

Reimbursement Policy

Testosterone

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I. Policy Description

Testosterone is a naturally occurring lipophilic androgen hormone that is produced by both males and females for various functions. In males, testosterone is produced by the interstitial cells of Leydig in the testis. In females, testosterone is primarily created and disseminated by the ovaries and adrenal glands. Testosterone is required for synthesis of dihydrotestosterone (DHT) as well as estradiol (E2). Sex hormone-binding globulin (SHBG) binds testosterone to aid in transport and intratesticular bioavailability.

Dysregulation in testosterone levels can lead to serious conditions, including hypogonadism and other testosterone excess or deficiency conditions. Additional hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin, play roles in development. As part of the hypothalamic-pituitary-gonadal axis, FSH and LH bind to gonadal receptors to modulate testosterone. During conditions of dyshomeostasis, such as hypogonadism, FSH, LH, and prolactin serum levels can be used as diagnostic tools (Bhasin et al., 2018; Gill-Sharma, 2018).

Terms such as male and female are used when necessary to refer to sex assigned at birth.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

- 1) Measurement of serum total testosterone (see Note 1) **MEETS COVERAGE CRITERIA** in **any** of the following situations:
 - a) For symptoms of androgen deficiency or androgen excess in males:
 - i) For initial screening, two measurements at least 24 hours apart.
 - ii) If the initial screening was normal but symptoms persist, follow-up testing is allowed no sooner than 60 days after the initial screening.
 - b) For the monitoring of treatment response in men taking enzyme inhibitors for prostate cancer.

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- c) For men receiving testosterone replacement therapy (every 2-3 months for the first year after initiation of therapy or after a change in therapeutic dosage; annually thereafter).
 - d) For gender-dysphoric/gender-incongruent persons (baseline, during treatment, and for therapy monitoring).
 - e) For symptomatic females (see Note 2) being evaluated for conditions associated with androgen excess (e.g., polycystic ovary syndrome and functional hypothalamic amenorrhea).
- 2) For males with total testosterone confirmed as low or borderline low **and** who have hypogonadism, gynecomastia, and/or other forms of testicular hypofunction, annual measurement of serum free testosterone, sex hormone-binding globulin (SHBG), and/or albumin **MEETS COVERAGE CRITERIA.**
 - 3) For individuals suspected of having a disorder that is accompanied by increased or decreased SHBG levels (see Notes 3 and 4), measurement of serum free testosterone using a medically accepted algorithm based on total serum testosterone, SHBG, and/or albumin or bioavailable testosterone **MEETS COVERAGE CRITERIA.**
 - 4) Prior to initiating testosterone therapy for males with gynecomastia, once per lifetime serum estradiol measurement **MEETS COVERAGE CRITERIA.**
 - 5) For individuals with ambiguous genitalia, hypospadias, or microphallus, measurement of serum dihydrotestosterone for the diagnosis of 5-alpha reductase deficiency **MEETS COVERAGE CRITERIA.**
 - 6) Measurement of serum free testosterone and/or bioavailable testosterone as a primary test (i.e., in the absence of prior serum total testosterone measurement) **DOES NOT MEET COVERAGE CRITERIA.**
 - 7) For asymptomatic individuals or for individuals with non-specific symptoms, measurement of serum total testosterone, free testosterone, and/or bioavailable testosterone **DOES NOT MEET COVERAGE CRITERIA.**
 - 8) For the identification of androgen deficiency in women, measurement of serum testosterone **DOES NOT MEET COVERAGE CRITERIA.**

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

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- 9) The use of saliva for the measurement of testosterone **DOES NOT MEET COVERAGE CRITERIA.**
- 10) For all other situations not mentioned above, measurement of serum dihydrotestosterone **DOES NOT MEET COVERAGE CRITERIA.**

NOTES:

Note 1: Serum total testosterone sample collection should occur in the early morning, after fasting. Due to considerable variability in serum total testosterone levels, the Centers for Disease Control and Prevention (CDC) developed a standardization program for total testosterone assays (Hormone Standardization [HoSt]/Testosterone). An assay certified by the CDC's HoSt/Testosterone program is standardized to within $\pm 6.4\%$ of the CDC total testosterone reference standard. It is **STRONGLY RECOMMENDED** that serum total testosterone measurement be performed with an assay that has been certified by the CDC HoSt/Testosterone program (Bhasin et al., 2018). A list of CDC-certified assays is available on the HoSt website (CDC, 2023).

Note 2: When measuring serum total testosterone in females, please note that the technology used for measurement must be sensitive enough to detect the low serum total testosterone levels that are normally found in females.

Note 3: Conditions associated with decreased SHBG concentrations according to the 2018 Endocrine Society Guidelines (Bhasin et al., 2018):

- Obesity
- Diabetes mellitus
- Use of glucocorticoids, progestins, and androgenic steroids
- Nephrotic syndrome
- Hypothyroidism
- Acromegaly
- Polymorphisms in the SHBG gene

Note 4: Conditions associated with increased SHBG concentrations according to the 2018 Endocrine Society Guidelines (Bhasin et al., 2018):

- Aging
- HIV disease
- Cirrhosis and hepatitis
- Hyperthyroidism
- Use of some anticonvulsants
- Use of estrogens

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- Polymorphisms in the SHBG gene

III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

IV. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
82040	Albumin; serum, plasma or whole blood
82642	Dihydrotestosterone (DHT)
82670	Estradiol; total
82681	Estradiol; free, direct measurement (eg, equilibrium dialysis)
84270	Sex hormone binding globulin (SHBG)
84402	Testosterone; free
84403	Testosterone; total
84410	Testosterone; bioavailable, direct measurement (eg, differential precipitation)

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Evidence-based Scientific References

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