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TFTs Revisited - TSH Reference Range Changes

*With the imminent implementation of a major chemistry analyzer change on the horizon (see **A new laboratory VISTA**), there will be changes in a few laboratory reference ranges. The most noticeable (and potentially most significant) will affect TSH. This article will review thyroid laboratory tests and current controversies/ recommendations associated with their use. In the interest of (the author's) time management, some of the text below has been lifted from previous articles.*[1-3]

Thyrotropin (a.k.a. thyroid stimulating hormone or TSH) is secreted by the pituitary gland and provokes the thyroid gland to synthesize and release thyroxine (T4) and triiodothyronine (T3) into the blood. Both hormones circulate in the blood predominantly bound to one of three transport proteins - thyroid binding globulin or TBG (70%), transthyretin (20%), and albumin (10%). Minute amounts of the hormones (0.03% of T4 and 0.3% of T3) circulate in the physiologically active "free" form. While T4 concentration is at least tenfold higher than T3 concentration, T3 is four times more potent. In peripheral tissues (particularly the liver), up to one third of T4 is converted to T3. TSH secretion is regulated by thyrotropin releasing hormone (TRH) produced by the hypothalamus. A negative feedback loop maintains homeostasis where increased levels of free T3/T4 (FT3/FT4) inhibit synthesis and release of TRH and TSH while decreased FT3/FT4 promote TRH/TSH secretion. ***A log linear relationship exists between TSH and FT4 such that a twofold change in FT4 will ultimately result in a 100-fold inverse change in TSH.*** The circulating half-lives of TSH, T3, and T4 are roughly one hour, one day, and one week respectively.

A variety of physiologic, pathologic and pharmacologic events affect the levels of circulating TSH, T4, T3, FT4 and FT3. Causes include inhibition of the pituitary-thyroid axis, alterations in binding protein concentrations, changes in peripheral metabolism of thyroid hormones, and a variety of medication effects. In pregnancy, human chorionic gonadotropin has a "TSH-like" effect which may lower TSH levels while increasing T4 and T3. Nonthyroidal illness (NTI) may produce a variety of abnormalities in TFT's, while the patient remains clinically and functionally euthyroid ("euthyroid sick syndrome"). In acutely ill patients, the overwhelming majority of "abnormal" TFT's are attributable to this phenomenon. The discussion that follows is not applicable to patients suspected of having pituitary or hypothalamic disease.

TFT's - Old School

- **T4** - The most concentrated (and hence easiest to measure). Enjoyed immense popularity on "executive metabolic panels" when this type of laboratory testing was in vogue. Of limited value as a stand alone thyroid function test, because its concentration can be influenced by a variety of factors as discussed above.
- **T3 Resin Uptake (T3U)** - Also referred to as "resin uptake ratio". Used to correct for changes in binding protein concentrations. Inversely proportional to unsaturated thyroid hormone binding sites. Decreased T3U suggests either increased protein binding sites or decreased thyroid hormone (e.g. hypothyroidism) while increased T3U indicates decreased protein binding sites or increased thyroid hormone (e.g. hyper-thyroidism). Worthless as a stand-alone test, but useful in conjunction with T4 to calculate the FTI.
- **Free Thyroxine Index (FTI)** - Referred to by some as "T7". A calculated value (FTI = T4 x T3U) which correlates reasonably well with FT4. Indeed the FTI was probably a more accurate representation of FT4 than some of the early methods that measured FT4 directly, but it may yield abnormal results in the setting of NTI.
- **Reverse T3 (rT3)** - Biologically inactive. Elevated in NTI or starvation (e.g. anorexia nervosa). Few, if any, indications for current use.

T4, T3U and FTI are still available at Rex, although they are not recommended for first or even second line testing. T4 may be helpful in the setting of pregnancy as discussed below.

A New Laboratory VISTA

The laboratory plans to implement a new chemistry instrumentation by early November. The Dade Vista® will replace the Dade Dimension® as the workhorse chemistry analyzer. There will be slight adjustments to reference ranges in a few chemistry tests, most notably TSH, as discussed in the accompanying article. We anticipate the Vista® will improve turnaround time and reduce some sources of analytic error (e.g. "short sampling") compared to the Dimension®. Thanks to Debbie Brown, MT(ASCP) Rex Core Laboratory and Renee McDade, MT, SBB (ASCP) Rex Information Technology for their extensive efforts to validate the instrument and establish an interface with the Cerner system.

REX PATHOLOGY ASSOCIATES, P.A.

John D. Benson, M.D.	(919) 784-3059	F. Catrina Reading, M.D.	(919) 784-3255
Timothy R. Carter, M.D.	(919) 784-3058	Vincent C. Smith, M.D.	(919) 784-3056
Stephen V. Chiavetta, M.D.	(919) 784-3060	John P. Sorge, M.D.	(919) 784-3062
Keith V. Nance, M.D.	(919) 784-3286	Rhonda Humphrey, Practice Manager	(919) 784-3063

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TFT's - Right Here, Right Now

- **TSH** - The most significant advancement in TFT's is the remarkable improvement in sensitivity of TSH assays. Each "generation" of TSH assays represents a 10-fold improvement in sensitivity. The original assays had a functional sensitivity of 1 mIU/L. The second generation assay ("sensitive TSH") improved to 0.1 mIU/L, while the third generation ("supersensitive") detected 0.01 mIU/L. (Our new Vista analyzer will detect 0.005 mIU/L.) The improved sensitivity of the newer assays allows reasonably efficient separation of hyperthyroid patients from NTI. Almost all hyperthyroid patients will have values < 0.01 mIU/L, while over 90 percent of those with values between 0.01 - 0.1 mIU/L have NTI or drug effect (most commonly glucocorticoid therapy).[4] The likelihood of hyperthyroidism in patients with a TSH between 0.1 - 0.4 mIU/L is low.[5] A testing strategy recognizing the power of the newer TSH assays can eliminate the need for many TFT's and reduce a lot of the confusion regarding the interpretation of "abnormal" results. (See enclosed TSH Algorithm.) TSH is a labile hormone. Any abnormality should be repeated, when the patient is stable, prior to beginning treatment.
- **FT4** - Equilibrium dialysis is the "reference method", but most laboratories use immunoassays as they are less expensive and more rapid. While early immunoassays were overly sensitive to the level of binding proteins in the specimen, the current generation of FT4 immunoassays is less affected by this or the presence of thyroid antibodies. FT4 levels by any method (including equilibrium dialysis) can be affected by NTI, drugs, pregnancy, etc. as discussed above. FT4 is less sensitive to the effects of NTI than the FTI and thus represents a superior test. For optimum diagnostic efficiency, FT4 should be interpreted in conjunction with (and perhaps in deference to) TSH.
- **T3** - Useful as a third-order test in patients with undetectable or suppressed (0.01 mIU/L) TSH and normal FT4 to exclude the possibility of T3 hyperthyroidism ("T3 thyrotoxicosis"), but subject to overutilization (see "T3 or not T3"). Not necessary in cases with suppressed TSH and elevated FT4 or in the evaluation of hypothyroidism. Frequently low in NTI.
- **FT3** - Generally provides similar information as T3, but more expensive. May be helpful in evaluating patients with suspected abnormal binding proteins.

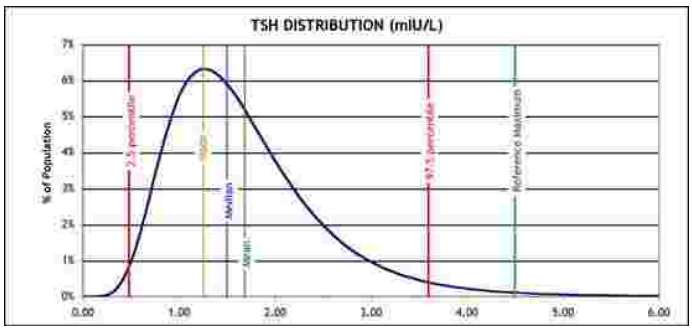
Problems with TFTs

Despite improvement in the analytical performance of thyroid tests, problems remain. As with any immunoassay, interfering substances (particularly heterophil antibodies) may lead to spurious results with any of the above tests.[6] In addition, there are no reference methods available for any of the above tests, which can lead to significant differences in analytical results obtained by different methods, particularly for "free hormones", which are present in exceedingly small quantities.[6-8] Some free hormone methods are more sensitive to changes in concentration of binding proteins (e.g., the increase in TBG that occurs with pregnancy).[6]

This is compounded by ***inherent problems in defining a reference range*** for TFTs, particularly TSH.[9] T4, T3, FT4, FT3 and TSH all have a low index of individuality (the ratio of intra-individual to inter-individual variability in test results). For any given person, there is a relatively constant FT4 set-point.[10] As a result, individual variation in TFTs in healthy individuals is very narrow compared to population based laboratory reference ranges. ***Thus a "normal" TSH, T4, T3, FT4 or FT3 does not necessarily indicate normal thyroid function.*** An individual's personal "normal range" is roughly half as wide as a laboratory reference range for the above tests.[10,11] (For TSH, an individual's normal reference range has a width of approximately 0.75 mIU/L.)[9-11] In this context, distinction between subclinical and overt thyroid disease becomes somewhat arbitrary, depending upon where an individual's FT4 set-point resides within the laboratory reference range.[11] Individuals with an FT4 set-point in the upper portion of laboratory reference range would require a relatively small increase in FT4 to be classified as "hyperthyroid", but a relatively large decrease in FT4 to be classified as "hypothyroid". The opposite would be true for an individual with an FT4 set-point in the lower portion of the laboratory reference range.[11] Unfortunately, an impractically large number of repeated tests are necessary to determine an individual's set point. However, given the log linear relationship between FT4 and TSH, an abnormal TSH result (outside the laboratory reference range) will precede the development of an abnormal FT4 result (outside the laboratory reference range).[9-11] Stated another way, in (out)patients with stable thyroid status, a consistently abnormal TSH coupled with a normal (F)T4 or (F)T3 suggests that the latter tests are outside the patient's individual normal reference range.[9-11]

TSH Reference Range - A (thyroid) storm front

Laboratory TSH reference ranges have changed considerably over the past three decades.[9] Initial TSH assays had either no lower limit (due to lack of sensitivity for detecting low TSH levels) or a lower limit of 1 mIU/L, while possessing an upper limit of 10 mIU/L. With the advent of second and third generation tests, the lower limit of reference range was generally between 0.3-0.4 mIU/L, with an upper limit initially at 5-6 mIU/L, followed by 4-5 mIU/L.[9] There are now strong advocates for creating an empiric upper limit of normal for TSH of 2.5-3.5 mIU/L. There are several reasons to consider this. While most laboratory test reference ranges display a Gaussian distribution in a frequency plot of the number of test subjects vs. concentration, the current TSH reference range is skewed at the upper limit of normal as illustrated below.



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Some of this is due to analytical (different assays probably measure different TSH isoforms; heterophil antibodies), statistical (euthyroid outliers), physiologic (see above), and

pathologic (central hypothyroidism with biologically inactive TSH isoforms; thyroid hormone resistance) factors. However, the biggest reason for skew is the high prevalence of subclinical hypothyroidism, primarily due to autoimmune thyroid disease, particularly among women. Large population studies have shown the prevalence of mild hypothyroidism is five percent for women in their 30's and rises to 15-20 percent for those in their 80's.[12,13] Thyroperoxidase (TPO) antibodies were observed in 11.3 percent, more prevalent in women, and associated with thyroid disease.[12] TPO antibodies alone are not sufficient to screen out patients either with or destined to develop subclinical hypothyroidism. Ultrasonographic thyroid hypoechogenecity may precede the development of TPO antibodies in patients at risk for hypothyroidism.[9] Thus, to obtain a truly valid reference range study, subjects would have to undergo extensive screening to exclude: personal or family history of thyroid disease, presence of a goiter, medications that would interfere with thyroid function, presence of TPO antibodies, and abnormal thyroid ultrasound. Given the impractical nature of this, an empiric TSH reference range has been proposed by the American Association of Clinical Endocrinologists (AACE) and the National Association of Clinical Biochemistry (NACB). The AACE proposes the adoption of a TSH reference of 0.3-3.0 mIU/L.[14] The NACB proposes a reference range of 0.3-2.5 or 3.0 mIU/L.[9] It should be noted that both of these are proposals, not mandates. Nevertheless, the proposals have generated considerable debate. The author is not aware of any laboratory that has adopted the empiric reference range, but the new TSH assay to be implemented at Rex in the near future will have a reference range that comes darn close (see TFTs at Rex).

Subclinical hypothyroidism (SH)

The debate is essentially an extension of the already contentious issue of defining and managing subclinical hypothyroidism (an elevated TSH with normal FT4). Some individuals in this SH category (particularly men or those without TPO antibodies) may be euthyroid outliers.[15] Some endocrinologists point out that symptoms of hypothyroidism may not improve with treatment, studies looking at the relationship of hyperlipidemia, atherosclerosis and SH are not convincing, and there is no evidence that treating SH prevents progression to overt hypothyroidism.[15-17] Finally there is concern that placing such patients on thyroid replacement therapy would increase the need for clinical and laboratory monitoring and put them at risk for iatrogenic hyperthyroidism.[15] Lowering the upper level of the reference range will dramatically increase the number of patients with SH and thus exacerbate the situation.

Those in favor of lowering the upper limit of the TSH reference range recognize the limitations of population based laboratory reference ranges described above. A lower reference range would facilitate recognition of early SH, particularly those at increased risk, such as those with diabetes, autoimmune disease, celiac disease, hyperlipidemia, cardiovascular disease, or normal women contemplating pregnancy.[9,17] Proponents of lowering the upper limit cite studies suggesting benefit for treatment of patients with SH, and describe limitations in studies that don't support this point of view (inappropriate patient stratification, insensitive parameters {nonspecific symptoms, total cholesterol} chosen to observe treatment effect, and suboptimal L-thyroxine therapy).[9,18] In addition, there appears to be increased risk of developing overt hypothyroidism in those with TSH repeatedly greater than 2.5 - 3.0 mIU/L, particularly if accompanied by the presence of TPO antibodies or goiter.[19] (The risk of development of overt hypothyroidism in women with SH and (+) TPO antibodies is five percent per year.)[9,17] A lower reference range would facilitate recognition of early SH, particularly those at increased risk, such as those with diabetes, autoimmune disease, celiac disease, hyperlipidemia, cardiovascular disease, neck irradiation, certain medications (lithium, amiodarone), history of hyperthyroidism or postpartum thyroiditis, or normal women contemplating pregnancy.

There is general consensus regarding the need to treat SH patients with TSH > 10 mIU/L.[19] For patients with values above the reference range (empiric or otherwise), but < 10 mIU/L, it would appear to be appropriate to individualize management based on symptoms, comorbid conditions (as described above), family history, TPO antibody status, and physical/sonographic assessment of the thyroid gland.[9,16,17,19] Stated another way, there is no single TSH level which clinical intervention for SH is either indicated or contraindicated, the higher the level, the more likely treatment is warranted.[16] If no treatment is prescribed, annual TSH monitoring (and determination of TPO status) is recommended.[9,17] Before contemplating treatment in patients with SH, due to the TSH lability described above, it is important to confirm the laboratory abnormality with repeat TSH and FT4, generally a month after the initial test to help exclude the possibility of non-thyroidal illness or drug effect.

TFTs at Rex

We currently offer the following tests: TSH, FT4, T4, T3, and FT3. We do not offer a thyroid panel, as there is no longer one approved by Medicare. Requests for a "thyroid panel" will be treated as an order for a TSH, since this is widely recognized as the preferred screening test for thyroid function. Some like to include a FT4 with TSH request. This may help screen for central (pituitary, hypothalamic) hypothyroidism. It may also cause confusion if the TSH and FT4 results are discordant. As discussed above, TSH is generally the superior test, in most settings.

There have been occasions when results obtained at Rex have not been duplicated at other labs. The usual scenario is that a TSH or FT4 at Rex is "abnormal". The patient is referred to an endocrinologist, where the test is repeated elsewhere with a "normal" result. Those of you who have read this far now recognize that there can be several reasons for this, including TSH lability, inherent problems with defining TFT reference ranges, as well as individual patient factors. The reference ranges for our outgoing (Dade RxL) and incoming (Dade Vista) chemistry analyzers are given below, along with the corresponding ranges for Mayo Medical Laboratories and LabCorp. Note that the Rex TSH reference range is narrower than the other laboratories (and thus closer to the proposed empiric range).

TSH & FT4 Reference Ranges

	TSH (mIU/L)	FT4 (ng/dL)
Dade RxL (old)	0.34-4.82	0.77-1.61
Dade Vista (new)	0.358-3.74	0.76-1.46
Mayo Medical	0.3-5.0	0.8-1.8
LabCorp	0.35-5.05	0.7-1.53 male 0.61-1.76 female

To investigate reports of discordant results between our laboratory and others (presumably LabCorp or Quest), we analyzed 19 samples in triplicate between the Dade Dimension, the Dade Vista and Mayo Medical Laboratory, deliberately choosing specimens at the cut-points of the lower and upper reference range limits. The statistical findings are presented below.

Rex Dade RxL/Dade Vista - Mayo Correlation June 2007 (n = 19)

	Slope	Y-intercept	Corr Coef
Dade RxL vs. Mayo TSH	1.394	-0.08	0.97
Dade Vista vs. Mayo TSH	1.015	0.04	0.99
Dade RxL vs. Mayo FT4	1.259	0.08	0.97
Dade Vista vs. Mayo FT4	1.077	0.08	0.99

While the numbers are admittedly small, the correlations are very good for the (outgoing) RxL, even better for the (incoming) Vista. A slight low bias was present for both tests (Rex values slightly lower than Mayo) for the RxL. There is no bias for TSH for the Vista, and a minimal low bias for the Vista FT4. Thus I suspect discordant values between laboratories are due, in large part, to the issues discussed above, and the fact that our TSH reference range is narrower than others. Again, a value within a "normal laboratory population based reference range" does not necessarily equate to the absence of disease, as discussed above.

Dade performed reference range studies for the Vista using 199 healthy patients for the FT4 range and 300 for the TSH. We validated the Vista's reference ranges with 25 healthy blood donors. Neither we nor Dade adhered to the NACB recommendations for screening (personal or family history of thyroid disease, presence of a goiter, medications that would interfere with thyroid function, presence of TPO antibodies, and abnormal thyroid ultrasound.)

T3 or not T3

In 1999, we reviewed 69 consecutive requests for T3 analysis ($67 in 1999).[1] Some of these appeared to have been ordered to evaluate for "T3 thyrotoxicosis" in the setting of decreased TSH and normal FT4/FTI. The majority appeared to have been ordered as part of general thyroid testing (e.g. TSH normal or elevated). In only one case did the T3 result add useful information. The cost of finding the one case of T3 thyrotoxicosis in this sample set of 69 cases (efficiency of 1.4 percent) was $4623. If the enclosed algorithm (i.e. reserving testing for those cases where TSH is suppressed and FT4 is not elevated) had been used, a total of three cases would have been tested for an efficiency of 33.3 percent and cost of $201.

TFT's in acutely hospitalized patients (You better think twice)

As discussed above, nonthyroidal illness (NTI) can produce a wide variety of abnormalities in TFT's, even the newer ones. This is usually a reflection of various physiologic, pathologic, and pharmacologic effects on the levels of circulating hormones, rather than "lab error". It is not commonly known that there is a significant normal diurnal variation in TSH levels. TSH peaks around midnight, then progressively decreases by 50 percent by 0800-0930, remaining relatively constant throughout the day, with a smaller drop in late afternoon, then begins to progressively rise over the evening.[6,9] A variety of medications can produce in vivo (estrogen, glucocorticoids, dopamine, propranolol, amiodarone, lithium, phenytoin, carbamazepine, furosemide) or in vitro (heparin) changes in TFTs. The net result is loss of specificity and poor positive predictive value for thyroid disease. The prevalence of hyperthyroidism in those with "abnormally low" TSH values is discussed above. (TFT's - Right Here Right Now). A similar phenomenon exists for patients with "abnormally high" TSH. In one study of hospitalized patients, 86 percent of patients with TSH greater than the reference range but less than 20 mIU/L had either NTI or medication effect, while 14 percent had hypothyroidism. If the threshold was raised to those having TSH > 20 mIU/L, the prevalence of hypothyroidism increased only to 50 percent, with the remainder representing NTI or medication effect.[5] Accordingly, evaluation of TFT's in acutely ill patients is not recommended unless there is a strong suspicion that thyroid dysfunction is contributing to the current illness. If TSH is evaluated in an acutely ill patient, the threshold for considering hyperthyroidism should be lowered to 0.1 or even 0.01 mIU/L, while that for hypothyroidism should be increased to 20 mIU/L.[4,5] Discordant TSH and FT4 results increase the likelihood of NTI/drug effect. Follow-up testing, preferably after the acute illness resolves, is recommended to confirm thyroid dysfunction prior to beginning therapy.[4]

Outpatient TFTs

The comments below represent a distillation of recommendations from various authorities, including the AACE, American College of Physicians, American College of Obstetrics & Gynecology, US Preventive Services Task Force, and College of American Pathologists' Laboratory Testing Strategy Task Force. These comments assume testing in outpatients to minimize interference from drugs or nonthyroidal illness, which are common in hospitalized patients. These recommendations do ***not*** *apply to those suspected of having* ***central (hypothalamic or pituitary)*** *disease.*

- Screening for thyroid disease is recommended for neonates, women over 50 years old or with a family history of thyroid disease, normal women contemplating pregnancy, patients with diabetes, autoimmune disease, celiac disease, hyperlipidemia, cardiovascular disease, neck irradiation, certain medications (lithium, amiodarone), history of hyperthyroidism or postpartum thyroiditis.

- Test others based on clinical signs and symptoms suggesting thyroid dysfunction.
- The preferred initial test for thyroid dysfunction is TSH.
- Patients with suppressed or significantly elevated TSH should be followed up with FT4 test.
- T3 testing should be reserved for those with suppressed TSH and normal FT4.
- Monitor thyroid replacement therapy and thyroid suppression therapy with TSH. Wait eight weeks after changing the dose to see effect.
- Monitor thyroid ablation for hyperthyroidism with FT4.

TFTs during pregnancy

Increased estrogen production during pregnancy increases TBG concentrations to two to three times prepregnancy levels by week 20.[6] This causes a 1.5 times increase in levels of T4 and T3 by 16 weeks gestation. The rise in HCG causes a fall in TSH during the first trimester. TSH levels may be below the lower limits of the reference range in 20 percent of normal pregnancies with a trough occurring around 10-12 weeks gestation.[6] In roughly two percent of patients, this may be associated with markedly elevated FT4 levels with hyperemesis and symptoms of thyrotoxicosis (hyperemesis gravidarum or gestational thyrotoxicosis). During the second and third trimester, FT4 levels typically decrease below the normal mean, and may fall below the lower limits of the reference range.[6] As a result of these physiologic changes, laboratory assessment of thyroid function can be challenging. TSH is a superior marker of thyroid function during pregnancy, again because of the log linear relationship with FT4 described above. FT4 tests are overly sensitive to changes in TBG and albumin during pregnancy that are method specific and non-predictable.[20] Given the predictable (1.5 times nonpregnant levels) rise in T4 as a result of TBG increases, some have suggested it is a superior adjunctive test to couple with TSH, rather than FT4.[20] There are currently no reliable trimester-specific reference ranges for TSH, in large part due to the issues described above (TSH Reference Range - A (thyroid) storm front).[20] Nevertheless, until better data becomes available, it is recommended that 2.5 mIU/L (some advocate 3.0 mIU/L) be adopted as an upper limit of normal for pregnancy to reduce the risk of impaired fetal neuropsychological development, placental abruption, and fetal death.[17,19,20,21] Women with TPO antibodies are at particular risk and should be monitored for increasing TSH levels during pregnancy.[17] It is generally recommended that the benefits of thyroxine therapy for mild (subclinical) hypothyroidism during pregnancy outweigh the risks.[17,19]

TFTs in Childhood

The National Academy of Clinical Biochemistry (in collaboration with a variety of other groups, including the American Association of Clinical Endocrinologists and the American Thyroid Association) suggested reference ranges for TSH and free T4 during childhood.[6] While we have not formally adopted the latter (due to the fact that the assay manufacturer has not validated them), we report the suggested reference ranges below to assist in patient management.

TSH and FT4 -Childhood[6]

Age	TSH (mIU/L)	Free T4 (ng/dL)
Fetus - Midgestation	0.7-11	0.15-0.34
Term Infant	1.3-19	0.8-1.9
3 days	1.1-17	1.8-4.1
10 weeks	0.6-10	0.8-1.7
14 months	0.4-7.0	0.6-1.4
5 years	0.4-6.0	0.8-1.7
14 years	0.3-5.0	0.6-1.4

John D. Benson, M.D.

The author is indebted to Catherine Hammett-Stabler, Ph.D., {Associate Professor of Pathology, UNC Dept. of Pathology and Laboratory Medicine; President NACB} for her comments.

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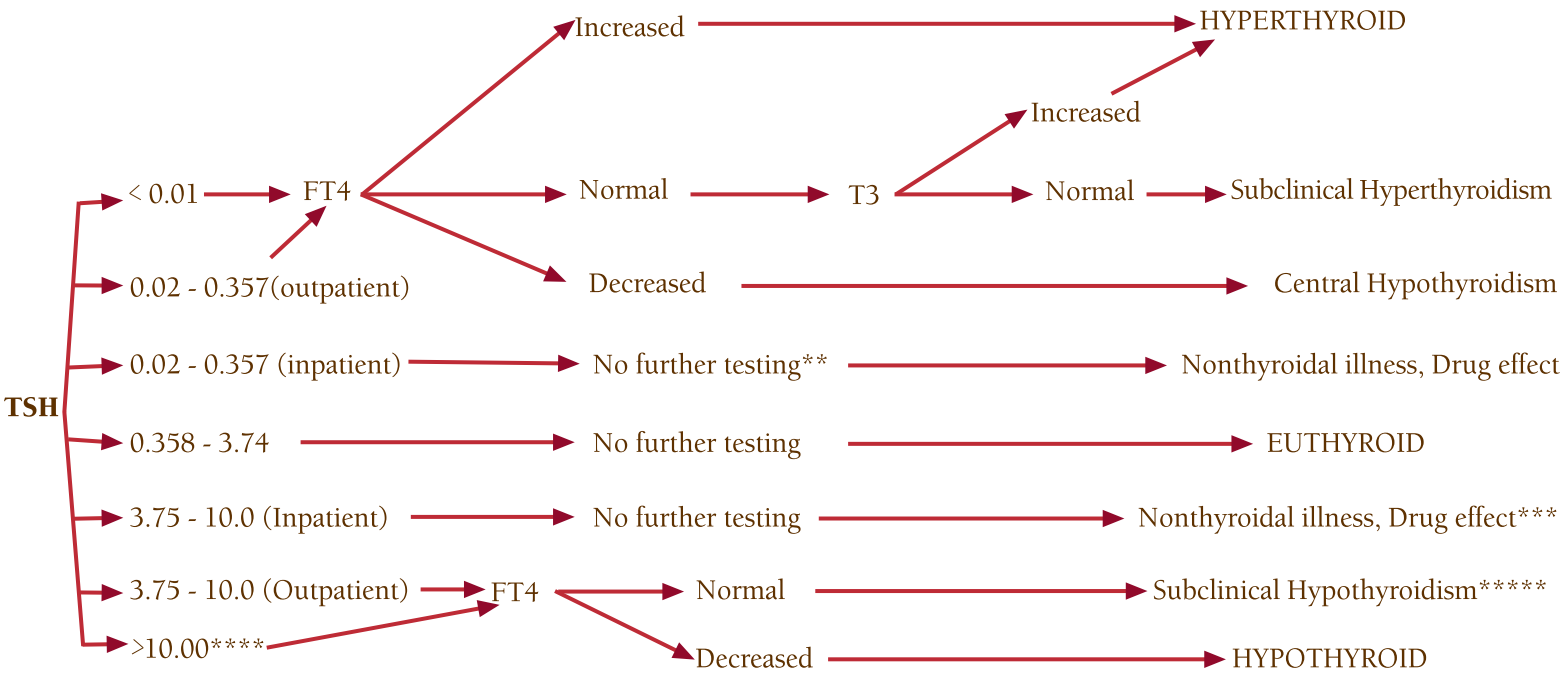
TSH Algorithm *

TSH (mIU/L)



* *Not applicable for patients suspected of having pituitary disease*
** *Perform FT4 only if concerned about central (pituitary, hypothalamic) hypothyroidism or symptoms suggesting hyperthyroidism*
*** *Repeat TSH after patient stabilizes as an outpatient*
**** *For inpatients, consider substituting 20.00*
***** *Controversial. Some endocrinologists favor treatment in some clinical scenarios. Determine TPO status and follow TSH annually*

J. Benson, M.D. 9/07

Rex Healthcare Laboratory (919) 784-3040. Telephone extensions are: Pathologists' Direct Line (3063), Robin Ivosic (Customer Service and Outreach Manager 3053), Elaine Patterson (Core Lab and Microbiology Manager 3054), Diane Young (Anatomic Pathology Manager 3888) Nora Giglio (Laboratory Billing & Registration Manager 3318), David McCoy (Rex Blood Services Manager 4763).
Client Response Center (919) 784-6000 (phone) (919) 784-6299 (fax)