AMERICAN **THYROID** ASSOCIATION **Optimal Thyroid Health for All** 

# Clinical Thyroidology<sup>®</sup> for the Public

### VOLUME 13 | ISSUE 2 | FEBRUARY 2020

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There are a few clinical studies that have looked at the risk of heart problems in terms of duration of disease and treatment of hypothyroidism. This study investigated the risk of heart problems events in a large, well-characterized population in Denmark, focusing on the long term effects of undertreatment and overtreatment of hypothyroidism.

Lillevang-Johansen M et al 2019 Duration of over- and undertreatment of hypothyroidism is associated with increased cardiovascular risk. Eur J Endocrinol 180:407–416. PMID: 31035256.

#### HYPERTHYROIDISM ......5 Antithyroid drug-induced severe liver injury in newly diagnosed patients with Graves' Disease in Japan

Antithyroid drugs have been used since the 1940s to treat Graves' disease and are usually very well tolerated. However, rarely, they can have severe and potentially fatal side effects, including low white blood cell counts, liver injury and inflammation of the blood vessels. The goal of this study was to evaluate the types of antithyroid drug-induced severe liver disease in patients with Graves' disease in Japan.

Suzuki N et al 2019 Analysis of antithyroid drug-induced severe liver injury in 18,558 newly diagnosed patients with Graves' disease in Japan. Thyroid 29:1390–1398. PMID: 31573408.

#### THYROID SURGERY......7 New frailty risk model is the best yet for patients undergoing thyroid or parathyroid surgery

Thyroid and parathyroid surgery is generally extremely safe and well tolerated by the majority of patients. However, there is likely a small subset of patients that are more "frail" and poor surgical candidates. The authors aimed to develop a risk calculator based on frailty-related factors to identify patients that are more likely to do poorly after surgery.

Mascarella MA et al 2019 Preoperative risk index among patients undergoing thyroid or parathyroid surgery. JAMA Otolaryngol Head Neck Surg. Epub 2019 Sep 5. PMID: 31486838

#### THYROID CANCER......9

Early postoperative unstimulated thyroglobulin may help determine use of radioactive iodine in patients with papillary thyroid cancer Papillary thyroid cancer is the most common type of thyroid cancer. The use of radioactive iodine therapy has markedly decreased in recent years as studies have shown that it provides little benefit to patients that are at low risk of cancer recurrence after surgery. This study aimed to evaluate whether levels of early post-operative unstimulated thyroglobulin can be used to determine which patients with papillary thyroid cancer may need radioactive iodine therapy.

McDow AD et al 2019 Utility of Early Postoperative Unstimulated Thyroglobulin in Influencing Decision Making in Patients with Papillary Thyroid Carcinoma. Ann Surg Oncol Jul 2. doi: 10.1245/s10434-019-07581-8. [Epub ahead of print]

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Papillary thyroid cancer is the most common type of thyroid cancer and overall has an excellent prognosis. Papillary thyroid cancer may be divided into several subtype categories, some of which are more aggressive. This study examines whether there is any relationship between the subtype of papillary thyroid cancer and overall survival of patients.

Limberg J et al. Does aggressive variant histology without invasive features predict overall survival in papillary thyroid cancer? A National Cancer Database analysis. Ann Surg. Epub 2019 Oct 9. PMID: 31599802.

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Historically, most patients with indeterminate thyroid nodule biopsies were referred for surgery, even though ~75% would be benign. Currently, gene tests can provide more information as to whether an indeterminate nodule is a cancer or not. The aim of this study was to determine the clinical performance of the Afirma<sup>™</sup> GSC vs GEC at one academic medical center.

Endo M et al 2019 Afirma Gene Sequencing Classifier compared with Gene Expression Classifier in indeterminate thyroid nodules. Thyroid 29:1115–1124.

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#### Editor

#### Alan P. Farwell, MD, FACE

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#### Clinical Thyroidology for the Public

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### EDITOR'S COMMENTS

Happy New Year and welcome to another issue of *Clinical Thyroidology for the Public*. In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We also provide even faster updates of late-breaking thyroid news through <u>Twitter</u> at *@thyroidfriends* and on <u>Facebook</u>. Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room. Also check out our friends in the <u>Alliance for</u> **Thyroid Patient Education**. The <u>Alliance</u> member groups consist of: the *American Thyroid Association, Bite Me Cancer, the Graves' Disease and Thyroid Foundation, the Light of Life Foundation, MCT8 – AHDS Foundation, ThyCa: Thyroid Cancer Survivors' Association, Thyroid Cancer Canada, Thyroid Cancer Alliance* and *Thyroid Federation International*.

We invite all of you to join our **Friends of the ATA** community. It is for you that the American Thyroid Association (ATA) is dedicated to carrying out our mission of providing reliable thyroid information and resources, clinical practice guidelines for thyroid detection and treatments, resources for connecting you with other patients affected by thyroid conditions, and cutting edge thyroid research as we search for better diagnoses and treatment outcomes for thyroid disease and thyroid cancer. We thank all of the *Friends of the ATA* who support our mission and work throughout the year to support us. We invite you to help keep the ATA mission strong by choosing to make a donation that suits you — it takes just one moment to give online at: www.thyroid.org/donate and all donations are put to good work. The ATA is a 501(c)3 nonprofit organization and your gift is tax deductible.

#### February is Hypothyroidism Awareness Month.

#### In this issue, the studies ask the following questions:

- What is the risk of heart problems in patients with hypothyroidism?
- What is the risk of liver problems in patients with Graves' disease treated with antithyroid drugs?
- Is there a risk assessment calculator for problems occurring after thyroid surgery?
- Does the unstimulated thyroglobulin level 6 weeks after surgery predict thyroid cancer recurrence?
- Do aggressive variants of papillary thyroid cancer affect survival?
- How does the new Afirma<sup>™</sup> GSG test perform in indeterminate thyroid nodules?

We welcome your feedback and suggestions. Let us know what you want to see in this publication. I hope you find these summaries interesting and informative.

— Alan P. Farwell, MD, FACE

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#### **HYPOTHYROIDISM**

### Hypothyroidism and risk for heart disease

#### BACKGROUND

Thyroid hormone has direct effects on heart function, blood vessels and cholesterol levels. In hypothyroidism, symptoms may include slowing of the heart rate, constriction of the blood vessels and increased blood pressure, retention of fluid and edema and an increase in cholesterol levels. Severe cases of hypothyroidism can cause heart failure and death. Hypothyroidism is treated with thyroid hormone replacement, which can reverse most of these negative effects. However, overtreatment of hypothyroidism can result in high thyroid levels and fast and irregular heart rates. There are a few clinical studies that have looked at the risk of heart problems in terms of duration of disease and treatment of hypothyroidism. This study investigated the risk of heart problems events in a large, well-characterized population in Denmark, focusing on the long term effects of undertreatment and overtreatment of hypothyroidism.

#### THE FULL ARTICLE TITLE

Lillevang-Johansen M et al 2019 Duration of over- and under-treatment of hypothyroidism is associated with increased cardiovascular risk. Eur J Endocrinol 180:407– 416. PMID: 31035256.

#### SUMMARY OF THE STUDY

This study was done in Denmark in 216,894 patients with no known thyroid or heart disease at entry and who had at least one serum thyroid-stimulating hormone (TSH) level measured between 1995 and 2011. Data obtained from patient charts over a time period of 7 years was analyzed. The patients with thyroid disease were further divided into groups based on whether they had received treatment with levothyroxine and what their TSH levels were at the start of the study and later on. Overall, 2680 individuals developed hypothyroidism - 622 had mild hypothyroidism (average TSH 5.5) and were not treated while 2058 individuals with an average TSH of 9.2 and were treated with levothyroxine. Individuals with mild hypothyroidism who were not treated had an 83% increased risk of developing heart problems as compared with individuals with normal thyroid function or hypothyroidism that was treated. Over a 5 years period as compared with individuals with normal thyroid function, individuals with mild hypothyroidism who were not treated had a 3-fold increased risk of developing heart problems, individuals with treated hypothyroidism with a low TSH had a 2.1-fold increased risk and treated individuals with a normal TSH had a 1.8-fold increased risk. The risk for heart problems was the highest in hypothyroid patients that were not treated when were >65 years of age.

# WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that patients with hypothyroidism had an increased risk of developing heart problems as compared with patient with normal thyroid function whether they were treated or not, with the lowest risk in those patients treated achieving a normal TSH as compared to those with a low TSH or who were not treated. Thus, both under treatment and over treatment of hypothyroidism may be linked to a higher risk of heart disease. Further studies may be needed to clarify this link further.

— Vibhavasu Sharma, MD, FACE

#### **ATA THYROID BROCHURE LINKS**

Hypothyroidism (Underactive): <u>https://www.thyroid.org/hypothyroidism/</u> Thyroid Hormone Treatment: <u>https://www.thyroid.org/thyroid-hormone-treatment/</u>

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#### **HYPOTHYROIDISM**, continued

#### **ABBREVIATIONS & DEFINITIONS**

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

Hypothyroidism: a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Treatment requires taking thyroid hormone pills.

Levothyroxine (T4): the major hormone produced by the thyroid gland and available in pill form as Synthroid<sup>™</sup>, Levoxyl<sup>™</sup>, Tirosint<sup>™</sup> and generic preparations.

Thyroid hormone therapy: patients with hypothyroidism are most often treated with Levothyroxine in order to return their thyroid hormone levels to normal. Replacement therapy means the goal is a TSH in the normal range and is the usual therapy.



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#### HYPERTHYROIDISM

### Antithyroid drug-induced severe liver injury in newly diagnosed patients with Graves' Disease in Japan

#### BACKGROUND

Graves' disease is the most common cause of hyperthyroidism in the United States. Treatment options include antithyroid drugs ((Methimazole, MMI, and propylthiouracil, PTU), radioactive iodine treatment and surgery. Antithyroid drugs have been used since the 1940's. These drugs are very effective in controlling the hyperthyroidism and are usually very well tolerated. However, rarely, they can have severe and potentially fatal side effects, including low white blood cell counts (agranulocytosis), liver injury and inflammation of the blood vessels (vasculitis). Druginduced liver injury has been reported in 0.03% to 0.5% of patients taking antithyroid drugs. The use of PTU has been associated to severe, potentially fatal, liver disease while MMI has been associated more with inflammation of the gall bladder tract (cholestatic disease). Again, these reaction are very rare. Recent reports from Asia have indicated that both drugs can cause either type of liver injury. The goal of this study was to evaluate the types of antithyroid drug-induced severe liver disease in patients with Graves' disease in Japan.

#### THE FULL ARTICLE TITLE

Suzuki N et al 2019 Analysis of antithyroid drug-induced severe liver injury in 18,558 newly diagnosed patients with Graves' disease in Japan. Thyroid 29:1390-1398. PMID: 31573408.

#### SUMMARY OF THE STUDY

The study included 18,558 patients with newly diagnosed Graves' disease who received antithyroid drugs for the first time between January 2005 and December 2016 at a single medical center in Japan. Among these, 14,271 patients received MMI and 4,287 patients received PTU. Study data was collected from the patients' medical records, and patients with prior history of liver disease were excluded.

The types of antithyroid drug-related liver disease were defined as follows: liver cell (hepatocellular) injury (levels of the liver enzyme ALT > 8 times the upper limit of normal anytime or >5 times the upper limit of normal

for more than 2 weeks), gall bladder (cholestatic) injury (serum total bilirubin levels >3 times the upper limit of normal) or mixed injury (both liver cell and gall bladder injury). The liver injury severity was graded from 1 to 5: Grade 1- mild disease; Grade 2- moderate; Grade 3- severe but not immediately life-threatening; Grade 4- life-threatening and needing urgent intervention (ALT >20 times the upper limit of normal, or 20 times the baseline if the baseline had been abnormal; or total bilirubin >10 times the upper limit of normal, or 10 times the baseline if the baseline level had been abnormal); Grade 5 - death.

A total of 461 patients (2.5% - 0.3% for males and 2.9% for females) had severe Grade 3 or 4 drug-induced liver injury. Nine women developed liver injury after exposure to both MMI and PTU. Severe liver injury was associated more often with PTU than MMI use (6.3% versus. 1.4%, respectively), and most patients (2.3%) had Grade 3 with a few patients having Grade 4 liver injury. There were no deaths or liver transplantations.

The majority of patients had a liver cell injury. Of the MMI-treated patients, 94% had liver cell injury, 2.5% had gall bladder injury (1 had Grade 4 drug-induced liver injury), and 3.5% had a mixed type. Of the PTU-treated patients, 90.9% had hepatocellular injury, 0.4% had cholestatic injury, and 0.7% had a mixed type. Severe drug-induced liver injury was more frequent in older patients treated with MMI but not PTU.

The average time to development of drug-induced liver injury was 30 days, and the average time to recovery was 28 days. The liver injury developed within 90 days after starting antithyroid drug therapy in 97% of cases. The average daily dose of MMI was 15 mg, while the average daily dose of PTU was 300 mg. No correlation between the antithyroid drug dose or serum thyroid function tests and the severity of the drug-induced liver injury was found. Half of the patients received no treatment for liver injury, while half received ursodeoxycholic acid therapy or glucocorticoids.

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#### **HYPERTHYROIDISM**, continued

#### WHAT ARE THE IMPLICATIONS **OF THIS STUDY?**

In this study from Japan, like other Asian countries, the prevalence of both PTU and MMI-induced liver disease was higher than that reported in the United States. The major type of MMI-induced liver injury was injury to the liver cells in Asian countries and elevated bilirubin in the United States. All studies have showed a higher risk of severe liver injury with PTU as compared to MMI. Thus, MMI is the preferred drug in treating hyperthyroid patients. Physicians should be aware that MMI can cause liver injury, however.

Although severe antithyroid drug-induced liver injury is rare, it can be potentially fatal. All patients who start antithyroid drug treatment should be aware of the possibility of hepatic complications and discontinue the drug if they develop symptoms concerning for liver disease. It would be advisable to refer the patients with severe antithyroid drug-induced liver injury to a specialized liver center that has the capability of performing liver transplantation.

- Alina Gavrila, MD, MMSC

#### **ATA THYROID BROCHURE LINKS**

Graves' Disease: https://www.thyroid.org/graves-disease/

#### **ABBREVIATIONS & DEFINITIONS**

Hyperthyroidism: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Methimazole: an antithyroid medication that blocks the thyroid from making thyroid hormone. Methimazole is used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Propylthiouracil (PTU): an antithyroid medication that blocks the thyroid from making thyroid hormone. Propylthiouracil is used to treat hyperthyroidism, especially in women during pregnancy.

Agranulocytosis: an acute and severe decrease in the white blood cell count that can result in life-threatening infections.

Vasculitis: inflammation of blood vessels.

Hepatocellular liver disease: a condition where there is damage to the liver cells that may affect the liver function.

Cholestatic liver disease: a condition where there is slowing of the bile flow in the liver.

Alanine aminotransferase (ALT): an enzyme normally present in the liver that is released into blood when the liver is damaged.

Bilirubin: orange-yellow pigment that results from the breakdown of red blood cells and is usually excreted in the bile. Cholestasis causes bile and bilirubin to build up in the bloodstream.

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#### **THYROID SURGERY**

# New frailty risk model is the best yet for patients undergoing thyroid or parathyroid surgery

#### BACKGROUND

Endocrine surgical procedures (thyroid and parathyroid) and generally extremely safe and well tolerated by the majority of patients. Recovery after surgery is usually routine and most patients quickly get back to their prior level of health before surgery. However, there is likely a small subset of patients that are more "frail" and poor surgical candidates and may be better served by following the disease progression or with non-surgical treatmentoptions. Pre-operative risk calculators have been developed for more complex surgeries to help better quantify for patients and their families the risks of post-operative problems or death associated with various surgeries. These calculators help patients and physicians determine the individual risk of the surgery and identify patients that could be benefit form additional treatment before surgery so as to have the best outcome. None currently exists for thyroid surgery, so the authors aimed to develop a Cervical Endocrine Surgery Risk Index, or CESRI) based on frailty-related factors.

#### THE FULL ARTICLE TITLE

Mascarella MA et al 2019 Preoperative risk index among patients undergoing thyroid or parathyroid surgery. JAMA Otolaryngol Head Neck Surg. Epub 2019 Sep 5. PMID: 31486838

#### SUMMARY OF THE STUDY

The authors analyzed more than 150,000 patients from the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database that had thyroid or parathyroid surgery from 2007 through 2016. They used sociodemographic, clinical, and frailty-related risk factors to create a risk model whose main outcome was a variable of any major adverse event

or death within 30 days after surgery. The authors then compared the ability of their scoring system to predict post-op problems and death to other scoring systems.

Factors that proved important and were included in the scoring system were were inpatient hospital status at the time of the procedure, surgical time more than 4 hours, functional/independence loss, age >50 (with increased by decade of age after age 50), low blood count, use of blood thinners, recent weight loss, low serum albumin levels, increased white blood cells, baseline shortness of breath, male sex, obesity, current smoking and type 1 and 2 diabetes mellitus. The CESRI scoring system seemed to provide equal estimates regardless of type of neck surgical procedure or diagnosis and performed better than other generic risk calculators. However, statistically the performance of the model was only "fair", with 'fair' sensitivity and specificity. Based on the CESRI point system, the probability of problems after surgery ranged from 0.010 if the CESRI score was ≤4 to 0.290 if the score was  $\geq 50$ .

#### WHAT ARE THE IMPLICATIONS **OF THIS STUDY?**

The newly developed CESRI could aid physicians in counseling patients before thyroid and parathyroid surgery, and even to recommend treatment such as nutritional supplementation prior to surgery to some patients. However, given the low risk of problems and death of these procedures, the model only performs "fairly" and does not help predict the more common complications in endocrine surgery of hypocalcemia and nerve injury.

- Melanie Goldfarb, MD

#### **ATA THYROID BROCHURE LINKS**

Thyroid Surgery: https://www.thyroid.org/thyroid-surgery/

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#### THYROID SURGERY, continued

#### **ABBREVIATIONS & DEFINITIONS**

Thyroidectomy: surgery to remove the entire thyroid gland. When the entire thyroid is removed it is termed a total thyroidectomy. When less is removed, such as in removal of a lobe, it is termed a partial thyroidectomy.

Parathyroidectomy: surgery to remove one or more of the 4 parathyroid glands

Parathyroid glands: usually four small glands located around the thyroid that secrete parathyroid hormone (PTH) which regulates the body's calcium levels. Frailty: decreased reserve to respond to health problems and stress

Frailty-related Risk Factors: age, gender, socioeconomic status, physical activity in routine work and education level



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#### **THYROID CANCER**

Early postoperative unstimulated thyroglobulin may help determine use of radioactive iodine in patients with papillary thyroid cancer

#### BACKGROUND

Papillary thyroid cancer is the most common type of thyroid cancer. Standard management includes surgery followed by radioactive iodine therapy when indicated. Radioactive iodine therapy significantly improves outcomes in patients with either persistence of cancer or at intermediate or high risk of cancer recurrence after surgery. However, the use of radioactive iodine therapy has markedly decreased in recent years as studies have shown that it provides little benefit to patients that are at low risk of cancer recurrence after surgery. It has recently been suggested that levels of post-operative thyroglobulin may be useful in deciding who may require radioactive iodine therapy after surgery. Thyroglobulin is a hormone made by thyroid cells and can be used as a cancer marker after initial treatment to detect persistent or recurrent cancer. It can be measured as unstimulated (at baseline) or stimulated (when thyroid stimulating hormone (TSH) levels are high). This study aimed to evaluate whether levels of early post-operative unstimulated thyroglobulin (6 weeks after surgery) can be used to determine which patients with papillary thyroid cancer may need radioactive iodine therapy.

#### THE FULL ARTICLE TITLE

McDow AD et al 2019 Utility of Early Postoperative Unstimulated Thyroglobulin in Influencing Decision Making in Patients with Papillary Thyroid Carcinoma. Ann Surg Oncol Jul 2. doi: 10.1245/s10434-019-07581-8. [Epub ahead of print]

#### SUMMARY OF THE STUDY

This was a study of 134 patients treated with surgery for papillary thyroid cancer at a single institution between 2015 and 2017. Only patients with appropriately low TSH were included as per the American Thyroid Association guidelines. Unstimulated thyroglobulin levels were measured at approximately 6 weeks following surgery. A level of  $\leq 0.2$  ng/ml was used to define excellent response postoperatively. Neck ultrasounds were done 6 and 12 months after surgery to evaluate for evidence

of persistent or recurrent cancer. Persistent cancer was defined as an unstimulated thyroglobulin >0.2 ng/ml, abnormal neck ultrasound, or persistent elevation of thyroglobulin antibodies at 6 months after initial therapy. Recurrent cancer was defined as evidence of cancer following previous achievement of an undetectable thyroglobulin level, negative thyroglobulin antibodies, and negative ultrasound.

The average patient age was 45 years-old and the majority of patients were female (74.6%) and white (92.5%). More than half of the patients (53.7%) received radioactive iodine therapy following surgery. Overall, 49.3% of patients had an excellent response to treatment with an unstimulated thyroglobulin level of  $\leq 0.2$  ng/ml, with 60% of them not receiving radioactive iodine therapy. Of these, 96.7% maintained an undetectable unstimulated thyroglobulin at 6 months and 94.1% at one year. All patients that received radioactive iodine therapy had an undetectable unstimulated thyroglobulin level both at 6- and 12-months following surgery.

Additionally, 69% of patients with an early postoperative unstimulated thyroglobulin higher than 0.2 ng/ml and up to 2.0 ng/ml achieved a goal of ≤0.2 ng/ml at 6 months if they received radioactive iodine therapy, compared to only 15.4% if they didn't receive radioactive iodine therapy. Only 30.8% of patients with an early postoperative unstimulated thyroglobulin >2.0 ng/ml achieved a goal of  $\leq 0.2$  ng/ml at 6 months if they received radioactive iodine therapy, compared to only 25.0% if they didn't.

#### WHAT ARE THE IMPLICATIONS **OF THIS STUDY?**

This study shows that early postoperative unstimulated thyroglobulin levels can be used to predict use of radioactive iodine therapy in patients with papillary thyroid cancer. Even though these findings are from a single institution, they are important for two main reasons: 1) this practice can help to decrease overtreatment with radioactive iodine therapy in patients who have

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#### THYROID CANCER, continued

low risk disease and 2) it can aid in identifying presence of persistent disease early in the treatment process. In the future, population-based studies can reinforce these results and help with personalizing treatment in patients with papillary thyroid cancer.

— Maria Papaleontiou, MD

#### ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): <u>https://www.thyroid.org/thyroid-cancer/</u> Radioactive Iodine Therapy: <u>https://www.thyroid.org/radioactive-iodine/</u>

#### **ABBREVIATIONS & DEFINITIONS**

Papillary thyroid cancer: the most common type of thyroid cancer.

Cancer recurrence: this occurs when the cancer comes back after an initial treatment that was successful in destroying all detectable cancer at some point.

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also, the best screening test to determine if the thyroid is functioning normally.

Thyroglobulin: a protein made only by thyroid cells, both normal and cancerous. When all normal thyroid tissue is destroyed after radioactive iodine therapy in patients with thyroid cancer, thyroglobulin can be used as a thyroid cancer marker in patients that do not have thyroglobulin antibodies. Thyroglobulin antibodies: these are antibodies that attack the thyroid instead of bacteria and viruses, they are a marker for autoimmune thyroid disease, which is the main underlying cause for hypothyroidism and hyperthyroidism in the United States.

Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-I3I is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and with an overactive thyroid.

Thyroid Ultrasound: a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and characterize nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

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#### **THYROID CANCER**

Is there a relationship between the subtype of papillary thyroid cancer and overall survival of patients?

#### BACKGROUND

Papillary thyroid cancer is the most common type of thyroid cancer and overall has an excellent prognosis. Despite this overall excellent prognosis, some patients do not do well and some may die of their cancer. Papillary thyroid cancer may be divided into several subtype categories by pathologists examining thyroid tissue removed at surgery. This study examines whether there is any relationship between the subtype of papillary thyroid cancer and overall survival of patients. The reason for the study was to determine if, after adjustment for the severity/extent of thyroid cancer, the subtype of papillary thyroid cancer itself predicted overall survival. This information could be used to counsel patients about their disease or potentially guide further treatments and follow-up.

#### THE FULL ARTICLE TITLE

Limberg J et al. Does aggressive variant histology without invasive features predict overall survival in papillary thyroid cancer? A National Cancer Database analysis. Ann Surg. Epub 2019 Oct 9. PMID: 31599802.

#### SUMMARY OF THE STUDY

The authors examined data on papillary thyroid cancer cancer patients treated between 2004 and 2015, who were recorded in the American College of Surgeons National Cancer Database (NCDB), which is a large American cancer registry. Patients were divided into those who had classic variant papillary thyroid cancer or another category of "aggressive variant" papillary thyroid cancer (including tall cell, diffuse sclerosing, or columnar cell variants). The authors analyzed data from a total of 170,778 patients, including 162,827 (95.3%) with classic papillary thyroid

cancer and 7951 (4.7%) with aggressive variant papillary thyroid cancer. Patients with aggressive variant papillary thyroid cancer were more likely than those with classic variant papillary thyroid cancer to have invasive features of their cancer (such as extension outside the thyroid, microscopic invasion into lymphatic channels or blood vessels within the thyroid, multiple thyroid tumors, positive lymph nodes, or distant metastases). The 5-year overall survival rate of patients with aggressive variants of papillary thyroid cancer (89%) was lower than that of patients with classic variant papillary thyroid cancer (95%), with a difference between groups also noted at 10 years. However, there was no significant difference in overall survival rate between these groups for patients without invasive disease, if the data were statistically adjusted for patient characteristics, cancer size at diagnosis, and the type of treatment.

#### WHAT ARE THE IMPLICATIONS **OF THIS STUDY?**

The authors conclude that for papillary thyroid cancer patients who do not have evidence of invasive features of thyroid cancer, the overall survival rate is not significantly different between patients with classic variant papillary thyroid cancer to more aggressive variants. An implication of this study is the importance of considering the presence of invasive features as well as the subtype of thyroid cancer in counseling patients with papillary thyroid cancer about long-term outcomes. A limitation of this study is that the authors did not examine the risk of papillary thyroid cancer persistence or recurrence (i.e. cancer not being cured or coming back in the future), which are relevant outcomes for future study.

- Anna M. Sawka, MD, PhD

#### **ATA THYROID BROCHURE LINKS**

Thyroid Cancer (Papillary and Follicular): <u>https://www.thyroid.org/thyroid-cancer/</u>

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#### THYROID CANCER, continued

#### **ABBREVIATIONS & DEFINITIONS**

Papillary thyroid cancer: the most common type of thyroid cancer. There are several variants (subtypes) of

papillary thyroid cancer, such as classic, follicular, tall cell, diffuse sclerosing, and columnar cell PTC.



AMERICAN **THYROID** ASSOCIATION Optimal Thyroid Health for All



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#### **THYROID NODULES**

## The Afirma<sup>™</sup> gene sequencing classifier (GSC) performs better in indeterminate thyroid nodules than the Afirma<sup>™</sup> gene expression classifier (GEC)

#### BACKGROUND

Thyroid nodules are very common, occurring in up to 50% of individuals. Thyroid cancer is found in ~5% of thyroid nodules, so the vast majority are benign (non-cancerous). A thyroid nodule biopsy can be benign (normal), malignant (cancer) or indeterminate. Indeterminate means the pathologist cannot tell if the nodule is benign or malignant with certainty. Historically, most patients with indeterminate thyroid nodule biopsies were referred for surgery though most would ultimately not have thyroid cancer (around 75% or more would have an "unnecessary surgery"). Currently, gene tests can provide more information as to whether an indeterminate nodule is a cancer or not. One such test is the Afirma gene test.

The original Afirma gene test was a gene expression classifier (GEC) that used a technology called a microarray that results in a pattern of gene expression. These gene patterns are better at ruling out thyroid cancer in an indeterminate nodule than confirming cancer. Therefore, a new version of the Afirma test was created called a gene sequencing classifier (GSC) to better predict thyroid cancers in indeterminate nodule while still being able to rule out cancer in benign nodules. The GSC incorporates nuclear and mitochondrial RNA transcriptome gene expression, RNA sequencing, and genomic copy number analysis.

The aim of this study was to determine the clinical performance of the GSC as compared with the GEC at one academic medical center.

#### THE FULL ARTICLE TITLE

Endo M et al 2019 Afirma Gene Sequencing Classifier compared with Gene Expression Classifier in indeterminate thyroid nodules. Thyroid 29:1115–1124.

#### SUMMARY OF THE STUDY

Patients with thyroid nodule biopsies with indeterminate cytology results were chosen for additional genetic testing; the Afirma GEC (during the period February 2, 2011–

July 11, 2017) or the Afirma GSC (during the period July 11, 2017–December 19, 2018).

Of the 343 nodules that underwent the GEC test, 178 cases (51.9%) were considered suspicious for cancer. The rest were called benign by the GEC. If all nonsurgical GEC benign cases were actually benign, when evaluating the cases that had surgery, the chance that a GEC suspicious nodule was actually cancer was 33.3% and the chance that a GEC benign nodule was actually benign at surgery was 98.2%. A total of 27 patients with GEC benign nodules had surgery for nodule growth or patient preference and 3 had a papillary thyroid microcarcinoma discovered at final pathology while the rest were benign.

Of the 164 nodules included in the study with the GSC test, suspicious nodules were found in 39 of the 164 nodules (23.7%). The benign call rate for GSC was 76.2%. Of the 164 GSC nodules, 29 (17.6%) underwent thyroid surgery. If all nonsurgical GSC benign cases were truly benign, the chance a suspicious nodule was truly a thyroid cancer was 60% and a benign nodule was benign was 100%.

# WHAT ARE THE IMPLICATIONS OF THIS STUDY?

These results show an improved accuracy for the GSC as compared with the GEC. Additionally, there is an increase in the benign call rate with GSC, which in this study decreased surgical interventions by 68%. This study indicates that the newer Afirma GSC test is superior to the Afirma GEC test by better predicting which indeterminate nodules are more likely to be cancers and should be removed while maintaining the same or better performance of predicting which indeterminate nodules are benign and can be monitored without surgery. With these genetic tests, patients and physicians have more information to feel confident about avoiding surgery or pursuing it based on the test results.

— Joshua Klopper, MD

in

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#### THYROID NODULES, continued

#### ATA THYROID BROCHURE LINKS

Thyroid Nodules: <a href="https://www.thyroid.org/thyroid-nodules/">https://www.thyroid.org/thyroid-nodules/</a>

#### **ABBREVIATIONS & DEFINITIONS**

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (Benign), ~5-10% are cancerous.

Thyroid fine needle aspiration biopsy: a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

Indeterminate thyroid biopsy: this happens a few atypical cells are seen but not enough to be abnormal (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS)) or when the diagnosis is a follicular or hurthle cell lesion. Follicular and hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or hurthle cell cancer from noncancerous adenomas. This occurs in 15-20% of biopsies and often results in the need for surgery to remove the nodule.

Genes: a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

microRNA: a short RNA molecule that has specific actions within a cell to affect the expression of certain genes.

Molecular markers: genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either to diagnose cancer or to determine that the nodule is benign. The two most common molecular marker tests are the Afirma<sup>™</sup> Gene Expression Classifier and Thyroseq<sup>™</sup>

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### **ATA Alliance for Thyroid Patient Education**

**GOAL** The goal of our organizations is to provide accurate and reliable information for patients about the diagnosis, evaluation and treatment of thyroid diseases. We look forward to future collaborations and continuing to work together toward the improvement of thyroid education and resources for patients.













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#### American Thyroid Association www.thyroid.org

Foundation

ATA Patient Resources: www.thyroid.org/thyroid-information/ Find a Thyroid Specialist: www.thyroid.org (Toll-free): I-800-THYROID

thyroid@thyroid.org

#### **Bite Me Cancer**

www.bitemecancer.org

#### Graves' Disease and Thyroid Foundation

www.gdatf.org (Toll-free): 877-643-3123 info@ngdf.org

#### **Light of Life Foundation**

www.checkyourneck.com info@checkyourneck.com MCT8 – AHDS Foundation

mct8.info Contact@mct8.info

#### Thyca: Thyroid Cancer Survivors' Association, Inc. www.thyca.org

(Toll-free): 877-588-7904 thyca@thyca.org

#### **Thyroid Cancer Alliance**

www.thyroidcanceralliance.org www.thyroidcancerpatientinfo.org Rotterdam,The Netherlands

#### **Thyroid Cancer Canada**

www.thyroidcancercanada.org 416-487-8267 info@thyroidcancercanada.org

#### Thyroid Federation International www.thyroid-fed.org tfi@thyroid-fed.org

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AMERICAN THYROID ASSOCIATION

ATA | Founded 1923

# Donate Now!



The ATA was a valuable resource for our family when my dad was diagnosed with Anaplastic Thyroid Cancer. When you're faced with a detrimental diagnosis where even a few days can make the difference in life or death, understanding your options quickly is critical. The ATA website offers a one-stop shop for patients and caregivers to find specialists, current clinical trials, general thyroid cancer information, and links to other patient support groups and information.

Mary Catherine Petermann

- Father who was diagnosed with Anaplastic Thyroid Cancer in 2006
- He was treated at Mayo Clinic
- He has clean scans as of October 2016

# **JOIN US**

# PLEASE JOIN OUR JOURNEY TO ADVANCED DISCOVERIES AND TREATMENT FOR THYROID DISEASE AND THYROID CANCER

As patients with thyroid disease navigate the challenges to their quality of life and researchers and physicians look for more effective directions, we at the ATA have our own destination– **funding for critical thyroid research, prevention, and treatment.** For 94 years, the ATA has led the way in thyroidology. It's a daily obstacle course to find new drugs, better treatments, advanced surgical methods, and more rapid diagnoses for the 20 million Americans who have some form of thyroid disease.

The ATA has paved the way with management guidelines for clinicians who diagnose and treat thyroid disease. For physicians treating pregnant women diagnosed with thyroid disease, our recent publication presents 97 evidence-based recommendations making sure that best practices are implemented with the latest, most effective treatment.



Through your generous support and donations, research takes the lead and hope is on the horizon. **Will you join us** in our campaign to raise **\$1.5 million** for thyroid research, prevention, and treatment? Your compassionate, tax-deductible gift will provide funds for:

- Research grants that pave the way for 1,700 ATA physicians and scientists who have devoted their careers to understanding the biology of and caring for patients affected by thyroid disease.
- Patient education for individuals and families looking for life-changing clinical trials, the best thyroid specialists, and cutting edge treatment and drugs.
- Professional education that offers a wealth of knowledge and leading-edge research for trainees and practitioners.
- A website that is the go-to resource for thyroid information for patients and practitioners alike. In 2016 alone, there were more than 3,700,000 website views of ATA's library of online thyroid information patient brochures.

Donations **of all sizes** will change the future for thyroid patients. You will make a direct impact on patients like Mary Catherine's father as he deals with Anaplastic Thyroid Cancer. You will help scientists like ATA Associate Member Julia Rodiger, Ph.D., a scientist at the National Institutes of Health, as she analyzes thyroid hormones for intestinal stem cell development.

# Hypothyroidism

### WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is normally located in the lower front of the neck. The thyroid's job is to make thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormone helps the body use energy, stay warm and keep the brain, heart, muscles, and other organs working as they should.

### WHAT IS HYPOTHYROIDISM?

Hypothyroidism is an underactive thyroid gland. Hypothyroidism means that the thyroid gland can't make enough thyroid hormone to keep the body running normally. People are hypothyroid if they have too little thyroid hormone in the blood. Common causes are autoimmune disease, such as *Hashimoto's thyroiditis*, surgical removal of the thyroid, and radiation treatment.

### WHAT ARE THE SYMPTOMS?

When thyroid hormone levels are too low, the body's cells can't get enough thyroid hormone and the body's processes start slowing down. As the body slows, you may notice that you feel colder, you tire more easily, your skin is getting drier, you're becoming forgetful and depressed, and you've started getting constipated. Because the symptoms are so variable and non-specific, the only way to know for sure whether you have hypothyroidism is with a simple blood test for TSH.

#### KEEPING OTHER PEOPLE INFORMED

Tell your family members. Because thyroid disease runs in families, you should explain your hypothyroidism to your relatives and encourage them to get periodic TSH tests. Tell your other doctors and your pharmacist about your hypothyroidism and the drug and dose with which it is being treated. If you start seeing a new doctor, tell the doctor that you have hypothyroidism and you need your TSH tested every year. If you are seeing an endocrinologist, ask that copies of your reports be sent to your primary care doctor.

#### WHAT CAN YOU EXPECT OVER THE LONG TERM?

There is no cure for hypothyroidism, and most patients have it for life. There are exceptions: many patients with viral thyroiditis have their thyroid function return to normal, as do some patients with thyroiditis after pregnancy.

Hypothyroidism may become more or less severe, and your dose of thyroxine may need to change over time. You have to make a lifetime commitment to treatment. But if you take your pills every day and work with your doctor to get and keep your thyroxine dose right, you should be able to keep your hypothyroidism well controlled throughout your life. Your symptoms should disappear and the serious effects of low thyroid hormone should improve. If you keep your hypothyroidism well-controlled, it will not shorten your life span.

### WHAT CAUSES HYPOTHYROIDISM?

There can be many reasons why the cells in the thyroid gland can't make enough thyroid hormone. Here are the major causes, from the most to the least common.

- Autoimmune disease. In some people's bodies, the immune system that protects the body from invading infections can mistake thyroid gland cells and their enzymes for invaders and can attack them. Then there aren't enough thyroid cells and enzymes left to make enough thyroid hormone. This is more common in women than men. Autoimmune thyroiditis can begin suddenly or it can develop slowly over years. The most common forms are *Hashimoto's thyroiditis* and atrophic thyroiditis.
- Surgical removal of part or all of the thyroid gland. Some people with thyroid nodules, thyroid cancer, or Graves' disease need to have part or all of their thyroid removed. If the whole thyroid is removed, people will definitely become hypothyroid. If part of the gland is left, it may be able to make enough thyroid hormone to keep blood levels normal.
- *Radiation treatment.* Some people with Graves' disease, nodular goiter, or thyroid cancer are treated with *radioactive iodine* (I-131) for the purpose of destroying their thyroid gland. Patients with Hodgkin's disease, lymphoma, or cancers of the head or neck are treated with radiation. All these patients can lose part or all of their thyroid function.

# Hypothyroidism

- Congenital hypothyroidism (hypothyroidism that a baby is born with). A few babies are born without a thyroid or with only a partly formed one. A few have part or all of their thyroid in the wrong place (ectopic thyroid). In some babies, the thyroid cells or their enzymes don't work right.
- *Thyroiditis. Thyroiditis* is an inflammation of the thyroid gland, usually caused by an autoimmune attack or by a viral infection. Thyroiditis can make the thyroid dump its whole supply of stored thyroid hormone into the blood at once, causing brief hyperthyroidism (too much thyroid activity); then the thyroid becomes underactive.
- *Medicines.* Medicines such as amiodarone, lithium, interferon alpha, and interleukin-2 can prevent the thyroid gland from being able to make hormone normally. These drugs are most likely to trigger hypothyroidism in patients who have a genetic tendency to autoimmune thyroid disease.
- *Too much or too little iodine*. The thyroid gland must have iodine to make thyroid hormone. Iodine comes into the body in food and travels through the blood to the thyroid. Keeping thyroid hormone production in balance requires the right amount of iodine. Taking in too much iodine can cause or worsen hypothyroidism.
- Damage to the pituitary gland. The pituitary, the "master gland," tells the thyroid how much hormone to make. When the pituitary is damaged by a tumor, radiation, or surgery, it may no longer be able to give the thyroid instructions, and the thyroid may stop making enough hormone.
- *Rare disorders that infiltrate the thyroid.* In a few people, diseases deposit abnormal substances in the thyroid and impair its ability to function. For example, amyloidosis can deposit amyloid protein, sarcoidosis can deposit granulomas, and hemochromatosis can deposit iron.

### HOW IS HYPOTHYROIDISM DIAGNOSED?

The correct diagnosis of hypothyroidism depends on the following:

- *Symptoms.* Hypothyroidism doesn't have any characteristic symptoms. There are no symptoms that people with hypothyroidism always have and many symptoms of hypothyroidism can occur in people with other diseases. One way to help figure out whether your symptoms are due to hypothyroidism is to think about whether you've always had the symptom (hypothyroidism is less likely) or whether the symptom is a change from the way you used to feel (hypothyroidism is more likely).
- Medical and family history. You should tell your doctor:
  - about changes in your health that suggest that your body is slowing down;
  - if you've ever had thyroid surgery;
  - if you've ever had radiation to your neck to treat cancer;
  - if you're taking any of the medicines that can cause hypothyroidism— amiodarone, lithium, interferon alpha, interleukin-2, and maybe thalidomide;
  - whether any of your family members have thyroid disease.
- *Physical exam.* The doctor will check your thyroid gland and look for changes such as dry skin, swelling, slower reflexes, and a slower heart rate.
- *Blood tests.* There are two blood tests that are used in the diagnosis of hypothyroidism.
- *TSH (thyroid-stimulating hormone) test.* This is the most important and sensitive test for hypothyroidism. It measures how much of the thyroid hormone thyroxine (T4) the thyroid gland is being asked to make. An abnormally high TSH means hypothyroidism: the thyroid gland is being asked to make more T4 because there isn't enough T4 in the blood.
- *T4 tests.* Most of the T4 in the blood is attached to a protein called thyroxine-binding globulin. The "bound" T4 can't get into body cells. Only about 1%–2% of T4 in the blood is unattached ("free") and can get into cells. The free T4 and the free T4 index are both simple blood tests that measure how much unattached T4 is in the blood and available to get into cells.

FURTHER INFORMATION



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Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association<sup>®</sup> website at *www.thyroid.org*. For information on thyroid patient support organizations, please visit the *Patient Support Links* section on the ATA website at *www.thyroid.org* 

# Hypothyroidism

### **HOW IS HYPOTHYROIDISM TREATED?**

THYROXINE (T4) REPLACEMENT.

Hypothyroidism can't be cured. But in almost every patient, hypothyroidism can be completely controlled. It is treated by replacing the amount of hormone that your own thyroid can no longer make, to bring your T4 and TSH levels back to normal levels. So even if your thyroid gland can't work right, T4 replacement can restore your body's thyroid hormone levels and your body's function. Synthetic thyroxine pills contain hormone exactly like the T4 that the thyroid gland itself makes. All hypothyroid patients except those with severe myxedema (life-threatening hypothyroidism) can be treated as outpatients, not having to be admitted to the hospital. For the few patients who do not feel completely normal taking a synthetic preparation of T4 alone, the addition of T3 (Cytomel<sup>®</sup>) may be of benefit.

#### SIDE EFFECTS AND COMPLICATIONS.

The only dangers of thyroxine are caused by taking too little or too much. If you take too little, your hypothyroidism will continue. If you take too much, you'll develop the symptoms of hyperthyroidism—an overactive thyroid gland. The most common symptoms of too much thyroid hormone are fatigue but inability to sleep, greater appetite, nervousness, shakiness, feeling hot when other people are cold, and trouble exercising because of weak muscles, shortness of breath , and a racing, skipping heart. Patients who have hyperthyroid symptoms at any time during thyroxine replacement therapy should have their TSH tested. If it is low, indicating too much thyroid hormone, their dose needs to be lowered.

### **FOLLOW-UP**

You'll need to have your TSH checked 6 to 10 weeks after a thyroxine dose change. You may need tests more often if you're pregnant or you're taking a medicine that interferes with your body's ability to use thyroxine. The goal of treatment is to get and keep your TSH in the normal range. Babies with hypothyroidism must get all their daily treatments and have their TSH levels checked as they grow, to prevent mental retardation and stunted growth. Once you've settled into a thyroxine dose, you can return for TSH tests about once a year.

YOU NEED TO RETURN SOONER IF ANY OF THE FOLLOWING APPLY TO YOU:

- Your symptoms return or get worse.
- You want to change your thyroxine dose or brand, or change taking your pills with or without food.
- You gain or lose a lot of weight (as little as a 10-pound difference for those who weren't overweight to begin with).
- You start or stop taking a drug that can interfere with absorbing thyroxine (such as certain antacids, calcium supplements and iron tablets), or you change your dose of such a drug. Medications containing estrogen also impact thyroxine doses, so any change in such a medication should prompt a re-evaluation of your thyroxine dose.
- You start or stop taking certain medicines to control seizures such as phenytoin or tegretol, as such medicines increase the rate at which thyroxine is metabolized in your body, and your dose of thyroxine may need to be adjusted.
- You're not taking all your thyroxine pills. Tell your doctor honestly how many pills you've missed.
- You want to try stopping thyroxine treatment. If ever you think you're doing well enough not to need thyroxine treatment any longer, try it only under your doctor's close supervision. Rather than stopping your pills completely, you might ask your doctor to try lowering your dose. If your TSH goes up, you'll know that you need to continue treatment.

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# FURTHER INFORMATION



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