

# Thyroid dysfunction screening

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Policy contains: hyperthyroid, hypothyroid, thyroid, thyroid dysfunction, thyroid screening.

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## Coverage policy

Thyroid dysfunction screening is clinically proven and, therefore, medically necessary in non-pregnant individuals in the following situations:

- Individuals with hypothyroid symptoms, to confirm or rule out disease.
- Individuals with hyperthyroid symptoms to confirm or rule out disease.
- Asymptomatic individuals at high risk for thyroid disease due to personal or family history.
- Individuals taking prescription drugs that interfere with thyroid function such as lithium, amiodarone, interferon, iodine, sulfa, tyrosine kinase inhibitors.

Thyroid dysfunction screening is clinically proven and, therefore medically necessary in early pregnancy or pre pregnancy planning if a history of:

- Prior thyroid surgery or thyroid dysfunction.
- Age >30 years.
- Goiter or other symptoms of thyroid dysfunction.

- TPOAb positivity.
- Autoimmune disorders or type 1 diabetes.
- Miscarriages or preterm delivery.
- Head or neck radiation.
- Family history of thyroid dysfunction.
- Morbid obesity (BMI  $\geq$  40 kg/m<sup>2</sup>).
- Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast.
- Infertility, or fertility evaluation.
- Residing in an area of known iodine deficiency.
- TSH, FT4, and TPOAb tests in postpartum depression (Alexander 2017, Ross 2018).

### Limitations

No limitations were identified during the writing of this policy.

### Alternative covered services

No alternative covered services were identified during the writing of this policy.

## Background

Thyroid dysfunctions are common within populations; an estimated 20 million Americans have some form of thyroid disease, and more than 12% of Americans will develop a thyroid condition during his/her lifetime (American Thyroid Association, 2021). About half of the population with thyroid dysfunction remain undiagnosed (Garmendia-Madariaga, 2014).

Cancer of the thyroid has the fastest-increasing incidence of any cancer. The age-adjusted rate has more than tripled (increased over 200%) since 1980. A total of 52,890 new cases were expected to be diagnosed among U.S. residents in 2020, while the prevalence of thyroid cancer survivors was estimated to be 859,838 on January 1, 2017 (Howlader, 2020). Nearly half of a typical endocrine practice involves thyroid conditions.

The most common thyroid diseases are hypothyroidism and hyperthyroidism. Hypo or hyperthyroidism occurs when the body fails to make sufficient amounts or secretes too much of thyroid hormones such as thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and thyrotropic releasing hormone. The most common cause of hypothyroidism is Hashimoto's disease, an autoimmune disease that mistakenly attacks the gland, preventing enough hormone from being produced. Another common autoimmune disorder affecting the thyroid gland is postpartum thyroiditis. The most common cause of hyperthyroidism, an overactive thyroid that produces excessive hormone, is Graves' disease, an immune abnormality. About 37% of subclinical hypothyroid cases resolve with no medical interventions (Diez, 2004).

Elevated thyroid-stimulating hormone is linked with clinical hyperthyroidism. Risk factors for elevated levels of this hormone include female sex, advancing age, white race, type 1 diabetes, Down syndrome, family history of thyroid disease, goiter, previous hyperthyroidism, and external-beam radiation in the head and neck area.

Low thyroid-stimulating hormone is linked with hyperthyroidism. Risk factors for a low levels of this hormone include female sex; advancing age; black race; low iodine intake; personal or family history of thyroid disease; and ingestion of iodine-containing drugs, such as amiodarone (LeFevre, 2015).

The primary screening test for thyroid dysfunction is serum thyroid-stimulating hormone testing. Multiple tests during the next 3 – 6 months should be performed to confirm or rule out abnormal findings. Follow-up testing of serum thyroxine (T4) levels in persons with persistently abnormal thyroid-stimulating hormone levels can differentiate between subclinical (normal T4) and overt (abnormal T4) thyroid dysfunction (LeFevre, 2015).

The normal range of thyroid-stimulating hormone is between 0.4 and 4.5 mU/l; results below and above the range indicates subclinical hyperthyroidism and hypothyroidism. Results in the range of 4.5 to 10.0 are considered mild cases of hypothyroidism, while those over 10.0 are considered serious (U.S. Preventive Services Task Force, 2015). Any result outside the normal range should undergo a T4 test to confirm a diagnosis of overt hyperthyroidism/hypothyroidism. Experts differ somewhat on ranges depending on variables and populations. In pregnant women, thyroid-stimulating hormone levels above 3.0 mU/l are considered high (Shomon, 2019).

A review of seven studies estimated prevalence of undiagnosed thyroid dysfunction in Europe to be 4.94% and 1.72% for hypothyroidism and hyperthyroidism, respectively. (Garmendia-Magariaga, 2014). U.S. prescriptions for levothyroxine sodium rose 42% from 50 million in 2006 to 71 million in 2010 (U.S. Preventive Services Task Force, 2015), and levothyroxine, used to treat hypothyroidism, was the second-most commonly prescribed drug in the U.S. in 2014 (Fuentes, 2018).

For many years, hypothyroidism has been one of the several dozen conditions used in screening all U.S. newborns. About 1 in 2,000 to 4,000 births, or at least 1,400 cases are diagnosed each year in the U.S. States vary in testing methods; 22 test thyroid-stimulating hormone first; 20 test for T4, and also thyroid-stimulating hormone if abnormal; and 9 test for both. Despite the relatively low rate of positive cases, early identification and immediate treatment with thyroid hormone can avoid the physical and mental growth limitations of hypothyroidism in young persons (Kilberg, 2018).

## Findings

The U.S. Preventive Services Task Force (2015) has recommended that screening for thyroid dysfunction is not medically necessary in asymptomatic non-pregnant adults, due to potential risks such as false-positive results, over diagnosis/over treatment of abnormal thyroid stimulating hormone (TSH) levels due to other factors or which may not progress or result in health issues due to disease possibly returning to normal over time. They also mention concern regarding possible psychological stigma and that risk outweighs potential benefits although unable to identify any study in an evidence review conducted by them, directly assessing benefits and harms of screening versus no screening for thyroid dysfunction (Rugge, 2015).

The Task Force also acknowledged that early detection and treatment of asymptomatic persons with abnormal serum thyroid-stimulating hormone levels with or without abnormal T4 levels may prevent longer-term morbidity and mortality from fractures, cancer, or cardiovascular disease, but cited insufficient supportive evidence in the literature and also recommend against thyroid cancer screening in asymptomatic adults who are deemed to be not at risk (U.S. Preventive Services Task force 2015, 2017).

The American Thyroid Association task force disagrees. Thyroid issues are a potential factor in infertility and new guidelines recommend Thyroid stimulating hormone testing for women seeking treatment for infertility with levothyroxine recommended in cases with overt hypothyroidism. In cases of subclinical hypothyroidism (normal T3 and T4 levels with abnormally high TSH levels), the task force notes that even with insufficient evidence in

support of fertility improvement, low dose levothyroxine treatment would be considered given the ability to prevent progression to serious disease once pregnancy has occurred (Alexander, 2017).

The American Thyroid Association guidelines since 2000 has recommended universal screening for thyroid dysfunction in all adults starting at age 35 and every five years thereafter. Individuals with symptoms consistent with thyroid dysfunction and those with risk factors may require more frequent testing (Ladenson, 2000).

More recently, the American Association of Clinical Endocrinologists and the College of Endocrinology issued a similar recommendation of an aggressive case-finding approach to include testing for thyroid dysfunctions for many non-specific symptoms among the population (Hennessey, 2016). Both the American Thyroid Association and the American Association of Clinical Endocrinologists recommend that routine testing be considered for adults over 60 (Garber, 2012).

The American College of Obstetricians and Gynecologists guideline on thyroid testing during pregnancy does not recommend universal screening for all women. It supports serum testing of thyroid-stimulating hormone and free thyroxine-4 for those women with symptoms of thyroid dysfunction (American College of Obstetricians and Gynecologists, 2015). The American Thyroid Association guideline supports universal screening for thyroid dysfunction in newly pregnant women, and those at increased risk for thyroid disease (Alexander, 2017).

The U.S. Preventive Services Task Force determined that currently, clinicians seem to be treating more persons with thyroid dysfunction, at earlier times after initial diagnosis, and at thyroid-stimulating hormone levels closer to normal, i.e., mU/l between 5.0 and 10.0 as opposed to over 10.0 (U.S. Preventive Services Task Force, 2015).

An evidence review conducted for the U.S. Preventive Services Task Force could not identify any study directly assessing benefits and harms of screening versus no screening for thyroid dysfunction (Rugge, 2015).

A systematic review of 22 studies of treatment of screen-detected hypothyroidism followed 1990 recommendations on screening from the Canadian Task Force on Preventive Health Care, which found fair evidence to exclude testing asymptomatic persons from screening for hyperthyroidism and hypothyroidism, a finding upheld recently (Birtwhistle, 2019; no authors listed, 1990). Randomized controlled trials suggested no benefit of treatment for subclinical hypothyroidism for the large majority of outcomes (Reyes, 2019).

A review of 10,424 abstracts and 707 studies on screening for thyroid cancer, done as a follow up to the U.S. Preventive Services Task Force guideline concluded that no clear evidence exists if population-based or targeted screening can decrease mortality or improve important patient health outcomes. The authors note that universal screening results and treatment of over-diagnosed cancer cases can pose real patient harms (Lin, 2017).

A study from the United Kingdom compared persons with new sub-clinical hypothyroidism treated versus not treated with levothyroxine, who were diagnosed in 2001 and followed until March 2009. Among 3,093 subjects age 40 – 70, the treated group had significantly lower rates of ischemic heart disease events (4.2% versus 6.6%), all-cause mortality (3.4% versus 6.4%), circulatory disease mortality (1.4% versus 2.4%), and cancer mortality (1.2% versus 2.2%). No significant differences were observed in any category for 1634 subjects age 70 or older (Razvi, 2012).

The evidence review for the U.S. Preventive Services Task Force identified four trials, each with between 40 and 100 subjects, evaluating quality of life for those treated with thyroxine versus those not treated/placebo. No

difference was found in between the thyroxine group and placebo in anxiety, depression, sex, worries, motivation, and an extensive list of other criteria (Rugge, 2015).

Nine trials cited by the Task Force included some evidence that thyroid treatment is associated with lower total and low-density lipoprotein cholesterol than placebo or no treatment. Treatment was not associated with beneficial effects on blood pressure, high-density lipoprotein cholesterol, triglyceride levels, or body mass index/weight. Two small, poor-quality trials found no differences between treatment of subclinical hyperthyroidism and no treatment on blood pressure, body mass index, bone mineral density, or lipid levels (Rugge, 2015).

A systematic review/meta-analysis of 50 studies found that persons with alopecia areata had elevated rates of abnormal findings on thyroid function tests, thyroid dysfunction, positive thyroid autoantibodies, and autoimmune thyroid diseases. Authors suggest that clinicians should screen persons with alopecia areata for signs and symptoms (Lee, 2019).

A Cochrane review addressed two randomized controlled trials of 26,408 pregnant women screened for thyroid dysfunction. Authors concluded that while universal screening for thyroid dysfunction in pregnancy increases the number of women with hypothyroidism who can be subsequently treated, no clear impact exists on maternal and infant outcomes (Spencer, 2015).

In a review of screening pregnant women for thyroid dysfunction, five articles showed case-finding screening missed 30% to 55% of cases. Conversely, four studies showed universal screening led to fewer miscarriages and complications during pregnancy. Authors conclude that the review lends increased support for universal screening for thyroid disorders in pregnant women (Jouyandeh, 2015).

## References

On January 18, 2022, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were hyperthyroid, hypothyroid, thyroid, thyroid dysfunction, thyroid screening, hashimotos, myxedema, TSH, T3, T4, Triiodothyronine. We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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## Policy updates

7/2019: initial review date and clinical policy effective date: 9/2019

5/2020: Policy references updated.

4/2021: Policy references updated.

4/2022: Policy references updated and additional current guidelines added.