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Provider practices in the management of primary hypothyroidism due to autoimmune thyroiditis

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**PROVIDER PRACTICES IN THE MANAGEMENT OF PRIMARY
HYPOTHYROIDISM DUE TO AUTOIMMUNE THYROIDITIS**

by

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B.A., University of California at Berkeley, 2011

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DEDICATION

To AC + BP

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ABSTRACT

Thyroid hormone is a master regulator of growth and development in all vertebrates. Thus, disruption of its synthesis and activity can lead to profound consequences. Past decade studies on thyroid function tests have established an efficient guideline for monitoring thyroid diseases, yet a significant proportion of healthcare providers do not defer to it in their practice. The aim of this study is to assess provider practices in the diagnosis and treatment of primary hypothyroidism due to autoimmunity at Boston Children's Hospital (CHB) for a primarily pediatric patient population. Commonly known as Hashimoto's thyroiditis (HT), this is the most common thyroid disease in the world as well as the most common manifestation of human autoimmune endocrine disease. Through CHB's bioinformatics institute, a rich data set was collected to assess the manner in which healthcare providers utilized relevant thyroid function tests (TFTs). This work assessed and confirmed the superior sensitivity of thyroid peroxidase autoantibodies (TPO) relative to thyroglobulin antibodies (TgAb) for diagnosing HT in children. We also verified proper utilization of thyroid stimulating hormone tests to monitor HT but concluded that there is a low utilization efficiency with regards to measurements of thyroid hormones (thyroxine and triiodothyronine). Based upon the observation of unnecessary monetary loss caused by improper TFTs utilization, it can be concluded that reflex testing at CHB may improve provider practices' efficiency for HT monitoring.

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LIST OF ABBREVIATIONS

Ab.....	Antibodies
AITD.....	Autoimmune thyroid disease
CHB.....	Boston Children's Hospital
FT4I.....	Free T4 Index
HT.....	Hashimoto's thyroiditis
i2b2.....	Informatics for Integrating Biology and the Bedside
ICD-9.....	International Classification of Diseases, Ninth Revision
NHANES.....	National Health and Nutrition Examination Survey
T3.....	Triiodothyronine
T4.....	Thyroxine
Tg.....	Thyroglobulin Antibody
TH.....	Thyroid hormone
THBR.....	Thyroid Hormone Binding Ratio
TPO.....	Thyroid Peroxidase Antibodies
TSH.....	Thyroid Stimulating Hormone

INTRODUCTION

All vertebrates produce thyroid hormone (TH), a tyrosine-based hormone with an all-encompassing and comprehensive role of initiating and sustaining an organism's development, proliferation, growth, and the most integral role of all, the maintenance of proper tissue and cellular metabolism. With the necessity of TH's biologic effects in virtually every organ system within the body, any disruption on thyroid function can lead to a wide-array of cascading problems; the myriad of negative consequences range from a child's inability to thrive physically and cognitively to an adult's lowered quality of life due to abnormal metabolic rate to an elderly person's rapid descent into osteoporosis due to imbalanced skeletal maintenance. Thus, preventing and treating thyroid-related complex diseases would require a pertinent, fundamental understanding of the thyroid system as well as proper application of thyroid function knowledge within the clinical setting.

Thyroid Hormone

Biochemically, TH is derived from the amino acid tyrosine, coupled with iodine; thus, dietary iodine intake has a significant role in regulating TH synthesis. However, the production of TH is primarily under the control of the hypothalamic-pituitary-thyroid axis (HPT axis; Figure 1) through negative feedback regulation (Molina, 2013). The hypothalamus produces thyrotropine/TSH releasing hormone (TRH), which binds its receptors in the anterior pituitary, signaling it to release thyroid stimulating hormone (TSH) via exocytosis into the systemic circulation. TSH then triggers the synthesis of TH

within the thyroid gland as well as its secretion, as triiodothyronine (T3) and thyroxine (T4), into the systemic circulation (Molina, 2013). The HPT axis's signal for TSH release receives negative feedback from T3, primarily through T4 to T3 conversion within the hypothalamus as well as several deiodination pathways in the anterior pituitary. These T3 conversions play a greater role in negative feedback than does the T3 within the circulation (Molina, 2013).

TSH's binding to its receptor in the thyroid gland leads to the initiation and activation of a protein kinase A signaling cascade with the eventual result of iodine uptake and organification as well as the transcription of several genes involved in TH production (Molina, 2013). Amongst the gene products are:

- Sodium-iodine (Na^+/I^-) symporter, involved in the transportation and concentration of iodide in the thyroid epithelial cell;
- Thyroglobulin (Tg), the glycoprotein that scaffolds tyrosine residues used for TH synthesis;
- Thyroid peroxidase (TPO), the enzyme involved in catalyzing iodide oxidation and incorporation into tyrosine residues of Tg.

For this reason, the TSH receptor is a frequent target for aberrant antibodies, leading to thyroid autoimmune disease. Autoantibodies can mimic the actions of TSH with both agonist or antagonistic roles (Nussey & Whitehead, 2001).

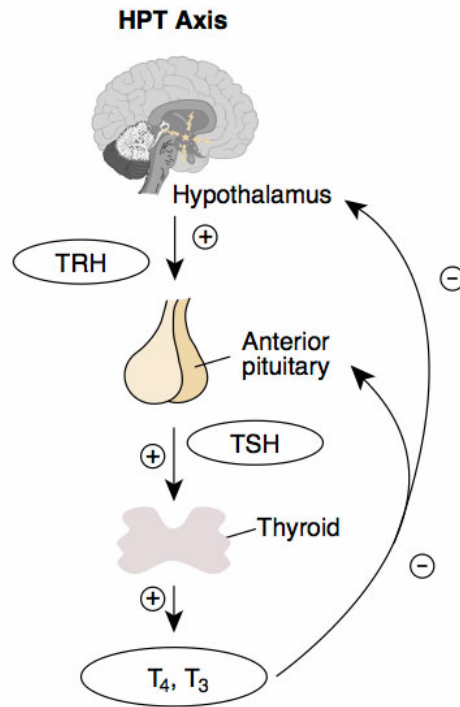


Figure 1. Schematic Depiction of Hypothalamus-Pituitary-Thyroid Axis (Adapted from Bartke & Hiller-Sturmhöfel, 1998)

The biochemistry of TH synthesis begins with Tg's multiple tyrosine residues. Tg is synthesized within the thyroid follicular epithelial cell before its secretion into the follicular lumen's apical side for further modification. Tg's tyrosine residues are then iodinated by I^+ (formed via the oxidation of I^- by TPO), a process called organification (Molina, 2013). This yields monoiodinated tyrosine (MIT) and diiodinated tyrosine (DIT). The coupling of MITs and DITs form T3 and T4, which is facilitated by TPO. The iodine needed for TH synthesis is absorbed from dietary sources, such as iodized salt, seafood, and plants grown in iodine-rich soil. Absorbed iodine is then confined within the extracellular fluid with 1/5 removed by the thyroid gland for TH production while the rest is excreted by the renal system. The saturation of iodine in the thyroid epithelial cells is TSH regulated and mediated by the Na^+/I^- symporter (Molina, 2013).

Aside from its crucial role in the synthesis of TH, TSH also holds an essential role in controlling the release of TH from the thyroid gland. TSH signals the endocytosis of vesicles within the follicular cell and the cleavage of TH from Tg; this scaffolding feature to Tg allows for the gland's ability to maintain up to three months' supply of TH. Once cleaved from the Tg pool, TH is released in both T4 and T3 forms (Molina, 2013). The thyroid gland releases greater amounts of T4 than T3 into the systemic circulation, leading to a forty-fold higher concentration of T4 than that of T3. Most peripheral T3 is produced from the deiodination of T4 within the liver (Nussey & Whitehead, 2001). Despite the much lower concentration, T3 is more active than T4 in terms of biologic activity due to T4's much lower affinity for TH receptors compared to that of T3. Within the circulation, most T4 and T3 is bound to proteins, such as thyroid-binding globulin and albumin, with a small fraction circulating in free form. T4 binds to proteins much more tightly than T3 does, leading to a longer half-life and lower clearance for T4 (Molina, 2013).

The activity of TH is present in virtually every organ, specifically with regards to regulating the metabolic rate of that organ. The specific mechanism with which TH maintains these rates differs from one tissue to another. For instance, other than in the brain, spleen, and testis, TH, through a variety of mechanisms, increases an organ's metabolic rate through the increase of mitochondria's production and size. This mitochondrial amplification can be accompanied by amplification in the production of proteins and enzymes involved in the respiratory chain (Nussey & Whitehead, 2001). Major roles of TH can be found within the cardiovascular system, fat tissues, brain, and

Table 1. Common Clinical Presentations of TH Imbalance with Laboratory Values (Amended based on Molina, 2013)

Hypothyroidism		Hyperthyroidism	
Clinical Presentation	Laboratory Values	Clinical Presentation	Laboratory Values
<p><i>Fetal Development:</i> Cretinism, mental and growth retardation</p> <p><i>Adult Acute:</i> Lethargy, constipation, decreased appetite, cold intolerance, hair loss, dry coarse skin, hoarse voice, abnormal menstrual flow</p> <p><i>Chronic:</i> Thickened features, myxedema, delayed muscle contraction and relaxation, reduced reflexes, decreased cardiac output, enlarged heart, slowing mental function, impaired memory and speech rate, hypothermia</p>	<p><i>Primary:</i> High TSH Low free T4 Low/Normal T3</p> <p><i>Secondary:</i> Low TSH, T4, T3</p>	<p>Palpitations, tachycardia at rest and during exercise, increased blood volume, palpable enlarged thyroid gland, hyperactivity, infiltrative ophthalmopathy, heart pounding, heat intolerance, weight loss, increased metabolic rate, fine tremor, excessive sweating, decreased or absent menstrual flow, warm and moist skin, proximal muscle weakness, fine hair</p>	<p><i>Primary:</i> Low TSH High T4 High T3</p> <p><i>Secondary:</i> High TSH, T4, T3</p>

liver. In many cases, TH manages crucial gene expression, such as genes involved in myelination of neurons within the brain and genes that produce channels important in maintaining cardiac activity (Molina, 2013). Besides controlling gene expression, TH also tends to have a more indirect modulatory role of activating signaling cascades, such as the ones involved in adipose reserve maintenance and in liver cell proliferation. TH is also important for normal growth and development, especially in neonates and children.

TH plays a crucial role in balancing the activities of osteoclasts and osteoblasts within bone tissues. An imbalance in children leads to growth defects while a deficiency in adults leads to an increased risk for osteoporosis (Molina, 2013; Nussey & Whitehead, 2001).

Due to the multi-faceted and ubiquitous nature of TH in terms of target organs, an imbalance could lead to multiple effects. Listed in Table 1 above are the more common clinical presentations of TH imbalance and the laboratory values attached to them, illustrating the expansive nature of TH's role within the body.

Hypothyroidism

Hypothyroidism is a thyroid disorder due to an insufficiency of thyroid hormone function. It is the most common thyroid disease in the world (Braverman & Utiger, 2005). Based on its etiology, hypothyroidism can be categorized according to the source of the dysfunction. Primary hypothyroidism is the most common form of this categorization, contributing to 95% of hypothyroidism observed within a clinical setting. Its etiology leads to a defect in the production or release of thyroid hormone by the thyroid gland itself (McDougall, 1992). Secondary and tertiary hypothyroidism are caused by a dysfunction in the central-thyroid axis required by the thyroid gland to perform its proper function; the former due to a pituitary-thyroid axis dysfunction and the latter due to a hypothalamus-thyroid axis dysfunction. Along with quaternary hypothyroidism, which is caused by peripheral resistance to thyroid hormones, these are the rarer forms of hypothyroidism (McDougall, 1992). Based on severity as inferred

through thyroxine levels, hypothyroidism can be categorized as clinical/overt and subclinical/mild. Both forms have hyperthyrotropinemia (high level of serum thyroid stimulating hormone) but only clinical hypothyroidism results in a low level of free thyroxine while subclinical retains a normal free thyroxine level (Almandoz & Gharib, 2012; McDougall, 1992).

The most commonly cited statistics for the prevalence of hypothyroidism is based on an analysis of the NHANES III on the US population from 1988-1994, stating a 4.6% prevalence of all forms of hypothyroidism, with 0.3% for clinical hypothyroidism's contribution to the statistics (Golden et al., 2009; Hollowell et al., 2002). A more updated analysis based on the 1999-2002 NHANES reports a prevalence of 3.7% overall but clinical hypothyroidism remains at 0.3% (Aoki et al., 2007). A brief overview of the epidemiology of hypothyroidism indicates that women and non-Caucasian subpopulations have a higher prevalence and risk for developing hypothyroidism. The risk also increases with age, leading to a higher prevalence in the elderly subpopulation (Almandoz & Gharib. 2012; Aoki et al., 2007; Hollowell et al., 2002).

The treatment of hypothyroidism is in the form of hormone replacement therapy and dates back to more than a century ago, when sheep thyroid extract was used for management. It is highly effective, cheap, and easy to manage, especially since the ability to monitor thyroid profiles allows for the mimicry of normal thyroid physiology (Woeber, 2005; Nussey & Whitehead, 2001). A variety of pharmacologic preparations are available on the market, including levothyroxine (L-T4), liothyronine (L-T3), liotrix (1:4 T3 and T4 combination). However, as mentioned before, T3 is the much more active form of TH

but is present in the circulatory system at a much lower concentration for a shorter period of time (faster clearance) when compared to T4. Thus, the most effective treatment of hypothyroidism is to administer T4 to serve as the prohormone to T3 production in the peripheral tissues, especially considering the fact that 80% of T3 production occurs in these tissues rather than the thyroid gland (Woeber, 2005). Combination T3:T4 drugs result in a small to no efficacy difference so that synthetic levothyroxine remains the best treatment for hypothyroidism (Almandoz & Gharib, 2012).

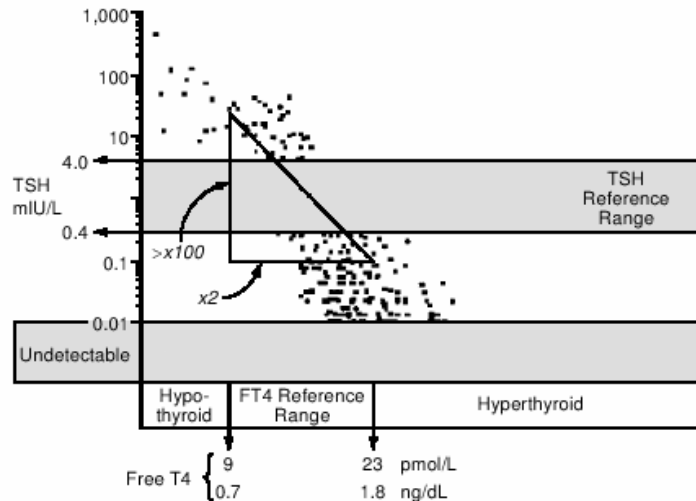


Figure 2. Serum TSH and Free T4 Negative Logarithmic-Linear Relationship (Adapted from Fish et al., 1987)

The goal of hormone replacement treatment is to achieve normal thyroid levels, leading to the resolution of clinical symptoms. The monitoring of treatment can be done simply through periodic measurements of TSH, typically every 6-12 months. The negative logarithmic-linear relationship between TSH and free T4 (Figure 2) depicts TSH's higher sensitivity relative to T4 in indicating thyroid function changes.

After the therapy adjustment period of 2-3 months, a patient's thyroid profile should begin to improve with clinical symptom resolution lagging behind for a month or two. Certain groups of patients require special attention for management, due to differences in T4 bioavailability caused by other factors. Commonly considered factors include but are not limited to, patients who are elderly, pregnant, or receiving treatment for certain cardiac diseases (Woeber, 2005) though more recent studies are increasingly suggesting that age is not a crucial factor in determining T4 bioavailability and treatment adjustments (Almandoz & Gharib, 2012).

Despite the effectiveness of hormone therapy, the actual practice to provide optimal treatment to patients is much more complex, with a variety of factors contributing to the mosaic of hypothyroidism monitoring. The most basic factor is the fact that hypothyroidism is often times a chronic disease that requires lifelong management. An individual's physiology may change over time, which calls for a corresponding adjustment of hormone treatment, e.g. the need for dosage adjustment due to weight change in a patient (Somwaru et al., 2009). Genetic, environmental, and presence of other diseases also contribute to the variability in response to treatment, necessitating tailoring and close monitoring of therapy for individual patients. Having proper knowledge on how to handle these variables becomes crucial, calling for the expertise of a thyroid specialist. However, there is an emerging trend of placing hypothyroidism monitoring responsibilities on primary care physicians and general practitioners (rather than thyroid specialists). The reason is simply that the thyroid specialist to hypothyroid patient ratio is low. This becomes problematic since many

general practitioners have voiced their concerns on having inadequate knowledge on how to properly utilize many specific laboratory tests, including those relevant for monitoring thyroid function (Okosieme et al., 2010; Kratz & Laposata, 2002).

One study reports that on average, only 40-60% of diagnosed hypothyroid patients taking hormone replacements are properly treated, as indicated by the maintenance of euthyroidism. This means that a significant portion of the hypothyroid patients are either under or over treated. The cited reasons for this are poor compliance, improper dosage prescriptions, and drug interaction. Over-treatment poses adverse risks, especially in the cardiovascular and skeletal systems; in particular, an increased risk for atrial fibrillation, osteoporosis, and bone fractures. On the other hand, poorly managed hypothyroidism is associated with chronic body weight problems as well as damaging effects on lipid profiles and blood pressure (Okosieme et al., 2010). A study on the pediatric population shows that uncorrected hypothyroidism in children is associated with impaired/lowered cognitive function, and this effect is detected in children by the time they reach 11 years of age. However, this is associated more significantly with over-treatment than under-treatment of hypothyroidism (Bongers-Schokking et al., 2013).

Primary Hypothyroidism

The most common cause of primary hypothyroidism in the world is iodine deficiency, leading to a defect in TH synthesis. Radiation treatments, surgical removal of thyroid gland (thyroidectomy), infiltrative diseases (such as scleroderma) and congenital defects can all lead to primary hypothyroidism but have a much smaller contribution as an underlying cause of primary hypothyroidism (Braverman & Unger, 2005). For this

study, the focus was on a form of primary hypothyroidism caused by autoimmunity called Hashimoto's thyroiditis. Also known as chronic autoimmune thyroiditis, this is the most common cause of primary hypothyroidism in populations with fulfilled iodine requirements, making it the most common cause of primary hypothyroidism in the United States (Almandoz & Gharib, 2012).

Hashimoto's Thyroiditis (HT)

HT Epidemiology

Hashimoto's thyroiditis (HT) is the most common clinical manifestation of autoimmune thyroid diseases (AITD) and leads to hypothyroidism. AITD is the most common autoimmune endocrine disease, as well as the most common autoimmune disease in the United States (Tomer, 2010) with an average prevalence of 5% for a given population anywhere in the world. The contribution of HT to this prevalence varies based on the decade when the study was done and the demographics of the population investigated (Dayan & Daniels, 1996; Hasham & Tomer, 2012).

HT has the highest prevalence within the age range of 30-50 years, with the risk of manifestation increasing with age, paralleling that of overall primary hypothyroidism's epidemiology (Dayan & Daniels, 1996). The worldwide incidence of HT per annum is estimated to be between 0.3 to 1.5 cases per 1000 persons. In the United States, the estimated incidence of HT is 1.3% in children between the ages of 11 to 18 years old. In adults, the incidence is 3.5 new cases per 1000 per annum in women but 0.8 per 1000 per annum in men, reflecting the statistics that HT heavily presents in women. The range of

HT prevalence falls between 1-2% in women while the men's prevalence is only a fraction, anywhere between 1/5 to 1/10, of the corresponding women population's statistics (Staii et al., 2010).

HT Etiology

HT is a complex disease, with both genetic and environmental factors affecting an individual's susceptibility and the development of disease (Eschler et al., 2011). The first major histocompatibility complex (MHC) gene region associated with both HT and Graves's Disease (GD, the other manifestation of AITD, resulting in hyperthyroidism) is from the HLA Class II gene, specifically the HLA-DR allele. The polymorphic nature of HLA leads to many of its alleles having significant roles in different autoimmune diseases, making it a proper candidate gene for finding a genetic cause for AITD (Hasham & Tomer, 2012). However, genetic association studies show that the HLA-DR allele is not as significantly associated with HT as it is with GD (Eschler et al., 2011). Nevertheless, more recent investigations from a structural biology angle have recouped this link by establishing a strong association between HT and the HLA-DR allele (Eschler et al., 2011; Hasham & Tomer, 2012).

The link between HLA-DR and HT is recapitulated by the discovery that the HLA glycoprotein produced by HLA-DR possesses a more positive protein binding pocket (due to an alanine or glycine substitution with an arginine). This subsequently leads to a change in binding selectivity, favoring autoantigenic peptides. In the case of HT, the autogenic peptides are commonly derived from thyroid peroxidase (TPO) and thyroglobulin (Tg) (Eschler et al., 2011; Hasham & Tomer, 2012).

Several non-MHC genes are also associated with HT (Eschler et al., 2011). The more commonly studied genes fall into one of two categories: immunoregulatory and thyroid-specific. Two well-investigated immunoregulatory genes associated with HT are the CTLA-4 gene and PTPN 22 gene. Both major alleles of these genes negatively modulate T-cell activity and proliferation through suppression and inhibition. Thus, associated alleles result in the loss of this negative modulatory role. Another non-MHC gene group contains thyroid-specific genes. For HT, the most significant one is the thyroglobulin gene (Tg gene) since Tg is a key antigen in HT's pathology (Eschler et al., 2011). The link and synergy between MHC and non-MHC genes leading to HT is still unclear. However, there is a significant inferred association between certain Tg gene alleles and the MHC gene's HLA-DR allele in terms of co-occurrence. Since early genome-wide association studies on HT in the 1980s, this Tg-HLA gene link has been qualitatively determined through the frequent observation of heightened autoimmunity in animal models that possess both the HLA-DR allele and a Tg-gene allele of HT-interest, relative to animals with only one or the other (Rose, 2011). With more recent advancements in computational biology and biostatistics, this association has been quantified and found to be significant and strong (Eschler et al., 2011).

The environmental contribution towards HT varies according to the studied population, much like its prevalence. Potential environmental mechanisms leading to HT range from direct toxicity towards thyroid cells to immune system over-stimulation to interference with thyroid activity and function (Hasham & Tomer, 2012). The following

are the most commonly discussed and more widely studied environmental factors influencing susceptibility for HT (Eschler, 2011; Hasham & Tomer, 2012):

- *Iodine intake.* Due to the crucial role of iodine in thyroid hormone synthesis, this is one of the most studied factors, especially within an epidemiological setting, e.g. to correlate and associate iodine intake levels with the prevalence and susceptibility for certain thyroid diseases. HT is associated more heavily with excess intake of iodine.
- *Medication.* Amiodarone is the medication that is most studied for HT due to the fact that it is an iodine-rich drug for managing tachyarrhythmia. Other medications include those that fall within the categories of antiretroviral and interferon- α treatments. Both classes are thought to play a role in over activating the T-cell population in an individual's thyroid gland as an adverse side effect.
- *Infectious agents.* Particularly from viruses and to a certain extent, bacteria. The viral infection most associated with HT is Hepatitis C (for which interferon- α is a treatment). Bacterial infection is less studied but is an emerging field. The most oft-associated bacterial infection is from gastrointestinal dysbiosis, or the loss of normal balance of gut microbiota (Mori et al., 2012). While other autoimmune diseases have been studied with more depth within the context of gut microbiota, the studies on HT are sparse and recently emerging. The enterobacteria of the GI tract play a key role in maintaining the balance between immune activation and immune tolerance in the gut-associated lymphoid tissue (GALT). Thus, the disruption of gut microbiota may have negative repercussions towards the balance

of GALT activities and subsequently, the immune tolerance in an individual's thyroid gland (Mori et al., 2012).

- *Environmental toxins.* Toxins are more associated with GD rather than HT. However, organic chemicals that fall into the polyhalogenated biphenyls (PBB) class are particularly linked to HT susceptibility. Individuals exposed to PBB on a regular basis are found to have consistently high levels of antimicrosomal antibodies as well as anti-thyroid peroxidase and anti-thyroglobulin antibodies; all of which are hallmark indicators for HT diagnosis.

Monozygotic twin studies have indicated that 79% of attributed causes of HT are genetic-based (Hasham & Tomer, 2012) while dizygotic twin studies estimate a lower genetic contribution, up to 50% at most, indicating the importance of environmental contribution in the etiology of HT (Hiromatsu et al., 2013). The interactions between genetic and environmental factors are still unclear as well, calling for further studies on epigenetic contributions (Hasham & Tomer, 2012).

HT and Clinical Presentation

The cellular mechanism that leads to hypothyroidism is the improper function of the immune system, leading to the activation of CD4 T-helper cells by the thyroid; this trigger mechanism performed by the thyroid unto itself is still unclear (Dayan & Daniels, 1996; Hiromatsu et al., 2013). Self-reactive CD4 cells then recruit toxic CD8 T-cells and autoreactive B-cells into the thyroid gland (lymphocytic infiltration) with three main targets: thyroid peroxidase, thyroglobulin, and thyroid stimulating hormone receptor.

Despite the recruitment of B-cells and the presence of antithyroid antibodies against its targets within the thyroid, CD8 T-cells are thought to be the main mechanism responsible for the destruction of the thyroid gland, typically leading to hypothyroidism. More specifically, it was found that HT thyrocytes express the Fas gene associated with apoptosis, an attribute not found within normal thyroid cells (Stuart, 2012). The interaction of Fas with the Fas ligand on the surface of HT thyrocytes is one of the hypotheses for the mechanism that triggers aberrant thyroid immunity, leading to lymphocytic recruitment and infiltration (Stuart, 2012). Another hypothesis is that a specific yet unidentified antigen is responsible for initiating the aberrant immune response (Dayan & Daniels, 1996).

HT usually presents clinically through hypothyroidism, goiter, or both. Goiter is usually the first sign, a diffuse enlarged thyroid gland with firm consistency and irregular surface. Histologically, HT has a hallmark of Hurtle cells, described as enlarged follicular cells with finely granular nuclei and deeply acidophilic cytoplasm. The mechanism and trigger that cause normal thyrocytes to transform into Hurtle cells are still unclear, especially since there are a minority of cases in which the resected thyroid glands contain Hurtle cells without the accompanying lymphocytic infiltrates (Stuart, 2012). The aforementioned activity of Fas gene/ligand interaction is thought to precede this cell transformation but this order's significance is unknown (i.e. whether or not the Fas interaction triggers the transformation). Additionally, the signal that causes the Fas gene product to interact with Fas ligand is largely unknown (Stuart, 2012).

HT Diagnosis

The typical symptom that triggers the steps for diagnosing HT is the presentation of a goiter accompanied by laboratory confirmation of high thyroid stimulating hormone level. A documentation of low serum free thyroxine would also be standard procedure, to confirm the differentiation between clinical and subclinical hypothyroidism. However, a significant proportion of HT patients initially present euthyroid laboratory measurements. Thus, the gold standard biochemical evidence for HT is a one-time documentation of a high serum titer for anti-thyroid antibodies, typically anti-TPO or anti-Tg. (Ajjan & Weetman, 2010; Weetman, 2005). The preferred anti-thyroid antibody for testing is anti-TPO because 95% of HT patients present this antibody, rendering it to be the most sensitive test while the next most sensitive test is measurement of anti-Tg, present in only 60% of HT cases. Normal levels of anti-TPO antibodies could lead to anti-Tg measurement for thorough biochemical evidence prior to diagnosis. Despite the presence of standards established based on the literature, there still exists variability in an individual physician's protocol in diagnosing HT, especially with regards to the types of thyroid function tests measured to confirm the HT diagnosis (Ajjan & Weetman, 2010; Dayan & Daniels, 1996).

HT Monitoring

Much like the lack of consistency in diagnosing HT, the presence of literature-supported standard monitoring protocols has not resulted in a uniform practice for primary hypothyroidism and HT monitoring. The bulk of medical care for any form of primary hypothyroidism, including HT, consists of routine measurements of certain

thyroid function tests, which could lead to several adjustments, such as the frequency of monitoring patient condition, the prescribed hormone replacement therapy dosage, etc.

Many professional medical societies have their own individual guidelines on how to manage thyroid disorders, especially with regards to thyroid function tests (TFTs) (Nordyke et al., 1998). Numerous studies have accepted TSH as the most sensitive test to monitor HT, especially relative to T4's sensitivity. The literature also suggests that T4 measurements be used sparingly, i.e. subsequent to the detection of a clinically significant change in TSH level relative to euthyroid condition or the patient's previous TSH level.

Table 2 below summarizes the suggestions of clinical standards from the past two decades, depicting the evolution of HT monitoring.

Table 2. Snapshots of Suggested Clinical Standard for Hypothyroidism and HT Management over Time*

Source	Suggested Clinical Standard
Schectman & Pawlson (1990)	<p><i>Reported:</i> ordering both free T4 and TSH is common practice despite suggestion that TSH only is highly sufficient</p> <p><i>Suggested:</i> T4 first or TSH first at physicians' discretion, leaving the cost vs. quality problem to individual providers but not both as the combination is costly, with low yield in care improvement gained from T4 tests added to TSH tests</p>
McDougall (1992)	States a preference to measure both free T4 and TSH although due to the need for repeated measurement, ordering either free T4 or TSH only might be simpler
Nordyke et al. (1998)	<p><i>Reported:</i> multiple health centers in Honolulu, Hawaii have three common patterns: measuring free T4 only, TSH only, or both</p> <p><i>Suggested:</i> ideally, the authors suggest reflex testing with measuring TSH first then free T4 if necessary. Recognizing</p>

	the lack of technology needed to do so in many medical facilities, the authors suggest simultaneous testing of both free T4 and TSH to be the best compromise between quality of care and cost
Kratz & Laposata (2002)	<i>Reported:</i> many redundant testing of free T4 without notice that the initial documentation for hypothyroidism diagnosis had been done <i>Suggested:</i> application of the reflex testing model in a healthcare facility to test free T4 only if TSH suggests necessity during management of thyroid disease; it was found at Massachusetts General Hospital where the reflex testing model was applied that this model reduces testing costs
Woeber (2005)	Because of the established sensitivity of TSH over any form of T4 measurement, monitoring lifelong hypothyroid patients should consist mainly of periodical TSH measurements
Leung & Farwell (2010)	With increased testing sensitivity for TSH, it should be the first measurement taken before other thyroid function tests are performed
Almandoz & Gharib (2012)	Measurement of TSH first then free T4 upon the detection of high TSH level

*'Reported' is defined as what the author(s) viewed to be common practice during their time. 'Suggested' is defined as the protocol suggested by the author in lieu of the common practice at the time.

The recommended standard in contemporary literature is to order TSH only before resorting to any peripheral T4 measurements. However, in a significant proportion of actual clinical practice, a form of peripheral thyroxine (T4) test is ordered simultaneously with TSH; in the 1990s, some common practice even favored the measurement of T4 tests only (Nordyke et al., 1998). One of the reasons for different practices with regards to testing TSH versus T4 stems from earlier practices when the

main goal was to balance cost and quality. A TSH test was more costly but yielded a more accurate clinical interpretation while a T4 test was cheaper. In 1998, Nordyke et al. performed an analysis on the quality and cost trade-off on TSH and free thyroxine testing based on Medicare reimbursements for these tests. The results of their analysis suggest that the ideal solution would be to apply reflex testing with the TSH test ordered first then thyroxine tested only if necessary based on the TSH result; both would be performed on the same blood sample. The total cost of TSH and free T4 was \$6.50 per blood sample, if measuring free T4 is found to be necessary. However, the cost of doing such tests without reflex testing would be a combination of \$4.61 per free T4 test and \$5.90 per TSH test since they would be performed from different blood samples taken from different dates of visitation. These are direct patient costs for those who are enrolled in the Medicare program. For patients who are not under Medicare, however, the cost of the tests is much higher. One 1990 study performed a cost analysis on T4 and TSH tests from laboratories in Washington, DC and found that thyroxine tests cost on average \$26 while TSH tests cost \$46 (Schechtman & Pawlson, 1990). Thus, to circumvent the problem, it was suggested by many professional organizations in the 1990s to order both tests on the same blood sample, regardless of the necessity of the thyroxine result for clinical purposes. The solution was thought to sacrifice quality the least, at slightly higher monetary cost (relative to ordering TSH only or thyroxine only but lower than ordering the two separately) and a higher waste on laboratory resources for cases in which the T4 test was unnecessary (Nordyke et al., 1998; Schechtman & Pawlson, 1990); the latter point is supported by the fact that ordering TSH and T4 leads to very few additional diagnosis

compared to ordering TSH alone with the estimation of one patient diagnosis missed for every 5000 patients monitored for hypothyroidism with the TSH-only method (Schectman & Pawlson, 1990).

The other major reason for the oversight to update practice with regards to thyroid disorder is the lack of expertise knowledge, especially from the part of non-thyroid specialists. These practitioners tend to rely on a large menu of laboratory assays, ordering tests without understanding their purpose. This often leads to unnecessary or superfluous clinical laboratory measurements (Kratz & Laposata, 2002). Gupta et al. exemplify this problem through their institution's provider practices by observing the TFT ordering patterns of clinicians at Gian Sagar Medical College in Banur, India. The authors found that only 46% of the TFT tests ordered were for TSH only and the most common pattern (47.5%) was to order thyroxine, TSH, and triiodothyronine (T3) tests together. However, in 77% of these patients, measurement of TSH alone would have been sufficient to show that the patients were euthyroid and no further action was needed based on the patients' other clinical symptoms. The authors credit the ordering of unnecessary tests to the fact that almost 4/5 of the test orders came from non-specific and non-endocrine related departments, namely departments of medicine and gynecology where the medical teams tend to lack solid knowledge of thyroid disorders (Gupta et al., 2011). Primary care and non-specialist providers have also voiced their concerns that they are often called upon to provide care that is beyond their scope (one in four physicians strongly agrees with this statement) while also stating that when they do not possess adequate knowledge to

diagnose or manage a case, they are only able to obtain definitive answers 30-50% of the time (Kratz & Laposata, 2002).

Study Objectives

Given the complex nature of thyroid diseases and the need for extensive clinical laboratory services, it would be in a hospital's best interest to be as efficient as possible in dealing with thyroid diseases, particularly HT, given its high prevalence and chronic nature. Aside from the cost reduction and the efficient use of resources arguments, a more important motivation for improving HT management is its requirement for a lifelong treatment and management regiment, which usually means proper adjustment of a patient's levothyroxine (or other hormone replacement therapy) dosage. Managements relies heavily on laboratory measurements of thyroid function. Based on the aforementioned problems recognized in the literature with regards to HT management as well as the oft-proposed solution of reflex testing implementation for monitoring HT, this study aimed to:

1. Gain knowledge concerning an effective utilization of a variety of software to perform data collection and analysis;
2. Investigate provider practices for patients with HT within the clinical setting of a major pediatric hospital and compare them against standard practices based on the literature;

3. Estimate the cost-effectiveness of the current practice in diagnosing and managing HT and then model how reflex testing would improve the effectiveness without sacrificing the quality of medical care.

This study is a part of a larger project with the objective of investigating the provider practices of various thyroid diseases. The aforementioned objectives render this study to be a form of test-run to identify and/or resolve common problems and limitations. Due to its high prevalence, HT provides the richest data set to test a software's capability and suitability, a query's accuracy, and an analysis's thoroughness. Therefore, this study's processes and results would generate invaluable and relevant knowledge to achieve the greater goal of analyzing the clinical practices of different thyroid dysfunctions.

METHODS

Through the establishment of biomedical informatics and computational biology research institutes, investigators have the ability to conduct clinical research with ease based on rich data sets that could be collected according to an individual project's specifications. Large database management is the crux of the interaction between biomedical sciences and current clinical practices; clinical data informs biomedicine of the problems at-hand while biomedicine provides the clinical field with novel and/or improved solutions. This renders the work of clinical investigators in academic medical centers to be highly dependent on the efficiency and advancement of a bioinformatics institute's development. For CHB, this vital institute, Informatics for Integrating Biology and the Bedside (i2b2), was established in 2004 with NIH funding. With i2b2, electronic records of clinical data can be systematically accrued and accessed with little difficulty. In the case of this study's initial patient data set, the data dates back to the early 1990s. With the simplicity of the user interface of i2b2, utilizing the data-mining software requires minor training (Murphy et al., 2009).

Initial Patient Dataset

The initial, general patient dataset was obtained through data-mining with i2b2's data querying software. Queries were run based on specific inclusion and exclusion criteria. This study's goal was to collect data from patients with primary hypothyroidism due to autoimmune thyroiditis. The inclusion and exclusion criteria were searched based on keywords and ICD-9 codes associated with the disorders/diagnoses while the

laboratory tests were retrieved through search terms. Two keywords, 'Hashimoto's disease' and 'chronic lymphocytic thyroiditis', as well as the ICD-9 code 245.2, were used to retrieve the patient population of interest. A set of exclusion criteria was also run within the same query (Figure 3). This investigator-based query resulted in the identifiers of patients (such as medical record number, full name, date of birth) who fulfilled the determined criteria. With this set of identifiers, an i2b2 staff retrieved the thyroid function tests (TFTs) needed for answering the study's questions through a software that can be queried only by the institute's programmers (investigators not staffed by i2b2 cannot initiate queries through this database as it does not have a general user's interface). An initial querying for the laboratory tests was done through the CPT-4 billing codes. However, i2b2 database was found to be more inclusive when the TFTs were searched through only keywords, i.e. the names of the tests. The final query is summarized in Figure 3.

The final output of the programmer-run query was a set of thyroid function tests with their corresponding dates and the test value/serum level results. Prior to any further data sorting, the age of the patients during each test was calculated in Excel (Microsoft, 2003). Subsequent codification of the patient set was done based on specific thyroid function test(s). These tests were ordered by physicians as a part of the standard practice for diagnosing primary hypothyroidism. The first three major data sorting queries were based on the patients' thyroid stimulating hormone (TSH) tests, Thyroglobulin antibody (TgAb) test and Thyroid Peroxidase Antibody (TPO) tests, and thyroxine (free T4, total T4, and free T4 index) tests. These queries were done by importing the Excel data into

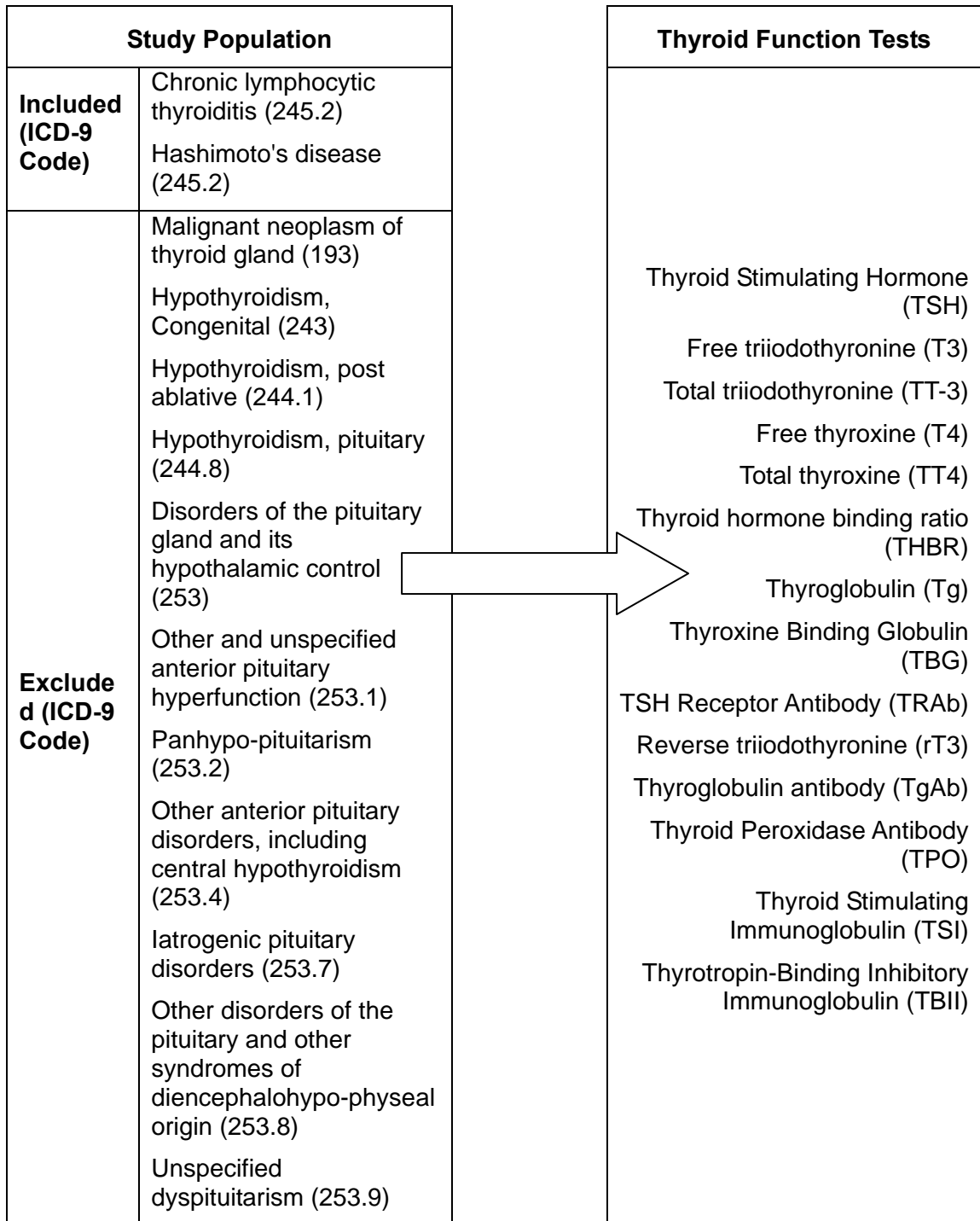


Figure 3. Initial Patient Set Query Process. (Right table contains the investigator-initiated query criteria to retrieve patient identifiers, left table contains the TFT keywords used by i2b2 programmers to retrieve TFT data)

the open-source database management software, MySQL (Oracle, 2007).

HT Diagnosis: Anti-thyroid Antibody Documentation

Documenting an elevated level of an anti-thyroid antibody is required for HT diagnosis. For analysis related to antibody documentation, the initial dataset from i2b2 was sorted into one of the following three categories: those with only TPO measurements, those with only TgAb measurements, and those for whom both TPO and TgAb were measured.

From patients for whom both TPO Ab and TgAb were measured, further categorization was performed as follows:

- Patients who had at least one elevated TPO Ab measurement, designated as Group A;
- Patients who had at least one elevated TgAb measurement, designated as Group B;
- Patients who had at least one elevated TPO Ab and at least one elevated TgAb measurement, designated as Group C; Group C is an intersection of Groups A and B.

Elevated TPO was determined to be greater than 14.9 IU/mL while elevated TgAb was any value greater than 24.9 IU/ml, per the reference range used by Boston Children's Hospital (DeBoer & LaFranchi, 2007). From the groupings above done via MySQL, two more groupings were made to determine the number of true positives and true negatives:

- True Positives: defined as patients who had an elevated TPO or TgAb measurement, designated as Group D: Group A + Group B - Group C.

- True Negatives: defined as patients who had an elevation in neither TPO nor TgAb measurement, designated as Group E: Total patients with both TPO and TgAb measured - Group D.

Sensitivity for both TPO and TgAb testing was then calculated according to the formulation model below, as illustrated in Table 3. Sensitivity ratios were calculated as 'True Positives' cases divided by 'HT Diagnosed' (the sum of 'True Positives' and 'False Negatives') cases.

Table 3. Formulation Model for Calculating Sensitivity of Anti-thyroid Antibodies

	HT Diagnosed (Group D)	HT Not Diagnosed (Group E)
Positive	<i>True Positives</i> Group A for TPO Group B for TgAb	<i>False Positives</i> defined as 0 because elevated TPO/TgAb is a hallmark of HT
Negative	<i>False Negatives</i> Group D - Group A for TPO Group D - Group B for TgAb	<i>True Negatives</i> Group E for both tests

HT Management: TSH Measurement and Diagnosis Date

One of the standard confirmations in diagnosing a patient with hypothyroidism is through an elevation in the patient's serum TSH level (hyperthyrotropinemia). Thus, a patient's date of diagnosis with hypothyroidism was considered to be the first time when an elevated TSH was recorded. Besides initial diagnosis, hypothyroidism monitoring and management could be done sufficiently with periodic measurements of TSH levels, every 6-12 months, as it is the most sensitive indicator of the thyroid status of a patient with primary hypothyroidism.

A patient's thyroid-related profile varies depending on the age of the patient, and TSH is no exception. For this study, the TSH reference range, as divided by age groups, was based on literature values (DeBoer & LaFranchi, 2007) and reconfirmed by the reference range list utilized by CHB's laboratory medicine. These parameters were especially important since many patients were managed by CHB from childhood into their teenage years; for some, the management was done by CHB even well into their adulthood. For TSH, the parameter to determine date of diagnosis with hypothyroidism was set as the following:

- Under two years old: the first date when TSH > 8.2 μ IU/L.
- Between 2-20 years old (inclusive on both end of range): first date when TSH > 5.7 μ IU/L.
- If over 20 years old: first date when TSH > 4.2 μ IU/L.

Using the date of diagnosis, several time ranges were calculated:

- The number of days between the diagnosis date and each laboratory test performed for a patient.
- The length of each patient's study period, defined as the number of years between the last laboratory test recorded for a patient and the diagnosis date.
- The age of the patient during diagnosis and during study exit (or last available test during this study, if the patient is still under CHB's care).

With these determinations, the TSH measurement rate was calculated, defined as the number of TSH tests performed per year during the patient's time under CHB's care.

HT Management: Peripheral T4 Measurements

The TSH and peripheral T4 tests included in this query were those that were performed after the determined date of diagnosis. The one-time documentation of a simultaneous TSH and a form of peripheral T4 measurement (total T4 or free T4 or free T4 index) is also standard for diagnosing primary hypothyroidism. Thus, this specific query aimed to observe physicians' practice in ordering any subsequent TSH and peripheral T4 tests after a diagnosis had been documented.

The first order of the query was to determine the reference ranges for both TSH and peripheral T4 tests. These were based on literature values (DeBoer & LaFranchi, 2007) that were reconfirmed with CHB's laboratory medicine's reference ranges. Table 4 lists the reference ranges for TSH, total T4, and free T4. Free T4 Index (FT4I) uses the same range as total T4 in the query, with the extra step of calculating free T4 index through the multiplication of the value of total T4 by the corresponding value of the thyroid hormone binding ratio (THBR) with both tests conducted on the same date/same blood draw.

Table 4. Reference Ranges for TSH and Peripheral T4 (Adapted from DeBoer & LaFranchi, 2007)

Age (years old)	TSH (μIU/L)	Age (years old)	Total T4/FT4I* (μg/dL)	Free T4 (ng/dL)
< 2	0.8-8.2	< 2	7.2-15.7	0.8-1.8
2-20	0.7-5.7	2-7	6.0-14.2	1.0-2.1
> 20	0.4-4.2	8-20	4.7-12.4	0.8-1.9
		> 20	5.3-10.5	0.9-2.5

* FT4I = Total T4 value x THBR value; both taken from the same blood draw

The manner in which the query was set-up was to apply the age categorization subquery first. This is especially important since the reference ranges overlap throughout the age range. The 2-20 years old range is inclusive at both ends of the range, i.e. patients who are exactly 2 or 20 years old fell within this category.

The next subqueries were based on the TSH and peripheral T4 tests:

- The 'reference range' subquery was applied to determine whether a patient's particular TSH and peripheral T4 test results were within, below, or above the reference range. Values within the range were designated as 'NORMAL', below as 'LOW', and above as 'HIGH'.
- The 'date' subquery was applied to pair-up a TSH and a peripheral T4 if both were taken on the same date (this assumes that the tests were done from the same blood draw); this results in pair(s) of TSH-peripheral T4 tests based on a particular date for each patient.
- Based on the values of the TSH-peripheral T4 pairs relative to their respective reference ranges, each was assigned to one of twelve possible patterns, as summarized in Table 5.
- For the categorization of FT4I, an extra step was performed to find total T4 and THBR test pairs based upon the same date of testing then these values were subsequently multiple with each other, resulting in a new column indicating the FT4I values; this was done before any of the aforementioned test-related subqueries were performed.

Table 5. Patterns of Simultaneous Peripheral T4 and TSH Tests

Pattern	Peripheral T4	TSH
1	Low	Not measured
2	Low	Low
3	Low	Normal
4	Low	High
5	Normal	Not measured
6	Normal	Low
7	Normal	Normal
8	Normal	High
9	High	Not measured
10	High	Low
11	High	Normal
12	High	High

Since the purpose of this query was to assess the usefulness of ordering any peripheral T4 tests, all data points considered must have a peripheral T4 test done on one particular date to be categorized into a pattern. The absence of a simultaneous measurement of TSH was assigned its own pattern.

HT Management: Cost of Peripheral T4 and T3 Measurements

The purpose of the previous section's queries is to determine the number of unnecessary peripheral T4 measurements that were done during HT monitoring. Once these numbers were obtained, a peripheral measurement was categorized as either 'waste' or 'artifact'. The former was defined as peripheral T4 measurements that did not add to what their paired TSH measurements could have indicated about thyroid function. The latter was defined as peripheral T4 measurements that seem to indicate abnormal thyroid function and/or new pathology but upon further investigation of patient history, offered

no new conclusion. This division allows for the calculation of lost cost from peripheral T4 measurements during HT monitoring for each individual patient. The formula is:

$$\begin{aligned} \text{Cost Peripheral T4} = & [(\# \text{ Waste Total T4} + \# \text{ Artifact Total T4})(\text{Total T4 Lab Cost})] \\ & + [(\# \text{ Waste Free T4 Index} + \# \text{ Artifact Free T4 Index})(\text{Free T4 Index Lab Cost})] + \\ & [(\# \text{ Waste Free T4} + \# \text{ Artifact Free T4})(\text{Free T4 Lab Cost})] \end{aligned}$$

Lost cost from peripheral T3 measurements was also calculated because standard practice does not call for monitoring peripheral T3 levels, rendering any measurement to be unnecessary. All peripheral T3 measurements were extracted after determined date of diagnosis. The formula to determine this cost for each patient is as follows:

$$\begin{aligned} \text{Cost Peripheral T3} = & (\# \text{ Total T3 Measured})(\text{Total T3 Lab Cost}) + (\# \text{ Free T3} \\ & \text{Measured})(\text{Free T3 Lab Cost}) \end{aligned}$$

For both formulae, the source of the lab cost pricings was LabCorp's 2013 Book Pricing Listing (see Appendix B). The original goal was to use lab cost average values from the pricing lists of ARUP, LabCorp, and Quest Diagnostics. However, only heavily discounted, contract price listings were available from ARUP and Quest Diagnostics.

RESULTS

Initial Patient Dataset

The original raw data obtained through i2b2 based on the query criteria and keywords contained thyroid function test (TFT) data from January 1993 to November 2013. There were a total number of 2,102 unique patients; 1,683 of the patients were female while 417 were male. The age at the time of testing ranged from 0-70 years old. Exclusively neonate (under 1 year old) patients were excluded from the study unless they were under CHB's care beyond the age of one. 97 data points from 31 patients were measured when the patient was under 1 year old and all but one patient did not resume care with CHB until entering teenage years (13 years or above).

Table 6. Breakdown Individual TFT Counts

TFT Name	Count of Individual Measurements
TSH (Thyroid Stimulating Hormone)	12075
T4, Total (Thyroxine)	6198
FT4 (Free T4)	5007
T3, Total (Triiodothyronine)	1387
FT3 (Free T3)	26
rT3 (Reverse T3)	6
TBG (Thyroxine Binding Globulin)	75
TBII (TSH Receptor Antibody)	353
THBR (Thyroid Hormone Binding Ratio)	4075
Tg (Thyroglobulin)	52
TgAb (Thyroglobulin Antibody)	1863
TPO (Thyroid Peroxidase Autoantibody)	2079
TSI (Thyroid Stimulating Immunoglobulin)	181

The total number of individual TFT values was 33,377 tests. 31,517 of the tests were taken from patients while they were aged 19 and under (94.4% of the total collected test data points). Male patients contributed 7,223 measurements while female patients

26,154 measurements. Table 6 breaks down the number of data points each TFT contributes to the overall total. Additionally, Figure 4 shows the proportion of patients who had at least one measurement of TSH and the various forms of thyroid hormone performed at CHB.

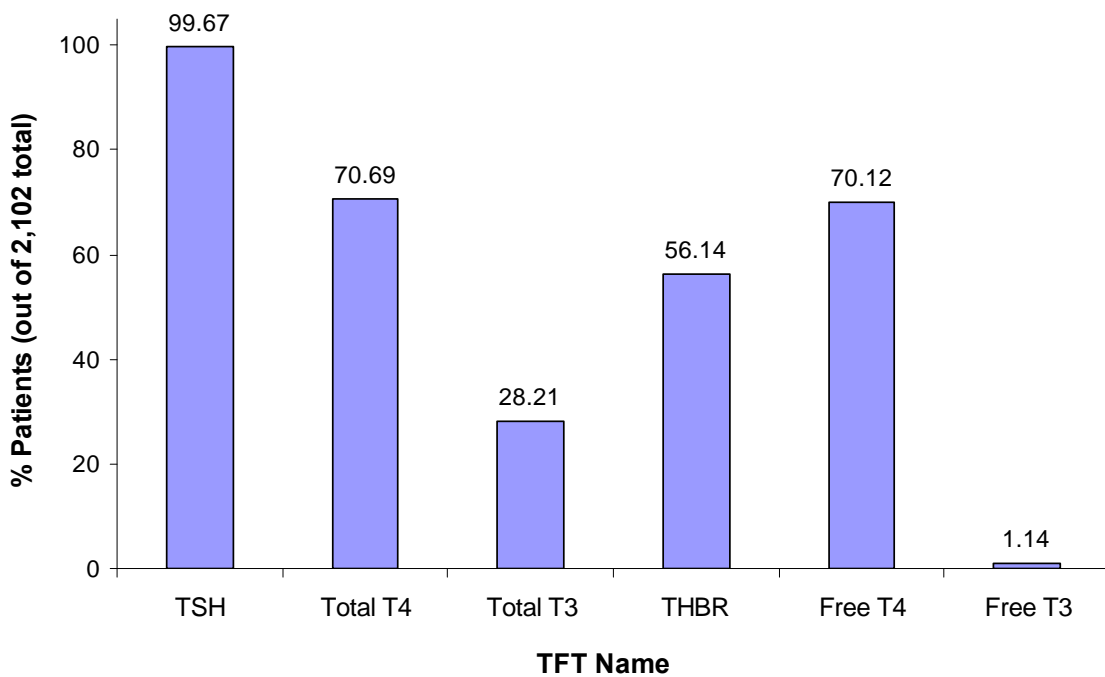


Figure 4. Proportion of Patients (from Initial Dataset) with TSH and Thyroid Hormone Levels Measured

Anti-thyroid Antibody Documentations

Based on the original dataset, a total of 1,340 patients (63.7% of total initial unique patients) had at least one anti-thyroid antibody measured. 19 patients had Tg Ab only measured throughout their time of care at CHB, 97 patients had TPO only measured, while 1,224 patients had both TPO and Tg Ab measured. The patient population data with

both TPO and Tg Ab measured (1,224 patients) was grouped according to the following criteria (Table 7):

Table. 7 Patient Counts for TPO and TgAb Sensitivity Measurements

Group	Definition	Patient Count
A	patients with elevated TPO measurement	716
B	patients with elevated Tg Ab measurement	565
C	patients with elevated measurements of both TPO and Tg Ab	339
D	patients with elevated TPO or elevated TgAb (True Positives: Group A + B - C)	942
E	patients elevated for neither TPO nor TgAb (True Negatives: total patient population - Group D)	282

TPO vs. TgAb Sensitivity

With these five groups, the sensitivity of TPO and TgAb tests was determined through the values in Tables 8 a and b. The sensitivity of TPO was found to be 76% while the sensitivity of TgAb was found to be 60%.

Table 8a. TPO Values for Sensitivity Ratio Calculation

	HT Diagnosed (942)	HT Not Diagnosed (282)
Positive	<i>True Positives:</i> 716	<i>False Positives:</i> defined as 0 because elevated TPO/TgAb is a hallmark of HT
Negative	<i>False Negatives:</i> 226	<i>True Negatives:</i> 282

Table 8b. TgAb Values for Sensitivity Ratio Calculation

	HT Diagnosed (942)	HT Not Diagnosed (282)
Positive	<i>True Positives:</i> 565	<i>False Positives:</i> defined as 0 because elevated TPO/TgAb is a hallmark of HT
Negative	<i>False Negatives:</i> 377	<i>True Negatives:</i> 282

HT Management: TSH Measurement

A total of 1,111 unique patients (52.8% of total initial unique patients) with at least one recorded hyperthyrotropinemia at CHB were included in this analysis. The patients who lacked a documented TSH elevation may reflect diagnoses performed outside of CHB. On the other hand, the proportion of patients with diagnosis date who had at least one measurement of TSH and the various forms of thyroid hormone performed is seen in Figure 5.

It was found that 8,465 of the individual TSH measurements were performed for the 1,111 patients, including and after the date of first TSH elevation was documented. To determine several statistics on the rate at which TSH was measured, 223 patients were excluded because their length of care at CHB was under 1 year, yielding insufficient time to calculate proper TSH rates. With 888 patients (679 of whom were females and 209 were males), it was determined that the age at the time of diagnosis ranged from 0 to 62 years old. 860 of these patients were aged 19 or under (96.8% of the total 888 patients).

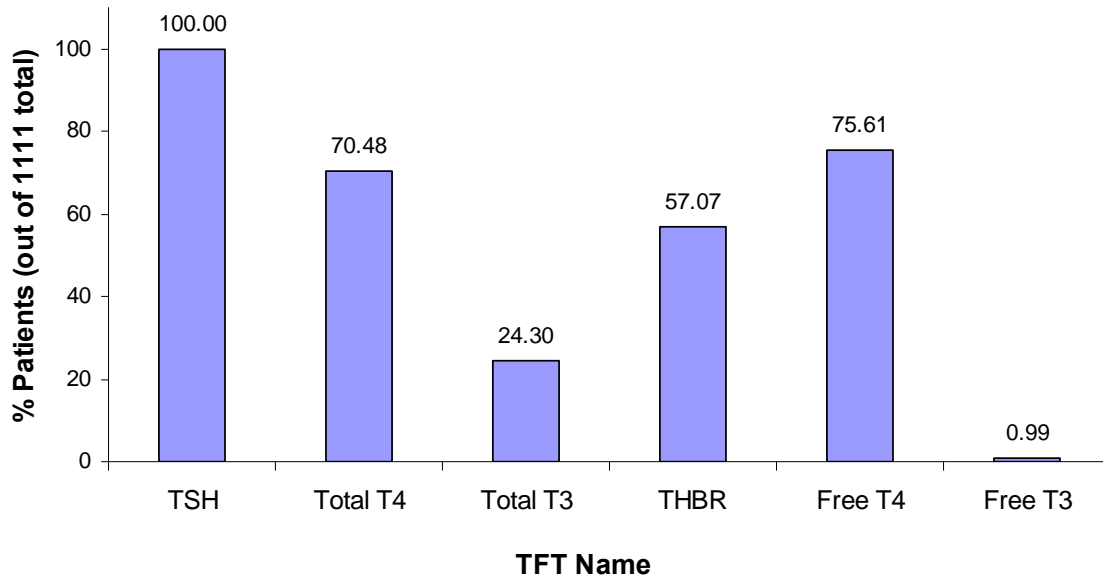


Figure 5. Proportion of Patients (with Diagnosis Dates) with TSH and Thyroid Hormone Levels Measured.

The average age of diagnosis was 11.2 years old with a median age of 11 years old. Subsequently, the age at the time of the last documented TFT record was defined as the age at the time of study exit. The age ranged from 3 to 70 years old; 747 patients were aged 19 or under (84.1% of 888 patients). The average age of study exit was 15.7 years old with a median of 16 years old. Subtracting the study exit age and the diagnosis date of each patient allowed for the calculation of TSH rate statistics. The range of TSH measurement rate was from 0.167 TSH tests/year to 9 TSH tests/year. An average of 2.13 TSH tests was done per year with a median of 2 tests/year. From the total 888 patients, 552 patients (62.1%) had a TSH rate between 1-2 per year. 201 patients (22.6%) had a TSH rate that was greater than 2 but less than 3 per year while 135 patients (15.2%) had a TSH rate of 3 or greater per year.

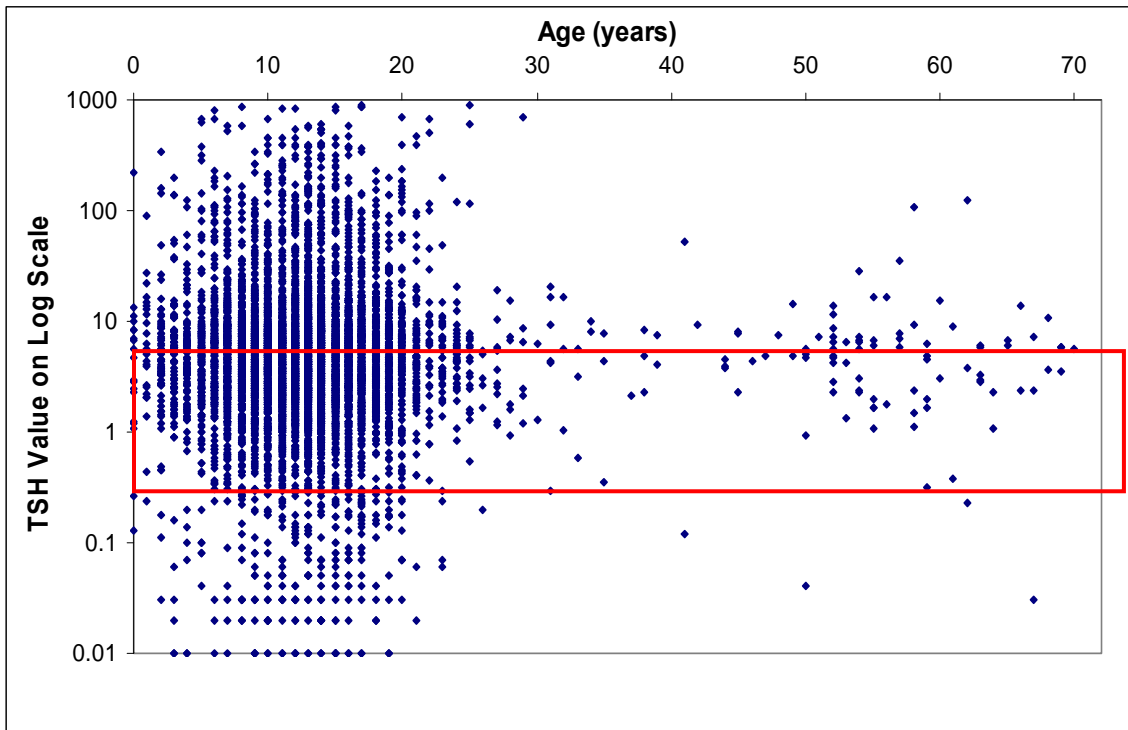


Figure 6. Distribution of TSH Values on a Logarithmic Scale (the normal TSH ranges across all ages are captured by the red box)

To visualize the majority of TSH values, a normalization of TSH values was performed with 7,741 individual TSH test values, which originated from 986 patients who had both a diagnosis date documented (out of the aforementioned 1,111 patients) at CHB and at least two or more TSH measurements taken during their period of care. TSH data points found within the normal range of TSH can be seen in Figure 6. 3,682 (47.6%) of the TSH values fall within the normal range between $0.3\mu\text{IU/L}$ to $5.0\mu\text{IU/L}$, which captured the normal ranges across all ages.

HT Management: Peripheral T4 Measurement

The results of peripheral T4 measurement practices are tabulated in Tables 9 a, b, c. Patterns 2, 3, 11, or 12 can be interpreted as revealing new pathology or as an artifact during monitoring period. If a patient's peripheral T4 measurement persistently stays in Patterns 2, 3, 11, or 12, the new pathology assessment was made. If these patterns preceded and/or succeeded Patterns 4, 6, 7, 8, or 10, they were concluded to be artifacts, adding no new information to what TSH alone has determined.

**Table 9a. Total T4 and TSH Measurement Assessments and Pairing Counts
(includes percentage proportion of each pattern out of total test pairs)**

Pattern	Total T4	TSH	Assessment	Test Pairs
-	-	-	TOTAL TEST PAIRS	1,349 (100%)
1	Low	Not measured	Not standard practice	0 (0%)
2	Low	Low	New pathology of central hypothyroidism or artifact	0 (0%)
3	Low	Normal	New pathology of central hypothyroidism or artifact	11 (< 1%)
4	Low	High	Overt hypothyroidism (no value added from T4)	92 (7%)
5	Normal	Not measured	Not standard practice	5 (< 1%)
6	Normal	Low	Subclinical hyperthyroidism (no value added from T4)	116 (9%)
7	Normal	Normal	Euthyroidism (no value added from T4)	620 (46%)
8	Normal	High	Subclinical hypothyroidism (no value added from T4)	471 (35%)
9	High	Not measured	Not standard practice	0 (0%)
10	High	Low	Overt hyperthyroidism (no value added from T4)	16 (1%)
11	High	Normal	New pathology of TSH resistance or artifact	15 (1%)
12	High	High	New pathology of TSH resistance or artifact	3 (< 1%)

**Table 9b. Free T4 Index and TSH Measurement Assessments and Pairing Counts
(FT4I = Total T4 x corresponding THBR; includes percentage proportion
of each pattern out of total test pairs)**

Pattern	Free T4 Index	TSH	Assessment	Test Pairs
-	-	-	TOTAL TEST PAIRS	2,435 (100%)
1	Low	Not measured	Not standard practice	0 (0%)
2	Low	Low	New pathology of central hypothyroidism or artifact	0 (0%)
3	Low	Normal	New pathology of central hypothyroidism or artifact	32 (1%)
4	Low	High	Overt hypothyroidism (no value added from FT4I)	141 (6%)
5	Normal	Not measured	Not standard practice	9 (< 1%)
6	Normal	Low	Subclinical hyperthyroidism (no value added from FT4I)	136 (6%)
7	Normal	Normal	Euthyroidism (no value added from FT4I)	1234 (51%)
8	Normal	High	Subclinical hypothyroidism (no value added from FT4I)	803 (33%)
9	High	Not measured	Not standard practice	0 (0%)
10	High	Low	Overt hyperthyroidism (no value added from FT4I)	35 (1%)
11	High	Normal	New pathology of TSH resistance or artifact	38 (2%)
12	High	High	New pathology of TSH resistance or artifact*	7 (< 1%)

**Table 9c. Free T4 and TSH Measurement Assessments and Pairing Counts
(includes percentage proportion of each pattern out of total test pairs)**

Pattern	Free T4	TSH	Assessment	Test Pairs
-	-	-	TOTAL TEST PAIRS	2,995 (100%)
1	Low	Not measured	Not standard practice	1 (~0%)
2	Low	Low	New pathology of central hypothyroidism or artifact	1 (~0%)
3	Low	Normal	New pathology of central hypothyroidism or artifact	13 (< 1%)
4	Low	High	Overt hypothyroidism (no value added from FT4)	186 (6%)
5	Normal	Not measured	Not standard practice	6 (< 1%)
6	Normal	Low	Subclinical hyperthyroidism (no value added from FT4)	189 (6%)
7	Normal	Normal	Euthyroidism (no value added from FT4)	1622 (54%)
8	Normal	High	Subclinical hypothyroidism (no value added from FT4)	895 (30%)
9	High	Not measured	Not standard practice	0 (0%)
10	High	Low	Overt hyperthyroidism (no value added from FT4)	47 (2%)
11	High	Normal	New pathology of TSH resistance or artifact	33 (1%)
12	High	High	New pathology of TSH resistance or artifact	2 (<1%)

A total of 1,091 unique patients contributed to at least one of the three pairing groups. 1,349 pairs of Total T4 and TSH measurements were included in this analysis while 2,435 pairs of Free T4 Index and TSH measurements were included; this entailed the inclusion of 3,784 individual total T4 measurements and 2,435 measurements of THBR for calculating the Free T4 Index data points. Lastly, 2,995 Free T4 and TSH pairs were included. From this breakdown, it was calculated that 6,779 peripheral T4 and TSH measurements were utilized for this section of analysis. All peripheral tests that fell into Patterns 2, 3, 11, or 12 were concluded to be artifacts.

HT Management: Cost of Peripheral T4 and T3 Measurements

The management period ranged from 0 to 20 years with an average of 3.5 years for a patient and median of 3 years for a patient. The cost of unnecessary peripheral T4 measurements originated from 1,091 patients, contributing 6,779 peripheral T4 values. It was determined that an average of \$399.43 was lost per patient with a median of \$330.00 per patient. The range of cost lost was \$30.50/patient to \$2,403.75/patient. The grand total of cost lost from peripheral T4 measurements amounted to \$437,375.75 for CHB patients included in this analysis. When broken down between the contribution of wasted peripheral T4 and artifact peripheral T4 measurements, the former category contributed 6,624 individual tests while the latter 155 individual tests. Wasted peripheral T4 ranged from \$30.50/patient to \$2403.75/patient with an average of \$390.62 per patient of lost cost and a median of \$317.75 per patient. The sub grand total of cost lost from wasted peripheral T4 was \$427,732.50. On the other hand, cost lost due to artifact peripheral T4 ranged from \$30.50/patient to \$471.25/patient. The average cost lost was \$96.43 per patient with a median of \$82.50 per patient. Artifact peripheral T4's contribution to the sub grand total of lost cost was \$9,643.25.

For cost lost due to peripheral T3, there were 280 patients who had at least one free T3 and/or total T3. 11 patients had free T3 measurements while 270 had total T3 measurements. Peripheral T3 cost lost ranged from \$93.25/patient to \$1,771.75/patient. The average was \$221.79 per patient with a median of \$93.25 per patient. The grand total of cost lost from peripheral T3 was \$62,100.50. When divided, free T3 contributed \$2,047.50 to the grand total while total T3 \$60,053.00. Free T3 cost lost ranged from

\$157.50/patient to \$472.50/patient with an average of \$186.13 per patient and median of \$157.50 per patient. Total T3 cost loss's range was \$93.25/patient to \$1,771.75/patient with an average of \$222.42 per patient and median of \$93.25 per patient. Table 10 below summarizes these values accordingly.

Table 10. Cost Loss from Unnecessary Measurements of Peripheral T4 and T3

	Average Cost per Patient (\$)	Median Cost per Patient (\$)	Range Cost per Patient (\$)	Grand Total for Each Test (\$)
Peripheral T4	399	331	31 - 2,404	437,376
Peripheral T3	221	93	93 - 1,772	62,101
			Grand Total Both Tests	\$499,477

DISCUSSION

Through software designed and maintained by i2b2 at CHB, data were collected on a largely pediatric patient population. Subsequently, data management and analysis were performed (via i2b2, Microsoft Excel, and MySQL) on provider practices with regard to thyroid function test measurements in the context of diagnosing and monitoring Hashimoto's thyroiditis. Major analyses consisted of the determination of the sensitivity of anti-thyroid antibodies test for HT diagnosis, the assessment of thyrotropine level measurements for HT monitoring as well as the necessity and cost analysis of peripheral thyroid hormone measurements during HT monitoring.

The most commonly measured antibodies are thyroid peroxidase autoantibodies (TPO) and thyroglobulin antibody (TgAb). Previous studies have indicated that in adult populations, TPO Ab is a more sensitive test than TgAb (95% vs.60% sensitivity ratios). However, the applicability of these sensitivities on children is still largely unknown (Weetman, 2005). Several patients had no records of antibody measurements; most likely the documentation of these tests were done outside of CHB since an elevated antibody is the gateway to confirm any HT diagnosis and its subsequent monitoring. It was found that few patients had these antibody tests ordered according to the recommended standard of ordering and documenting TPO only (less than 10% of the population). However, there were even fewer patients who were solely tested for TgAb (less than 2%), which is a good indicator that at least CHB care providers are for the most part aware of TPO's higher sensitivity. Simultaneous ordering of both tests still prevailed as the common practice at CHB. It was estimated that this led to redundancy of testing for close to 1/3 of

the patient population; they would have benefited from the application of reflex testing TPO first then TgAb if necessary as recommended for standard practice to confirm an HT diagnosis. As for sensitivity, it was found that the sensitivity of TPO was much lower in CHB's pediatric population when compared to the sensitivity reported in the literature for adult populations (76% vs. 95%) while TgAb's sensitivity in adults also held true in CHB's pediatric population (both 60%). Nonetheless, TPO was still the more sensitive anti-thyroid antibody test compared to TgAb (76% vs. 60%).

The recommended standard for measuring TSH as a part of HT monitoring is once every 6-12 months, translating to 1-2 TSH measurements per year. From the portion of the population who were diagnosed at CHB, the average annual TSH rate of two measurements reflected that physicians followed the recommended standard. Over 4/5 of the study population had TSH measured less than 3 times/year and 3/5 of the population had 2 or fewer TSH tests done per year. It could be inferred that when caring for children, CHB medical providers heavily favored the higher end of the recommended monitoring frequency of once every six months, which is an appropriate decision since the thyroid profile is less stable during the pediatric age range (compared to during adulthood) and any aberrance could impair a child's development. A look at the effectiveness of monitoring outcomes was based on observing the distribution of all TSH values from the data collected. Less than half of these values were within the euthyroid range, indicating significant presence of follow-through problems in management, such as patient compliance and adherence issues, improper treatment dosage, etc; this brief and

simplified indication of an important issue would warrant a deeper investigation in future developments of the study.

Despite a generally unanimous suggestion that measuring TSH only for HT is sufficient without sacrificing the quality of care, the practice of ordering TSH simultaneously with a form of peripheral T4 is still ubiquitous. Solely measuring a form of peripheral T4 for HT (and even other types of primary hypothyroidism) monitoring was once a common practice (Schechtman et al., 1990; Nordyke et al., 1998) although current standards dissuade this habit (as summarized in Table 2). At CHB, the practice of ordering a peripheral T4 only for monitoring is uncommon with less than 1% of the 6,997 peripheral T4 test being measured without TSH. As for peripheral T4 tests that were paired with TSH, they were concluded to be unnecessary with none of them revealing new pathology or offering information beyond the measurement of TSH only. It was also observed that total T4 only tests (Table 9a) had the lowest proportion of patterns indicating a euthyroid state when compared to the proportions of free T4 index and free T4 measurements (Table 9b & c). These euthyroid states were represented by Pattern 7 (with normal peripheral T4 and TSH levels). An explanation for this is that total T4 levels are affected by the concentration of bound T4 in systemic circulation (influenced by a wide range of factors, such as genetics, other medical conditions, medications, etc.) while free T4 is not (Leung & Farwell, 2010); even when free T4 index and free T4 were compared to each other, free T4 had a higher proportion of euthyroid assessments since free T4 index is still based on a total T4 measurement.

Based on unnecessary measurements of peripheral thyroid hormones levels, a substantial monetary loss was found. Peripheral T3 measurements are superfluous because it is an unreliable indicator of the thyroid state due to its fast clearance from the system, despite its more active role as a biologic effector. Peripheral T4 measurements should be reserved only if TSH values cannot provide the full picture on the thyroid state and/or give inconclusive assessments in relation to other clinical observations. These peripheral thyroid hormone tests, particularly nearly all peripheral T4 from this study, were measured simultaneously with TSH indicating the need for reflex testing implementation to prompt for test ordering only when necessary. Aside from prompting for testing, a reflex testing system should also have the ability to warn physicians during attempts to order unnecessary tests since many physicians habitually order superfluous thyroid function tests.

There are several efforts that have been discussed in literature to consolidate the difference between efficient recommended standards and provider practices in clinical settings. One emerging trend for tackling the lack of provider practice knowledge on thyroid function tests is the production of evidence-based guidelines. While in theory, this could work for a particular institution, it is complex and still does not resolve the heterogeneity of practice from one institution to another, leading to differing care standards should a patient have a change of medical care provider beyond an individual physician (Garber et al., 2012). To consolidate this problem, the American Association of Clinical Endocrinologists and the American Thyroid Association attempt to provide guidelines in diagnosing, managing, treating, and monitoring hypothyroidism based on

practice- and evidence based medicine that would be the gold standard for handling hypothyroidism. The guideline lists 52 recommendations, each with its own subrecommendations, based on the gender, age, race, sex, prior medical history, current medical condition, etc. of each patient (Garber et al., 2012). Despite the thoroughness of the guideline with proper amendments, it still does not resolve the problem of knowledge and information dissemination, i.e. the problem that non-specialists may be overwhelmed by the scope of knowledge they are expected to have. This caveat is further supported by the fact that many physicians are still not adhering to much simpler HT diagnosis and monitoring standards that have been established for at least a decade.

Another often proposed solution that has been touched upon for over a decade (Nordyke et al., 1998) is more relevant to this study: the implementation of reflex testing and the incorporation of laboratory medicine experts (who have a greater understanding of the purpose of each test) into the process of diagnosis and management. This would potentially lead to higher efficiency in terms of test ordering, medical errors reduction, and cost cuts in managing many diseases, including thyroid disorders. However, it would require a higher level of involvement from the laboratory medicine staff to provide feedback to physician queries as well as the physicians' additional communiqué to confirm or further inquire the laboratory staff's recommendations (dubbed 'curbside consultation'). Such a model has been approved for application and execution at Massachusetts General Hospital by its medical policy committee (Kratz & Laposata, 2002). The trial period includes reflex testing in the evaluation of the underlying pathophysiology leading to a prolonged partial thromboplastin time (i.e. the factor

deficiency or inhibitor presence that would need further investigation to result in proper diagnoses) as well as reflexively testing total T4 and thyroid hormone binding index (to calculate free T4 index) when a high value of TSH is detected (Kratz & Laposata, 2002). The study concludes that the reflexive testing algorithms applied have minimized the number of unnecessary tests and patient visitations while still ensuring that all necessary tests are performed. The curbside consultation also facilitates a two-way communication between laboratory medicine and the medical staff from all departments, leading to an improvement in care quality and a reduction in medical errors (Kratz & Laposata, 2002).

Another argument for the implementation of reflex testing within the context of hypothyroidism rather than HT is the higher prevalence of subclinical hypothyroidism (relative to overt hypothyroidism) that requires long term management with medication adjustments such as the dosage of thyroid hormone replacement taken, if the patient and physician agree to treat the mild hypothyroidism (Ayala et al., 2000). Thus, it would be futile to order a full panel TFT for every routine visitation. For this study, subclinical hypothyroidism was not included. Yet, it is an important point to stress that monitoring those at risk as well as diagnosing and managing those under treatment is complex feat, especially as the patients' age increases. This study's population generally began their care at Boston Children's Hospital from childhood or adolescence through adulthood. With a patient's age progression, a provider's practice evolves as well. In the realms of thyroid diseases, this is especially important for HT since it is the most common form of AITD in childhood and the most common thyroid disorder in iodine-sufficient areas (Marks & LaFranchi, 2010). An epidemiological study in Italy attempted to decipher the

patterns in TFT test results in childhood HT. The authors found that the first sign of goiter is more often the cause for subclinical hypothyroidism diagnosis rather than the biochemical assays, with about half of the patients having a euthyroid profile and about 41% exhibiting clinical or mild hypothyroidism. The mildly hypothyroid children are then placed under routine, surveillance care with about half of the population progressing towards HT while the other half of the population remain euthyroid for at least 5 years before HT begins to manifest. The risk is amplified in patients with elevated anti-thyroid antibodies, with most patients developing HT from subclinical hypothyroidism within three years' time (Marks & LaFranchi, 2010). With the much higher sensitivity of TSH relative to T4, the suggested method of monitoring pediatric patients with slow HT manifestation remains to be the testing of TSH only (DeLuca et al., 2013; Diez et al., 2005, Wasniewska et al., 2012) every 2-3 months for infants and 3-6 months for children and adolescents, rendering any other tests to be superfluous during the management of HT in pediatrics (Marks & LaFranchi, 2010), much like the standard literature consensus in care for adults.

FUTURE DIRECTION

The methods and queries performed on HT patient datasets in this study will serve as the template in analyzing other thyroid diseases, such as congenital hypothyroidism and spontaneous hyperthyroidism, that are diagnosed and managed at CHB. To strengthen the analytical results, similar analyses will be performed on primarily adult populations, with patient data sets originating from the Partner's Network of Brigham and Women's Hospital (BWH), one of CHB's affiliated hospital networks. The utilization of MySQL occasionally warranted verification of query results' accuracy with Excel, rendering the necessity for future analyses to be done with a more sophisticated and bioinformatics-oriented software, such as the Statistical Analysis System (SAS). This is particularly important for handling data from BWH, as it is predicted that analysis of the BWH patient set will involve a much larger data volume. For instance, the data set retrieved from BWH based on the criteria used in this study, relevant to provider practices for patients with Hashimoto's thyroiditis, is estimated to consist of approximately 15,000 patients and upward of 120,000 individual thyroid function tests measurements.

APPENDIX A

RELEVANT THYROID FUNCTION TESTS REFERENCE RANGES

Age (years old)	TSH (μIU/L)	Age (years old)	Total T4 (μg/dL)	Free T4/FT4I* (ng/dL)	TPO Antibody (IU/mL)	Tg Antibody (IU/mL)
< 2	0.8-8.2	< 2	7.2-15.7	0.8-1.8	0-14.9 (for all age)	0-24.9 (for all age)
2-20	0.7-5.7	2-7	6.0-14.2	1.0-2.1		
> 20	0.4-4.2	8-20	4.7-12.4	0.8-1.9		
		> 20	5.3-10.5	0.9-2.5		

(Amended from DeBoer & LaFranchi, 2007)

APPENDIX B

THYROID FUNCTION TESTS PRICE LIST

Test Name	LabCorp Price (\$)
Thyroid Stimulating Hormone (TSH)	76.25
TSH Spec 2	152.50
TSH Receptor Antibody (TRAb)	165.00
T4, Total (T4)	30.50
T4, Free (FT4)	82.50
T3, Free (FT3)	157.50
T3, Free Equilibrium Dialysis/HPLC-Tandem Mass Spectrometry	250.00
T3, Reverse (rT3)	196.50
T3, Total (T3)	93.25
FT4 + T4	99.25
FT4 + TSH	158.75
FT4 + FT3 + TSH	316.25
T4 + TSH	106.75
Thyroid Panel + TSH	137.50
Thyroid Panel	61.25
Tg Quantitative	152.50
Thyroid Peroxidase Autoantibody (TPO)	66.00
Tg Antibody	84.50
Thyroid Antibodies	150.50
Thyroid Hormone Binding Ratio (THBR) (listed as T3 Uptake)	30.75
Thyroid Stimulating Immunoglobulin (TSI)	270.00
Thyrotropin-Binding Inhibitory Immunoglobulin (TBII)	Not Listed

(Amended from the 2013 LabCorp Book Pricing List without any contract discounts)

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CURRICULUM VITAE

