Regence

NOTE: This policy is not effective until August 1, 2025.

Medical Policy Manual Laboratory, Policy No. 81

Testosterone Testing

Effective: August 1, 2025

Next Review: March 2026
Last Review: March 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Testosterone is a sex steroid hormone involved in many biologic processes, including sexual development and function. Testosterone testing is used to diagnose certain conditions and for monitoring hormone or prostate cancer treatment efficacy. Testing for free and bioavailable testosterone may be used for diagnosing testosterone deficiency when total testosterone does not accurately reflect the amount that is biologically active, due to altered levels of binding proteins.

MEDICAL POLICY CRITERIA

Notes: The services described in this medical policy may not be subject to routine medical necessity review, however, utilization may be subject to audit.

I. Total testosterone testing [84403] may be considered **medically necessary** when any of the following are met:

   A. Testing is for the purpose of diagnosing androgen deficiency or androgen excess in an individual with symptoms or a disorder known to affect testosterone levels (see Policy Guidelines); or

   B. Testing is for the purpose of establishing a baseline or monitoring response in an individual receiving one of the following treatments:

1. Testosterone replacement therapy for androgen deficiency (testing is covered for up to 6 tests per year for the first year, then annually); or
2. Sex steroid hormone treatment for gender dysphoria; or
3. Treatment for prostate cancer.

II. Total testosterone testing [84403] is considered **not medically necessary** when Criterion I. is not met.

III. Annual free testosterone testing [84402] and/or bioavailable testosterone testing [84410] may be considered **medically necessary** when all of the following are met**:**

A. Total serum testosterone levels are low or borderline low (see Policy Guidelines); and

B. The individual has signs or symptoms of testicular hypofunction (see Policy Guidelines).

IV. Free testosterone testing [84402] and bioavailable testosterone testing [84410] is considered **not medically necessary** when Criterion III. is not met, including but not limited to testing in the absence of prior total testosterone testing.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DISORDERS ASSOCIATED WITH ALTERED TESTOSTERONE LEVELS

Some disorders linked to altered testosterone levels include the following (not all inclusive):

- Primary or secondary hypogonadism
- Polycystic ovary syndrome
- Congenital adrenal hyperplasia
- Prostate cancer
- Ovarian cancer
- Adrenal tumors
- Adrenal insufficiency (Addison’s disease)
- Turner syndrome
- Pituitary dysfunction

TOTAL TESTOSTERONE LEVELS

There are no generally recognized age- and gender-specific cutoff points for testosterone levels that have been validated for making clinical predictions. In men with signs and symptoms of testosterone deficiency, testosterone levels are compared to the normal range for healthy young men, with a lower limit of 280 to 300 ng/dL (9.7 to 10.4 nmol/L).

SIGNS AND SYMPTOMS ASSOCIATED WITH TESTICULAR HYPOFUNCTION

These include, but are not limited to:

- Gynecomastia
- Erectile dysfunction

- Infertility
- Loss of bone and muscle mass
- Delayed puberty
- Libido loss
- Fatigue
- Depression

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes, including documentation of symptomology, applicable treatment history, and reason for testing
- Blood draw date
- Diagnosis

CROSS REFERENCES

1. Salivary Hormone Testing for Aging and Menopause, Laboratory, Policy No. 36
2. Screening Laboratory Testing, Laboratory, Policy No. 80

BACKGROUND

TESTOSTERONE

Testosterone is a steroid hormone involved in human development and sexual differentiation. It is required for the development of masculine physiological characteristics. In men, testosterone is generally produced by the testes, while in women it is produced mainly by the ovaries and adrenal glands.

Beyond its role in sexual development, testosterone is involved in promoting bone and muscle development, libido, sperm production, ovarian function, and appears to play a role in mood and cognition as well. Deficiencies in testosterone may be caused by primary or secondary hypogonadism, and testosterone levels naturally decrease in adults with age. Testosterone deficiency in adults may be associated with decreased libido and energy levels, loss of muscle and bone mass, and reduced body hair. Excess testosterone in women can be caused by a variety of conditions including polycystic ovary syndrome, and can lead to reduced fertility, male-pattern baldness, coarse facial hair, weight gain, and depression.

Only a small fraction of the total testosterone circulates as free testosterone (2% to 5%), with the majority bound either loosely to albumin or more tightly to sex hormone-binding globulin (SHBG). More than half of circulating testosterone is typically bound to SHGB, and this fraction is not biologically active, unlike the more loosely bound albumin-testosterone complex. Thus, the bioavailable testosterone is represented by the free and the albumin-bound fractions.

TESTOSTERONE TESTING

There are several types of testosterone testing available, with different indications for use:

Total Testosterone Testing

This test includes both free and bound forms of testosterone, and is the initial test used for diagnosing testosterone deficiency or excess in men or testosterone excess in women.

Free Testosterone Testing

This test measures only the small fraction of circulating testosterone that is not bound to either SHBG or albumin. Free testosterone testing may be useful for diagnosing testosterone deficiency when total testosterone levels are low or borderline low.

Bioavailable Testosterone Testing

Direct tests for bioavailable testosterone measure non-SHBG bound testosterone using a precipitation technique. The bioavailable testosterone can also be calculated based on total testosterone, SHBG, and albumin levels. This type of testing may be useful for diagnosing testosterone deficiency when an individual with signs and symptoms of hypogonadism has normal or borderline low total testosterone and a condition affecting SHBG levels.

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test requires the demonstration of three key components:

- Analytic validity, including reproducibility and precision.
- Clinical validity (i.e., sensitivity, specificity, and positive and negative predictive value) which describes the ability of a test to accurately predict clinical outcomes in appropriate populations of patients.
- Clinical utility is a key aspect of evaluating clinical test performance, and it reflects how the results of a study can be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Research has clearly demonstrated that there is clinical utility for testosterone testing in individuals with signs and symptoms of testosterone deficiency or excess is important for diagnosis and treatment. Additionally, testing may be needed to monitor testosterone supplementation treatment and enzyme inhibitor therapy for prostate cancer. The evidence, rationale, and recommendations for testing in these situations has been published in clinical practice guidelines (see Practice Guideline Summary below) and will not be reviewed here. The focus of the following literature review is on evidence related to the clinical utility of testosterone testing for other indications.

To establish clinical utility, evidence (ideally from randomized controlled trials) is required to demonstrate the following:

1. How test results are used to guide treatment decisions that would not otherwise be made in the absence of testing, and
2. Whether those decisions result in improved primary health outcomes associated with the disease or condition being treated.

Numerous observational studies have been published correlating total, free, or bioavailable testosterone levels with various clinical characteristics, such as hemoglobin and hematocrit levels[1], sleep disorders[2], and incontinence[3] in different populations. However, no studies were identified that evaluated the clinical utility for testing related to these indications.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

In 2019 (reaffirmed in 2024), ACOG published a committee opinion on the screening and management of hyperandrogenic adolescents, which included the following recommendations related to testosterone testing:[4]

- "The diagnosis of hyperandrogenism can be based on clinical symptoms or measurement of serum androgens.
- Monitoring serum androgens is not recommended."

The American College of Obstetricians and Gynecologists (ACOG) published a practice bulletin on PCOS in 2018.[5] For diagnosis, the bulletin recommends testing for hyperandrogenemia with total testosterone and sex-hormone binding globulin or bioavailable and free testosterone. The authors note that "there is no standardized testosterone assay in the United States and the sensitivity and reliability in the female ranges are often poor."

AMERICAN SOCIETY OF REPRODUCTIVE MEDICINE

The American Society of Reproductive Medicine published a committee opinion (2023) on the diagnostic evaluation of sexual dysfunction in the male partner in the setting of infertility, which states that for the detection of erectile dysfunction, a "physical examination should include blood pressure and the calculation of body mass index, as well as an assessment for signs of testosterone deficiency. Morning serum testosterone should be assayed, as should glucose and hemoglobin A1c levels, as well as lipid profile measurements, as indicated.":[6]

AMERICAN UROLOGICAL ASSOCIATION

Guidelines from the American Urological Association (AUA) on the evaluation and management of testosterone deficiency (2018, reaffirmed in 2024) included the following recommendations related to testosterone testing:[7]

- Clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone. (Moderate Recommendation; Evidence Level: Grade B)
- The diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. (Strong Recommendation; Evidence Level: Grade A)
- The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs. (Moderate Recommendation; Evidence Level: Grade B)
- Clinicians should consider measuring total testosterone in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary

dysfunction, and chronic corticosteroid use even in the absence of symptoms or signs associated with testosterone deficiency. (Moderate Recommendation; Evidence Level: Grade B)
- Clinicians should measure an initial follow-up total testosterone level after an appropriate interval to ensure that target testosterone levels have been achieved. (Expert Opinion)
- Testosterone levels should be measured every 6-12 months while on testosterone therapy. (Expert Opinion)

ENDOCRINE SOCIETY

Hypogonadism in Men

In 2018, the Endocrine Society published guidelines on testosterone therapy in men with hypogonadism, which included the following recommendations:[8]

- We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated). (Strong Recommendation; Evidence Quality: Moderate)
- We recommend against routine screening of men in the general population for hypogonadism. (Strong Recommendation; Evidence Quality: Low)

Additionally, the authors included the following technical notes:

- Testosterone concentrations exhibit significant diurnal and day-to-day variations and may be suppressed by food intake or glucose. Therefore, clinicians should measure total testosterone concentrations on two separate mornings when the patient is fasting. Clinicians should use an accurate and reliable method, optimally, an assay that has been certified by an accuracy-based standardization or quality control program [e.g., Centers for Disease Control and Prevention (CDC) Hormone Standardization Program for Testosterone].

- In men who have conditions that alter sex hormone–binding globulin (SHBG), or whose initial total testosterone concentrations are at or near the lower limit of the normal range, clinicians should determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, SHBG, and albumin concentrations. Clinicians should not use direct analog-based free testosterone immunoassays, as they are inaccurate.

- Clinicians should not test men for testosterone deficiency who have or are recovering from an acute illness or are engaged in short-term use of medications (e.g., opioids) that suppress testosterone concentrations.

Functional Hypothalamic Amenorrhea

The Endocrine Society published guidance on functional hypothalamic amenorrhea (FHA) in 2017, which recommends that: “Clinicians should obtain total testosterone and dehydroepiandrosterone sulfate (DHEA-S) levels in patients with clinical hyperandrogenism and 8 am 17-hydroxyprogesterone levels if clinicians suspect late-onset congenital adrenal hyperplasia (CAH).” (Strong Recommendation; Evidence Quality: High)[9]

Gender Dysphoria

Endocrine Society guidelines on endocrine treatment for gender-dysphoric/gender-incongruent persons (2017) include the following"[10]

- Regarding treatment of adolescents: "We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment." (Weak Recommendation; Evidence Quality: Low)
- Regarding hormonal therapy for adults: "We suggest clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender." (Weak Recommendation; Evidence Quality: Low)
- Regarding adverse outcome prevention and long-term care: "We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly." (Weak Recommendation; Evidence Quality: Low)

Polycystic Ovary Syndrome

Guidelines for the diagnosis and treatment of PCOS from the Endocrine Society (2013) suggested that androgen excess (such as elevated total, free, or bioavailable serum testosterone levels), along with polycystic ovaries and ovulatory dysfunction be considered as diagnostic criteria, with any two being sufficient for a PCOS diagnosis.[11]

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The NCCN guidelines for prostate cancer (v.1.2025) state that castrate levels of testosterone should be documented for castration-resistant and castration-sensitive prostate cancer (CRPC, CSPC) if clinically indicated, including if progression occurs on ADT in metastatic CRPC.[12]

SUMMARY

There is research showing that testing for total testosterone levels is important for the diagnosis of disorders associated with testosterone deficiency or excess. This testing may also be used for monitoring hormone or prostate cancer treatment efficacy. Evidence-based clinical practice guidelines have recommended total testosterone testing for a variety of indications, including suspected testosterone deficiency in men when there are specific signs and symptoms, testosterone excess in women, establishing a baseline and monitoring testosterone treatment for gender dysphoria, and for certain individuals with prostate cancer. Therefore, this testing may be considered medically necessary for these indications.

There is not enough research to show that total testosterone testing is necessary for other purposes, including routine testing with more than six tests per year for the initial year of testosterone replacement therapy or more than annually afterward. Therefore, this testing is considered not medically necessary.

Testing for specific subfractions of testosterone, such as free or bioavailable testosterone is generally only useful for diagnosing a testosterone deficiency when there are altered levels of testosterone binding proteins. Therefore, annual testing for either free or bioavailable

testosterone may be considered medically necessary in this situation. Testing for these subfractions is considered not medically necessary for other indications, including but not limited to routine monitoring.

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CODES

Codes	Number	Description
CPT	84402	Testosterone; free
	84403	Testosterone; total
	84410	Testosterone; bioavailable, direct measurement (eg, differential precipitation)
HCPCS	None	

Date of Origin: *March 2025*