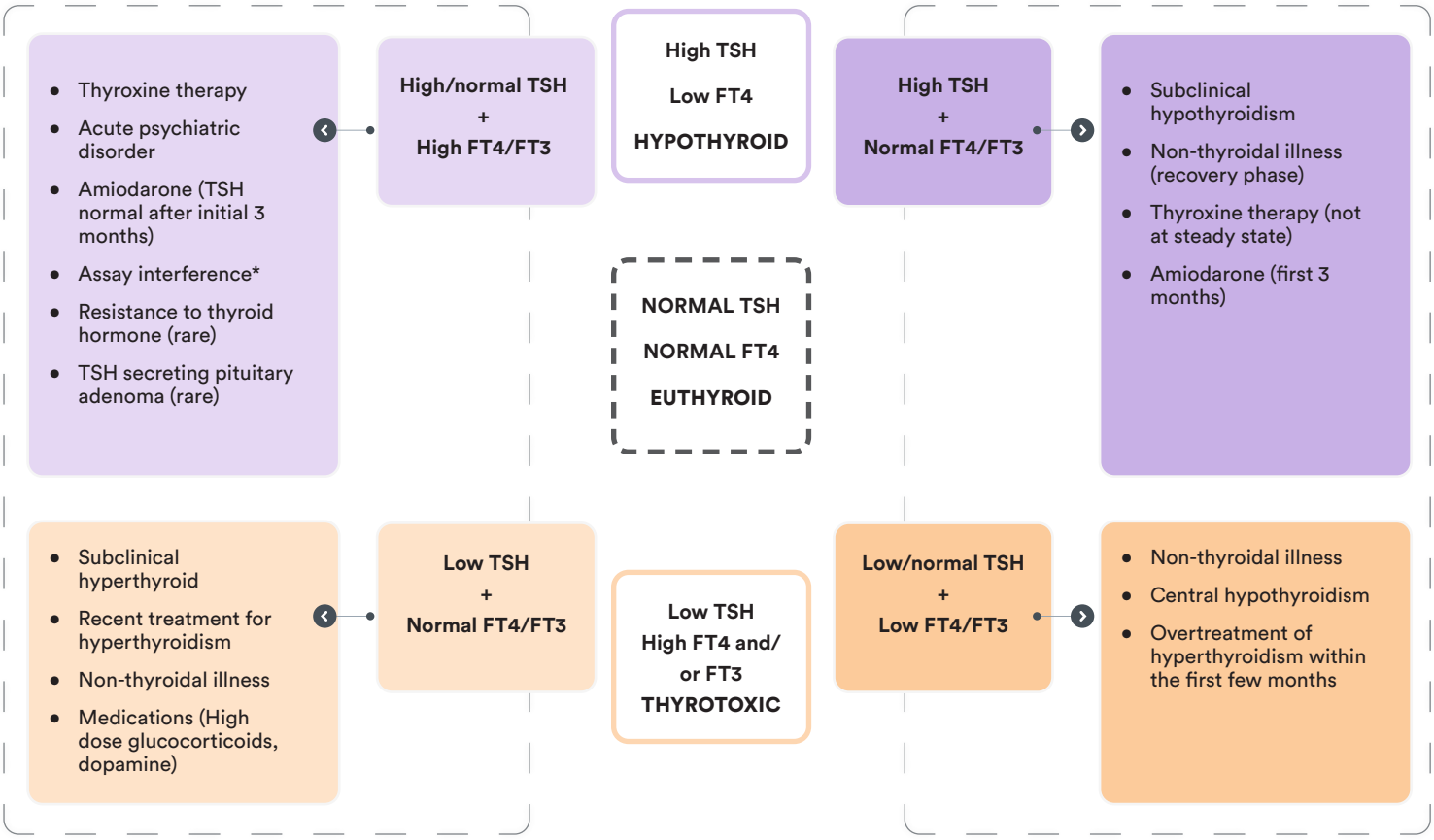
Thyroid antibodies are used to investigate the aetiology of hypo- or hyperthyroidism and to monitor thyroglobulin levels in the follow-up of thyroid cancer.

Table 3. Thyroid antibody testing at Clinical Labs:

INDICATION	TEST	COMMENTS
Hypothyroidism	Thyroid peroxidase (TPO) antibodies +/- Thyroglobulin (Tg) antibodies	Present in most cases of autoimmune lymphocytic "Hashimoto's" thyroiditis, the most common cause of hypothyroidism in Australia. TPO antibodies are more sensitive and specific than Tg antibodies.
Hyperthyroidism	Thyroid stimulating immunoglobulin (TSI)	A positive TSI is consistent with Graves' disease. Its presence is also crucial during pregnancy, as TSI may cross the placenta and affect the foetal thyroid.
Thyroid cancer follow-up	Thyroglobulin antibodies	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.

Interpretation 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 Graves' 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.

TSI measurement is a useful first-line test. A positive TSI is consistent with Graves' disease.

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.

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.

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To access Dr Stanford's complete article, 'Simplifying diagnosis: A comprehensive exploration of thyroid function test interpretation,' simply scan the QR code.

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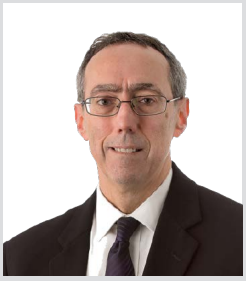

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