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DRAFT: Thyroid Function Tests in the Diagnosis and Monitoring of Thyroid Function Disorder

DRAFT FOR EXTERNAL REVIEW: The online questionnaire is available at https://survey.health.gov.bc.ca/thyroid.

Scope

This guideline addresses the detection of thyroid dysfunction in patients (pediatric and adult), including pregnant women or women planning pregnancy, and the monitoring of patients treated for primary thyroid function disorders. This guideline outlines thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3) and anti-thyroid peroxidase (TPO) testing. Information on other tests, including thyroglobulin/ antithyroglobulin (Tg/anti Tg) and antibodies to the thyroid stimulating hormone receptor (TRAb), are covered in the associated BC guideline *Hormone Testing – Indications and Appropriate Use*.

Key Recommendations

- **Routine thyroid function testing is not recommended in asymptomatic patients** (outside of the newborn screening program in operation in BC). However, testing may be indicated when non-specific signs and symptoms are present in patients at risk for thyroid disease.
- **A TSH value within the reference interval excludes the majority of cases of primary overt thyroid disease.**
- **If initial TSH testing is normal, repeat testing is unnecessary unless there is a change in clinical condition.**
- **Measurement of fT3 is rarely indicated in suspected thyroid disease.**
- **Ideally, thyroid function tests should not be performed during non-thyroid illness in hospitalized patients** unless hyperthyroidism or hypothyroidism is the suspected cause of the clinical presentation or represents a significant co-morbidity.
- If a woman is pregnant or planning pregnancy, TSH testing is indicated if she has specific risk factors (see Table 3).

Indications for Testing

Routine thyroid function testing is not recommended in asymptomatic patients (outside of the newborn screening program in operation in BC). However, testing may be indicated when non-specific signs and symptoms are present in patients at risk for thyroid disease.

Considering the high prevalence of thyroid disease, particularly hypothyroidism in women and that some studies have shown that affected women may benefit from early treatment, **it is recommended that clinicians investigate individuals with vague symptoms that could be related to thyroid dysfunction.**

If initial testing is normal, repeat testing is unnecessary unless there is a change in clinical condition.

Risk Factors

Risk factors for thyroid disease include:[1]

- men ≥ 60 years;[2]
- women ≥ 50 years;[2]
- personal history or strong family history of thyroid disease;
- diagnosis of other autoimmune diseases;
- past history of neck irradiation;
- drug therapies such as lithium and amiodarone.

For risk factors during pregnancy, see Table 3 in the Thyroid Disease in Pregnancy section below.

Signs and Symptoms

Table 1: Signs and symptoms of thyroid disease[1,3,4]

Hypothyroidism	
Signs	**Symptoms**
• Decreased mental function • Slow movement • Slowing of ankle jerk • Weight gain • Goitre • Slow pulse • Hair loss	• Coarse, dry skin and hair • Cold intolerance • Constipation • Decreased hearing • Diminished sweating • Physical tiredness • Hoarseness • Abnormal skin sensation (paresthesia) • Periorbital puffiness • Menstrual irregularities (menorrhagia) • Depression
Hyperthyroidism	
Signs	**Symptoms**
• Distracted attention span • Tremors • Proximal muscle weakness • Tachycardia • Hypertension • Widened pulse pressure • Atrial fibrillation • Weight loss • Goitre • Overactive or overresponsive reflexes (hyperreflexia) • Dry eyes, inflamed conjunctiva, proptosis or dysconjugate gaze • Hair loss	• Nervousness and irritability • Heat intolerance • Increased frequency of stools • Increased sweating (clammy hands) • Fatigue • Blurred or double vision • Erratic behavior • Restlessness • Heart palpitations • Restless sleep • Decrease in menstrual cycle (amenorrhea/oligomenorrhea) • Increased appetite

Tests

Thyroid Stimulating Hormone (TSH)

Measurement of TSH is the principal test for the evaluation of thyroid function in the vast majority of circumstances[5] **provided the hypothalamic-pituitary axis is intact**. Hypothalamic and pituitary disease can cause central hypothyroidism, which is rare.[6,7]

A TSH value within the reference interval excludes the majority of cases of primary overt thyroid disease.[3] The TSH reference interval will vary depending on the testing laboratory. Laboratories in BC retain specimens for 2 to 7 days in case add-on testing is required. If TSH is ordered initially in combination with fT4 or fT3, the laboratory will perform the TSH test first and then perform the fT4 and fT3 if required, as described in Appendix 1 (see Appendix 1: BC Laboratory Algorithm for Thyroid Tests).

If TSH is abnormal, measure fT4 for further diagnostic classification and assessment of disease severity (see Figure 1).

Free Thyroxine (fT4) and Free Triiodothyronine (fT3)

Measurements of fT4 and fT3 have replaced those of total T4 and total T3 levels. Laboratories are permitted to substitute free hormone assays when total T3 or T4 have been ordered.

Measurement of fT3 is rarely indicated in suspected thyroid disease.[3,8] This is reserved for situations where thyroid disease is suspected clinically and TSH is abnormal, but fT4 is inappropriately normal.

Anti-thyroid peroxidase (TPO)

In patients with a goitre, thyroid peroxidase antibody measurement is used to evaluate whether the cause is autoimmune thyroiditis.[8] Thyroid peroxidase antibody measurement may also be used to determine whether the cause of primary hypothyroidism is autoimmune (Hashimoto's thyroiditis).[8] Thyroid peroxidase antibody positivity increases the risk of developing hypothyroidism in patients with subclinical hypothyroidism, autoimmune diseases (e.g. type 1 diabetes), chromosomal disorders (e.g. Turner syndrome and Down syndrome) or patients who are on certain drug therapies (e.g. lithium, amiodarone), are pregnant or postpartum (see Thyroid Disease in Pregnancy section below).[8,9] Repeat analysis of thyroid peroxidase antibody levels is rarely indicated.

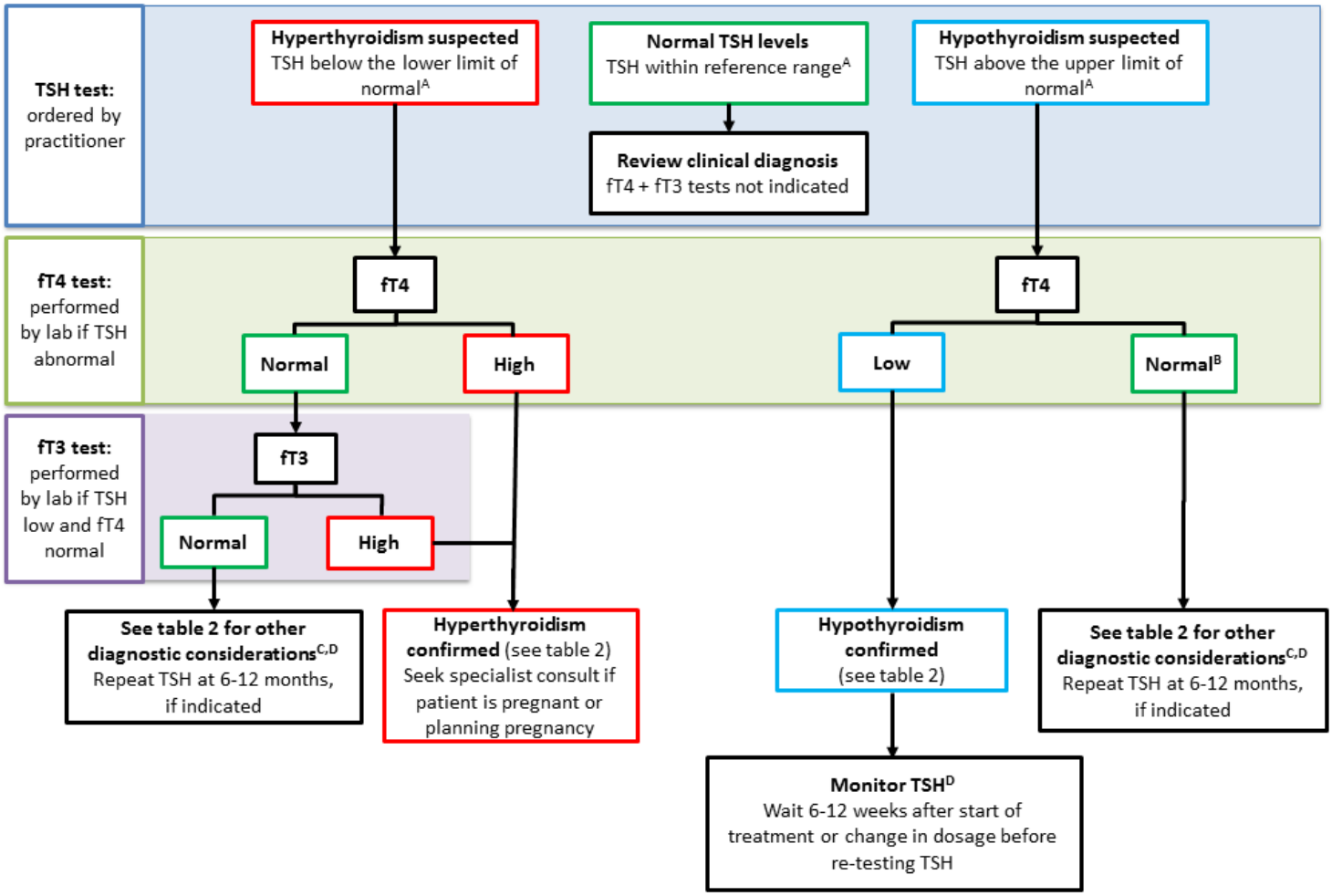
Follow-Up Testing

In most cases, ordering a different test is more useful than repeating the same test (e.g. if a patient has specific clinical findings and a TSH result does not appear to correlate with the patient's clinical status, it may be more appropriate to follow with an fT4 measurement).

Consultation with the lab physician is recommended when the test result is in conflict with the clinical presentation so that investigation for analytical interferences or rare conditions can be undertaken.

Figure 1: Algorithm for Thyroid Function Tests for Diagnosis and Monitoring in Symptomatic Patients or in Pregnant Women with Risk Factors (see Thyroid Disease in Pregnancy section).

This algorithm only applies to patients with an intact hypothalamic pituitary axis and does not apply to hospitalized patients (Sick Euthyroid Syndrome).



Notes:

A. TSH testing intervals may vary depending on the testing lab and whether the patient is pregnant (see the Thyroid Disease in Pregnancy section below).[9]

B. The diagnosis of overt hypothyroidism can still be made if fT4 levels are borderline low when TSH levels are sufficiently high (e.g. greater than 20 mU/L).

C. An abnormal TSH level which is not confirmed by an abnormal fT4 measurement (or fT3 if T3 thyrotoxicosis is suspected) may be due to subclinical thyroid disease or may be caused by a patient-specific laboratory artefact requiring further investigation for clarification.

D. During pregnancy, target TSH and testing intervals may vary (see the Thyroid Disease in Pregnancy section below).[9]

Table 2. Potential causes of abnormal hormone levels (TSH, fT4 and fT3)

Causes of High TSH[10,11]	Laboratory Result	Follow-up
Hypothyroidism • Autoimmune	**TSH ↑, fT4 ↓**[3]	See Monitoring: Hypothyroidism or Thyroid Disease in Pregnancy
Subclinical hypothyroidism • Typically asymptomatic	**TSH ↑ (usually less than 10 mU/L)**[A]**, fT4 normal**[8,12] **(fT3 not indicated)** *Consider assay artefact*[B]	See Subclinical Hypothyroidism or Thyroid Disease in Pregnancy
Recovery from non-thyroidal illness • Sick Euthyroid Syndrome	**Testing not usually indicated** As patients recover, TSH may normalize or become elevated[13]	See Sick Euthyroid Syndrome
Very rare: secondary hyperthyroidism • Pituitary disease	**TSH ↑ (or normal), fT4 ↑**[10,11] *Consider rare situations such as assay artefact*[B] *Consult with a specialist*	See Monitoring: Hypothalamic or Pituitary Disease
Causes of Low TSH[10,11]	**Laboratory Result**	**Follow-up**
Hyperthyroidism • Excessive thyroid hormone replacement (levothyroxine) • Graves' disease • Thyroiditis (viral) • Toxic (multinodular) goitre	**TSH ↓, fT4 ↑**[3] **(fT3 not indicated)**	See Monitoring: Hyperthyroidism See Thyroid Disease in Pregnancy
Hyperthyroidism • T3 thyrotoxicosis (e.g. autonomous nodule) • Excessive thyroid hormone replacement (liothyronine or desiccated thyroid)	**TSH ↓, fT4 normal/low, fT3 ↑**[3]	See Monitoring: Hyperthyroidism See Thyroid Disease in Pregnancy
Subclinical hyperthyroidism • Recovery of hyperthyroidism • Pregnancy related[9,14]	**TSH ↓**[A]**, fT4 normal, fT3 normal**[15] *Consider assay artefact*[B]	See Subclinical Hyperthyroidism See Thyroid Disease in Pregnancy
Sick Euthyroid Syndrome • Hospitalized patients, recovery from severe illness	**Testing not usually indicated** Any abnormality in levels is possible • Usually: TSH ↓ or normal, fT4 ↓ or normal, fT3 ↓[7,11] • As patients recover, TSH may normalize or become elevated[13]	See Sick Euthyroid Syndrome
Rare: secondary hypothyroidism • Hypopituitarism	**TSH ↓ (or normal), fT4 ↓**[3] *Consider assay artefact*[B]	See Monitoring: Hypothalamic or Pituitary Disease

A. Treatment is considered when TSH is above 10 mU/L[12] or below 0.1 mU/L[15] for subclinical hypothyroidism or subclinical hyperthyroidism, respectively.

B. Assay artefact may cause abnormal laboratory results. Immunoassays for thyroid function tests are subject to analytical interference due to heterophile antibodies,[16] variant TSH isoforms by glycosylation,[16] macro TSH (TSH in combination with IgG antibody),[16] or high dose biotin administration.[17]

Monitoring of Thyroid Disease

Hypothyroidism

Since TSH values change slowly,[18] frequent repeat testing is not indicated. TSH may be repeated after at least 6-12 weeks following a change in thyroid hormone replacement dose or in a patient's clinical status.[8] Once TSH has normalized with treatment, it should be checked annually unless a new indication arises. This confirms adequacy of treatment dose and compliance with therapy. Note that within the normal reference interval, TSH levels in the same individual can vary by 50% when measured at different times of day, with lowest values in the late afternoon and highest values at midnight.[19] In individuals with subclinical hypothyroidism, TSH values can vary by up to 40% even when measured at the same time on different days without indicating a change in thyroid function.[20]

Hyperthyroidism

To monitor patients on treatment for Graves' disease or other causes of hyperthyroidism, allow at least one month or longer before repeating fT4 and TSH levels since pituitary secretion of TSH may be suppressed for protracted periods following hyperthyroidism.[15] Until TSH suppression resolves, initial treatment and dosing decisions should be based on fT4.[15]

Hypothalamic or Pituitary Disease

TSH is only useful as a measure of thyroid disease if the hypothalamic-pituitary-thyroid axis is intact. When pituitary or hypothalamic disease is suspected, fT4 measurement is required to make the diagnosis or assess adequacy of thyroid replacement therapy.[6,7]

Subclinical Thyroid Disease

Subclinical thyroid disease may be asymptomatic, is more common in women, and prevalence increases with advanced age.[12,15]

Subclinical Hypothyroidism

In subclinical hypothyroidism, TSH levels are elevated in the presence of normal levels of fT4 (see Table 2).[8,12]

Treatment for subclinical hypothyroidism is recommended when TSH rises above 10 mU/L.[12] Treatment can be considered when TSH is between the upper limit of the reference interval but ≤10 mU/L and any of the following are present:

- elevated thyroid peroxidase antibodies;[8]
- goitre;
- strong family history of autoimmune disease; or
- pregnancy (see Thyroid Disease in Pregnancy section below).[8]

The prevalence of subclinical hypothyroidism in the general population is between 4.3%-8.5%.[8] Every year, 2.6% of subclinical hypothyroidism patients without elevated thyroid peroxidase antibodies and 4.3% of subclinical hypothyroidism patients with elevated thyroid peroxidase antibodies progress to overt hypothyroidism.[8] In patients with subclinical hypothyroidism and TSH ≤ 10 mU/L, thyroid hormone therapy may not be required as previous studies have shown that thyroid hormone replacement therapy does not result in improved survival or quality of life.[21,22]

Monitoring of TSH in untreated patients with subclinical hypothyroidism at 6-12 month intervals is indicated.[23]

Subclinical Hyperthyroidism

In subclinical hyperthyroidism, the TSH levels are suppressed in the presence of normal levels of fT4 (see Table 2).[15] Subclinical hyperthyroidism is less common, with a prevalence of 0.7%.[15]

Patients with atrial fibrillation and osteoporosis should be screened for hyperthyroidism. In patients over age 60 with TSH < 0.1 mU/L but with a normal fT4, the relative risk for atrial fibrillation increases threefold.[24] Post-menopausal women with subclinical hyperthyroidism may have an increased rate of bone loss.[25] In the elderly, there is a higher cardiovascular risk and an increased risk of fracture. **Treatment of subclinical hyperthyroidism should be considered in the elderly.**[15,26] Patients with subclinical hyperthyroidism due to multi-nodular goitre or functioning adenoma are unlikely to normalize and are therefore more likely to benefit from treatment.

Sick Euthyroid Syndrome

In Sick Euthyroid Syndrome (Non-Thyroidal Illness Syndrome), the hypothalamic-pituitary-thyroid axis is affected by a non-thyroid illness. It occurs in patients without a previously diagnosed thyroid disease.[27]

Almost any condition that can make a person ill can cause Sick Euthyroid Syndrome and the elderly are more susceptible because of multiple co-morbid conditions.[10] The syndrome is acute and spontaneously reverses and occurs commonly after surgery, during fasting, during many acute febrile illnesses, and after acute myocardial infarction. Malnutrition, renal and cardiac failure, hepatic diseases, uncontrolled diabetes, cerebrovascular diseases, and malignancy can also produce abnormalities in thyroid function tests.[10]

Testing

Ideally, thyroid function tests should not be performed during non-thyroid illness in hospitalized patients unless hyperthyroidism or hypothyroidism is the suspected cause of the clinical presentation or represents a significant co-morbidity. However, where thyroid testing has occurred, any abnormal results should be interpreted with caution and with a realization that Sick Euthyroid Syndrome is the most likely explanation for the finding if performed in hospitalized patients rather than true thyroid disease.

Multiple patterns of hormone levels are possible (see Table 2); abnormalities fluctuate during the course of illness and recovery. However, usually fT3 is low, fT4 is low in some sicker patients, and TSH is low or normal.[7,11] As patients recover from their illness, TSH may normalize or become elevated.[13]

TSH levels must be interpreted with caution in hospitalized individuals. However, values below < 0.1 or > 20 mU/L merit a consultation.[5] Levothyroxine replacement has not been shown to be beneficial and should not be used in patients with Sick Euthyroid Syndrome.[7]

Thyroid Disease in Pregnancy

If a woman is pregnant or planning pregnancy, TSH testing is indicated if she has any of the risk factors listed in Table 3.

Table 3. Risk factors for thyroid disease in women who are pregnant or anticipating becoming pregnant[9,14,28,29]

- Age > 30 years
- More than 2 prior pregnancies
- History of pregnancy loss, preterm delivery, or infertility
- Type 1 diabetes or other autoimmune disorders
- Morbid obesity (BMI ≥ 40 kg/m^2)
- History of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction
- Family history of autoimmune thyroid disease or thyroid dysfunction (1st degree relative)
- History of head or neck radiation or prior thyroid surgery
- Known thyroid peroxidase antibody positivity or presence of a goitre
- Currently receiving levothyroxine replacement
- Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast

Hypothyroidism in Pregnancy

Research data support a possible connection between untreated overt maternal hypothyroidism and neuropsychological impairment in the offspring.[30,31] If hypothyroidism or subclinical hypothyroidism has been diagnosed before or during pregnancy, **treatment should be adjusted to achieve a TSH level within the normal trimester and method-specific reference interval**.

As the laboratory will typically not have information on the patient's pregnancy status, only normal reference intervals for non-pregnant adult women are provided with the patient's reported TSH result. **Consequently, information to guide the interpretation of trimester-specific TSH and fT4 measurements, performed in BC laboratories, is included in Appendix 2** (see Appendix 2: Interpretation of Pregnancy TSH and fT4 Measurements in BC)**.**

After starting thyroid hormone replacement or a dose change, TSH should be re-measured every 4-6 weeks.[14,28] Levothyroxine replacement dosage may need to increase by 25%-50% during pregnancy, particularly in the first trimester.[14,28]

Thyroid peroxidase antibody positivity can indicate whether a patient may develop hypothyroidism while pregnant. However, routine testing of thyroid peroxidase antibodies before or during pregnancy is not indicated.[14,28] When thyroid peroxidase antibody status is known to be positive in euthyroid women, TSH should be measured every 4 weeks.[9]

Postpartum

After delivery, most women treated for hypothyroidism need a decrease in the levothyroxine dosage they received during pregnancy. TSH should be evaluated 6 weeks after the dose change.[9]

Hyperthyroidism in Pregnancy

Hyperthyroid patients should have specialist consultation when contemplating pregnancy or during pregnancy. TSH may be suppressed as a normal finding within the first trimester of pregnancy or with certain conditions such as multiple gestation, nausea and vomiting (hyperemesis gravidarum) and molar pregnancy.[9] In this context a normal fT4 generally excludes hyperthyroidism.[9,14]

Postpartum

There is an increased incidence of postpartum thyroiditis and new cases/relapse of Graves' disease in the postpartum interval.[9] One study found that after delivery, hyperthyroidism diagnosed within 3 months was most often caused by postpartum thyroiditis while hyperthyroidism diagnosed after 6.5 months was caused by Graves' disease.[32]

Postpartum Thyroiditis

Postpartum thyroiditis is an autoimmune disorder and the presence of anti-thyroid peroxidase antibodies increases the risk of disease.[33] Postpartum thyroiditis may occur in approximately 5% of women in the first year postpartum.[33]

There is insufficient evidence to recommend screening all women for postpartum thyroiditis. Women previously known to be thyroid peroxidase antibody positive should have a TSH performed at 3 and 6 months postpartum or as clinically indicated.[28] Postpartum thyroiditis is often mild and transient. The disorder may present as hyperthyroidism followed by hypothyroidism and subsequent recovery of normal thyroid function. Some women may present with hypothyroidism without a hyperthyroid interval and may remain hypothyroid.[9] Ten to fifty percent of women with a history of postpartum thyroiditis have an increased risk of developing permanent primary hypothyroidism after a postpartum thyroiditis episode.[9]

An annual TSH is recommended in patients with a history of postpartum thyroiditis.[9] There is a significant risk for recurrent postpartum thyroiditis in subsequent pregnancies.[9]

Resources

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Abbreviations

TSH	Thyroid stimulating hormone
fT4	Free thyroxine
fT3	Free triiodothyronine
TPO	Thyroid peroxidase

Diagnostic Codes: 244 (Hypothyroidism), 242 (Hyperthyroidism)

Appendices

- Appendix 1: BC Laboratory Algorithm for Thyroid Tests
- Appendix 2: Interpretation of Pregnancy TSH and fT4 Measurements in BC

This guideline is based on scientific evidence current as of the Effective Date. This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

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The principles of the Guidelines and Protocols Advisory Committee are to:

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- recommend actions that are sufficient and efficient, neither excessive nor deficient
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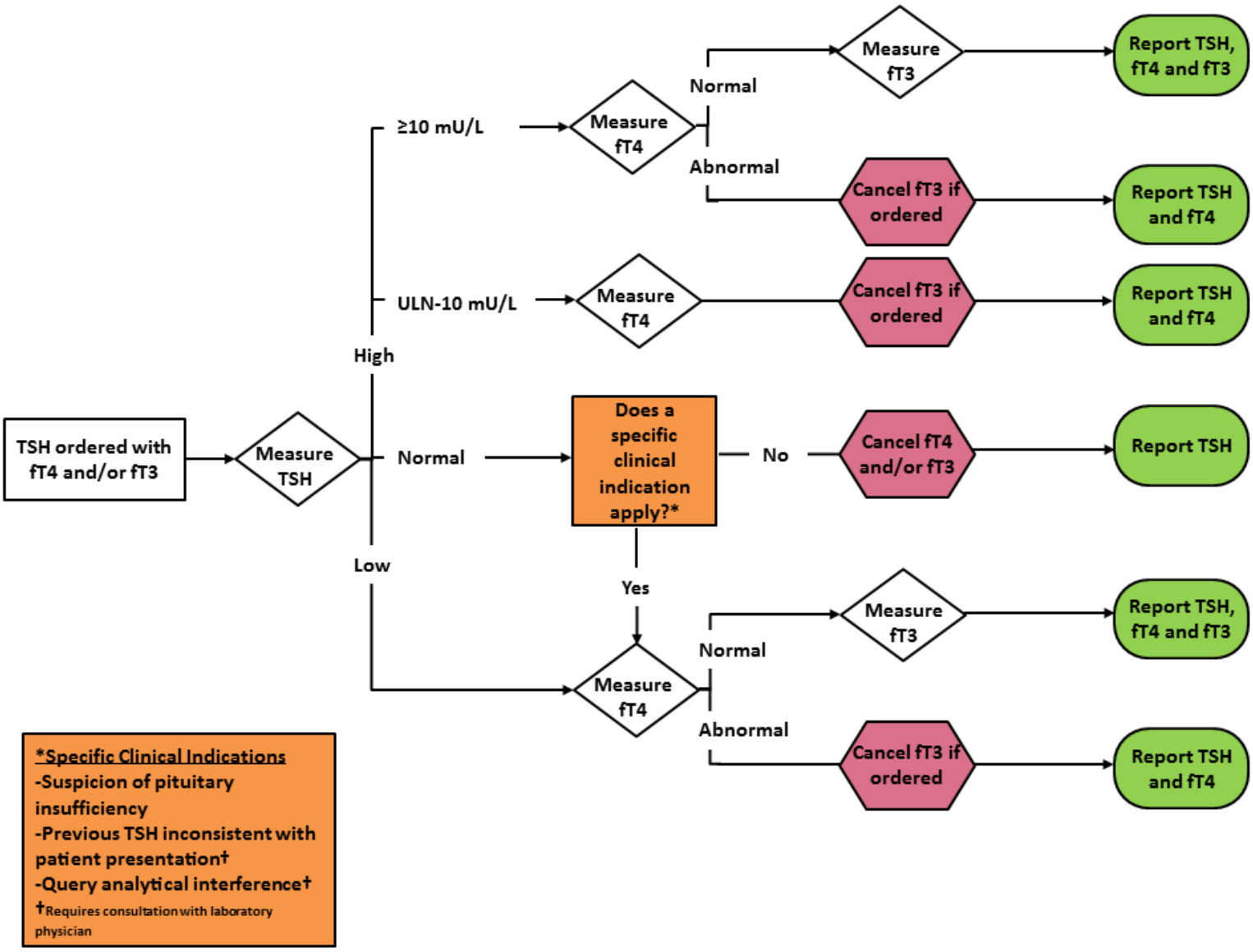
Appendix 1: BC Laboratory Algorithm for Thyroid Tests

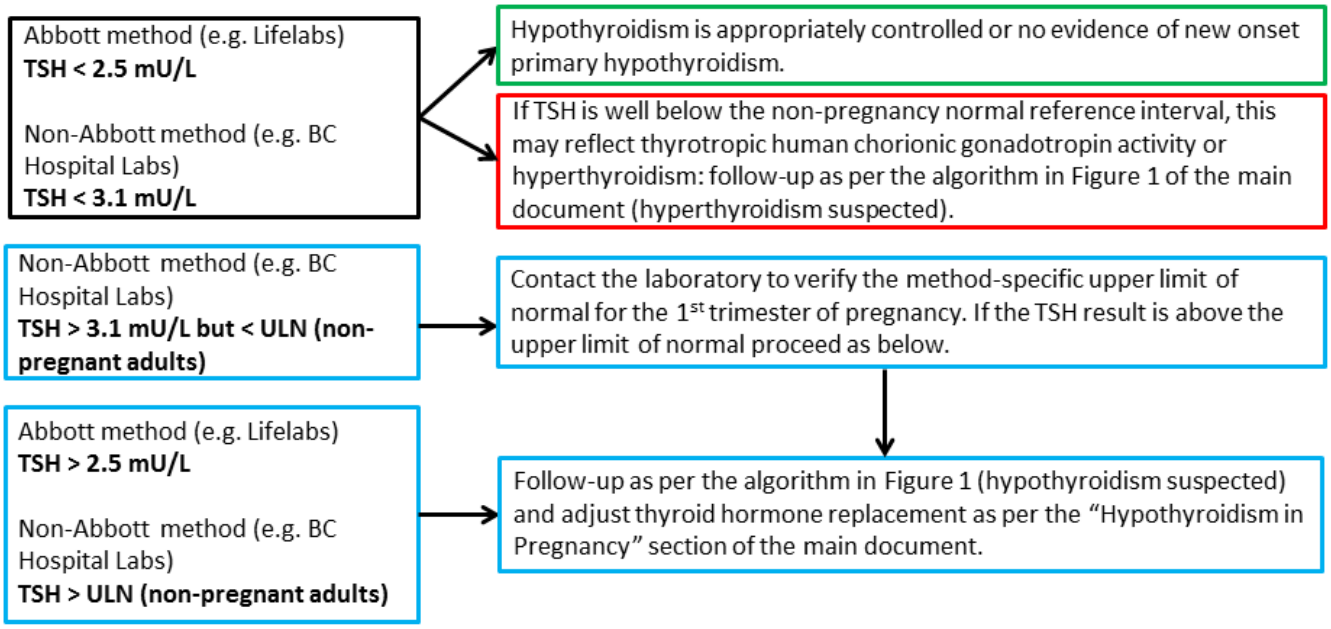


Appendix 2: Interpretation of Pregnancy TSH and fT4 Measurements in BC

Table 1. Utility of non-pregnant adult reference intervals.[1–4]

Test	Trimester	Lower Limit of Normal	Upper Limit of Normal
TSH	1st	Do **not** use non-pregnant reference interval – see **Figure 1** below	
	2nd / 3rd	Use non-pregnant lower limit from lab	Compared to non-pregnant upper limit: • 20% less in 2nd trimester • 10% less in 3rd trimester
fT4	1st	Use non-pregnant reference interval from lab to guide interpretation	
	2nd / 3rd	Compared to non-pregnant lower limit: • 10 to 30% less in latter two trimesters	Compared to non-pregnant upper limit: • 10 to 30% less in latter two trimesters

Figure 1. Interpretation of 1st Trimester TSH (mU/L) determined using BC non-pregnant reference intervals adjusted based on the literature[1–4] and laboratory method (Abbott or non-Abbott). ULN = upper limit of normal.



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