If a conflict arises between a Clinical Payment and Coding Policy and any plan document under which a member is entitled to Covered Services, the plan document will govern. If a conflict arises between a CPCP and any provider contract pursuant to which a provider participates in and/or provides Covered Services to eligible member(s) and/or plans, the provider contract will govern. “Plan documents” include, but are not limited to, Certificates of Health Care Benefits, benefit booklets, Summary Plan Descriptions, and other coverage documents. Blue Cross and Blue Shield of TX may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. Blue Cross and Blue Shield of TX has full and final discretionary authority for their interpretation and application to the extent provided under any applicable plan documents.

Providers are responsible for submission of accurate documentation of services performed. Providers are expected to submit claims for services rendered using valid code combinations from Health Insurance Portability and Accountability Act approved code sets. Claims should be coded appropriately according to industry standard coding guidelines including, but not limited to: Uniform Billing Editor, American Medical Association, Current Procedural Terminology, CPT® Assistant, Healthcare Common Procedure Coding System, ICD-10 CM and PCS, National Drug Codes, Diagnosis Related Group guidelines, Centers for Medicare and Medicaid Services National Correct Coding Initiative Policy Manual, CCI table edits and other CMS guidelines.

Claims are subject to the code edit protocols for services/procedures billed. Claim submissions are subject to claim review including but not limited to, any terms of benefit coverage, provider contract language, medical policies, clinical payment and coding policies as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

Testosterone

Policy Number: CPCPLAB009

Version 1.0

Approval Date: Sept. 13, 2024

Plan Effective Date: Jan. 1, 2025 (Blue Cross and Blue Shield of Texas Only)

Description

The plan has implemented certain lab management reimbursement criteria. Not all requirements apply to each product. Providers are urged to review Plan documents for eligible coverage for services rendered.

Reimbursement Information:

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

1. Measurement of serum total testosterone (See **Note 1**) **may be reimbursable** 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.
    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 measurements of serum free testosterone, sex hormone-binding globulin (SHBG), and/or albumin **may be reimbursable**.

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 **may be reimbursable.**

4. Prior to initiating testosterone therapy for males with gynecomastia, once per lifetime serum estradiol measurement **may be reimbursable.**

5. For individuals with ambiguous genitalia, hypospadias, or microphallus, measurement of serum dihydrotestosterone for the diagnosis of 5-alpha reductase deficiency **may be reimbursable.**

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 **is not reimbursable.**

7. For asymptomatic individuals or for individuals with non-specific symptoms, measurement of serum total testosterone, free testosterone, and/or bioavailable testosterone **is not reimbursable.**

8. For the identification of androgen deficiency in women, measurement of serum testosterone **is not reimbursable.**

9. The use of saliva for the measurement of testosterone **is not reimbursable.**

10. For all other situations not mentioned above, measurement of serum dihydrotestosterone **is not reimbursable.**

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 ±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, 2022).

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 estrogen
- Polymorphisms in the SHBG gene

Procedure Codes

The following is not an all-encompassing code list. The inclusion of a code does not guarantee it is a covered service or eligible for reimbursement.

Codes
82040, 82642, 82670, 82681, 84270, 84402, 84403, 84410

References:

A. Salonia (Chair), C. B., J. Carvalho, G. Corona, T.H. Jones, A. Kadioglu, I. Martinez-Salamanca, S. Minhas (Vice-Chair), E.C. Serefoğlu, P. Verze. (2022). European Association of Urology: Sexual and Reproductive Health. https://uroweb.org/guideline/sexual-and-reproductive-health/

AAP. (2017, 10/02/2017). *Avoid ordering LH and FSH and either estradiol or testosterone for children with pubic hair and/or body odor but no other signs of puberty*. ABIM Foundation. Retrieved 10/19/2018 from http://www.choosingwisely.org/clinician-lists/aap-soen-testing-children-pubic-hair-no-other-signs-puberty/

ACOG. (2018a). ACOG Committee Opinion No. 728: Müllerian Agenesis: Diagnosis, Management, And Treatment. *Obstet Gynecol*, *131*(1), e35-e42. https://doi.org/10.1097/aog.0000000000002458

ACOG. (2018b). ACOG Practice Bulletin No. 194: Polycystic Ovary Syndrome. *Obstet Gynecol*, *131*(6), e157-e171. https://doi.org/10.1097/aog.0000000000002656

ACOG. (2019). Screening and Management of the Hyperandrogenic Adolescent: ACOG Committee Opinion, Number 789. *Obstet Gynecol*, *134*(4), e106-e114. https://doi.org/10.1097/aog.0000000000003475

Andersson, C. R., Bergquist, J., Theodorsson, E., & Strom, J. O. (2017). Comparisons between commercial salivary testosterone enzyme-linked immunosorbent assay kits. *Scand J Clin Lab Invest*, *77*(8), 582-586.

https://doi.org/10.1080/00365513.2017.1339231

Bhasin, S., Brito, J. P., Cunningham, G. R., Hayes, F. J., Hodis, H. N., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., Wu, F. C., & Yialamas, M. A. (2018). Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, *103*(5), 1715-1744. https://doi.org/10.1210/jc.2018-00229

Burger, H. G. (2002). Androgen production in women. *Fertil Steril*, *77 Suppl 4*, S3-5. https://doi.org/10.1016/s0015-0282(02)02985-0

Carnegie, C. (2004). Diagnosis of hypogonadism: clinical assessments and laboratory tests. *Rev Urol*, *6 Suppl 6*(Suppl 6), S3-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1472884/

Cauley, J. A., Ellenberg, S. S., Schwartz, A. V., Ensrud, K. E., Keaveny, T. M., & Snyder, P. J. (2021). Effect of testosterone treatment on the trabecular bone score in older men with low serum testosterone. Osteoporos Int, 32(11), 2371-2375. https://doi.org/10.1007/s00198-021-06022-1

CDC. (2012). *Total Testosterone*. Centers for Disease Control and Prevention. Retrieved 10/23/2018 from https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/tst_g_met.pdf

CDC. (2022, 07/01/2022). *HoSt/VDSCP: Certified Participants*. Centers for Disease Control and Prevention. Retrieved 10/21/2022 from https://www.cdc.gov/labstandards/hs_certified_participants.html

Corona, G., Goulis, D. G., Huhtaniemi, I., Zitzmann, M., Toppari, J., Forti, G., Vanderschueren, D., & Wu, F. C. (2020). European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males. *Andrology*, *8*(5), 970-987. https://doi.org/10.1111/andr.12770

Corona, G., Rastrelli, G., Di Pasquale, G., Sforza, A., Mannucci, E., & Maggi, M. (2018). Endogenous Testosterone Levels and Cardiovascular Risk: Meta-Analysis of Observational Studies. *J Sex Med*, *15*(9), 1260-1271. https://doi.org/10.1016/j.jsxm.2018.06.012

Gill-Sharma, M. K. (2018). Testosterone Retention Mechanism in Sertoli Cells: A Biochemical Perspective. *Open Biochem J*, *12*, 103-112. https://doi.org/10.2174/1874091x01812010103

Goldman, A. L., Bhasin, S., Wu, F. C. W., Krishna, M., Matsumoto, A. M., & Jasuja, R. (2017). A Reappraisal of Testosterone's Binding in Circulation: Physiological and Clinical Implications. *Endocr Rev*, *38*(4), 302-324. https://doi.org/10.1210/er.2017-00025

Gordon, C. M., Ackerman, K. E., Berga, S. L., Kaplan, J. R., Mastorakos, G., Misra, M., Murad, M. H., Santoro, N. F., & Warren, M. P. (2017). Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, *102*(5), 1413-1439. https://doi.org/10.1210/jc.2017-00131

Hammond, G. L., & Bocchinfuso, W. P. (1995). Sex hormone-binding globulin/androgen-binding protein: steroid-binding and dimerization domains. *J Steroid Biochem Mol Biol*, *53*(1-6), 543-552. https://doi.org/10.1016/0960-0760(95)00110-l

Hassanabad, M. F., & Fatehi, M. (2018). Androgen Therapy in Male Patients Suffering from Type 2 Diabetes: A Review of Benefits and Risks. *Curr Diabetes Rev*. https://doi.org/10.2174/1573399814666180731125724

Heidenreich, A., Bastian, P. J., Bellmunt, J., Bolla, M., Joniau, S., van der Kwast, T., Mason, M., Matveev, V., Wiegel, T., Zattoni, F., & Mottet, N. (2014). EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*, *65*(2), 467-479. https://doi.org/10.1016/j.eururo.2013.11.002

Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., Rosenthal, S. M., Safer, J. D., Tangpricha, V., & T'Sjoen, G. G. (2017). Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, *102*(11), 3869-3903. https://doi.org/10.1210/jc.2017-01658

Kanakis, G. A., Nordkap, L., Bang, A. K., Calogero, A. E., Bartfai, G., Corona, G., Forti, G., Toppari, J., Goulis, D. G., & Jorgensen, N. (2019). EAA clinical practice guidelines-gynecomastia evaluation and management. *Andrology*, *7*(6), 778-793. https://doi.org/10.1111/andr.12636

Khashchenko, E., Uvarova, E., Vysokikh, M., Ivanets, T., Krechetova, L., Tarasova, N., Sukhanova, I., Mamedova, F., Borovikov, P., Balashov, I., & Sukhikh, G. (2020). The Relevant Hormonal Levels and Diagnostic Features of Polycystic Ovary Syndrome in Adolescents. *J Clin Med*, *9*(6). https://doi.org/10.3390/jcm9061831

Kinter, K. J., & Anekar, A. A. (2020). *Biochemistry, Dihydrotestosterone*. StatPearls Publishing, Treasure Island (FL). https://www.ncbi.nlm.nih.gov/books/NBK557634

Legro, R. S., Arslanian, S. A., Ehrmann, D. A., Hoeger, K. M., Murad, M. H., Pasquali, R., & Welt, C. K. (2013). Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, *98*(12), 4565-4592. https://doi.org/10.1210/jc.2013-2350

Longcope, C. (1986). Adrenal and gonadal androgen secretion in normal females.

Clin Endocrinol Metab, *15*(2), 213-228. https://doi.org/10.1016/s0300-595x(86)80021-4
Lynch, K. L. (2016). CLSI C62-A: A New Standard for Clinical Mass Spectrometry. *Clinical Chemistry*, *62*(1), 24-29. https://doi.org/10.1373/clinchem.2015.238626
Meldrum, D. R., Gambone, J. C., Morris, M. A., Esposito, K., Giugliano, D., & Ignarro, L. J. (2012). Lifestyle and metabolic approaches to maximizing erectile and vascular health. *Int J Impot Res*, *24*(2), 61-68. https://doi.org/10.1038/ijir.2011.51

Mezzullo, M., Fazzini, A., Gambineri, A., Di Dalmazi, G., Mazza, R., Pelusi, C., Vicennati, V., Pasquali, R., Pagotto, U., & Fanelli, F. (2017). Parallel diurnal fluctuation of testosterone, androstenedione, dehydroepiandrosterone and 17OHprogesterone as assessed in serum and saliva: validation of a novel liquid chromatography-tandem mass spectrometry method for salivary steroid profiling. *Clin Chem Lab Med*, *55*(9), 1315-1323. https://doi.org/10.1515/cclm-2016-0805

Mohammed, M., Al-Habori, M., Abdullateef, A., & Saif-Ali, R. (2018). Impact of Metabolic Syndrome Factors on Testosterone and SHBG in Type 2 Diabetes Mellitus and Metabolic Syndrome. *J Diabetes Res*, *2018*, 4926789. https://doi.org/10.1155/2018/4926789

Molina-Vega, M., Munoz-Garach, A., Damas-Fuentes, M., Fernandez-Garcia, J. C., & Tinahones, F. J. (2018). Secondary male hypogonadism: A prevalent but overlooked comorbidity of obesity. *Asian J Androl*. https://doi.org/10.4103/aja.aja_44_18

Mulhall, J. P., Trost, L. W., Brannigan, R. E., Kurtz, E. G., Redmon, J. B., Chiles, K. A., Lightner, D. J., Miner, M. M., Murad, M. H., Nelson, C. J., Platz, E. A., Ramanathan, L. V., & Lewis, R. W. (2018, 2018). *Evaluation and Management of Testosterone Deficiency*. American Urological Association. Retrieved 10/22/2018 from https://www.auanet.org/guidelines-and-quality/guidelines/testosterone-deficiency-guideline

Nassar, G. N., & Leslie, S. W. (2023). Physiology, Testosterone. In *StatPearls*. StatPearls Publishing LLC. https://www.ncbi.nlm.nih.gov/books/NBK526128/

NCCN. (2023a). *Neuroendocrine and Adrenal Tumors Version 1. 2023*. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

NCCN. (2023b). *Prostate Cancer, Version 4.2023*. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Rochira, V., Antonio, L., & Vanderschueren, D. (2018). EAA clinical guideline on management of bone health in the andrological outpatient clinic. *Andrology*, *6*(2), 272-285. https://doi.org/10.1111/andr.12470

Sachdev, S., Cucchiara, A. J., & Snyder, P. J. (2020). Prostate Specific Antigen Concentrations in Response to Testosterone Treatment of Severely Hypogonadal Men. *Journal of the Endocrine Society*. https://doi.org/10.1210/jendso/bvaa141

Sartorius, G., Ly, L. P., Sikaris, K., McLachlan, R., & Handelsman, D. J. (2009). Predictive accuracy and sources of variability in calculated free testosterone estimates. *Ann Clin Biochem*, *46*(Pt 2), 137-143. https://doi.org/10.1258/acb.2008.008171

Schulster, M., Bernie, A. M., & Ramasamy, R. (2016). The role of estradiol in male reproductive function. *Asian J Androl*, *18*(3), 435-440. https://doi.org/10.4103/1008-682x.173932

Shukla, A., Sharda, B., Bhardwaj, S., Kailash, U., Kalani, R., Satyanarayana, L., & Shrivastava, A. (2018). Association Between Serum Testosterone and Serum PSA Among Men With and Without Partial Androgen Deficiency. *Indian Journal of Clinical Biochemistry*, 1-5. https://link.springer.com/article/10.1007/s12291-018-0785-3

Skinner, R., Mulder, R. L., Kremer, L. C., Hudson, M. M., Constine, L. S., Bardi, E., Boekhout, A., Borgmann-Staudt, A., Brown, M. C., Cohn, R., Dirksen, U., Giwercman, A., Ishiguro, H., Jahnukainen, K., Kenney, L. B., Loonen, J. J., Meacham, L., Neggers, S., Nussey, S.,. . Green, D. M. (2017). Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Lancet Oncol*, *18*(2), e75-e90. https://doi.org/10.1016/s1470-2045(17)30026-8

Snyder, P. J. (2020). *Clinical features and diagnosis of male hypogonadism*. Wolters Kluwer. https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-male-hypogonadism

Stanworth, R. D., & Jones, T. H. (2008). Testosterone for the aging male; current evidence and recommended practice. *Clin Interv Aging*, *3*(1), 25-44. https://doi.org/10.2147/cia.s190

Star-Weinstock, M., & Dey, S. (2019). Development of a CDC-certified total testosterone assay for adult and pediatric samples using LC–MS/MS. *Clinical Mass Spectrometry*, *13*, 27-35. https://www.sciencedirect.com/science/article/pii/S2376999819300017

Sun, G., Xue, J., Li, L., Li, X., Cui, Y., Qiao, B., Wei, D., & Li, H. (2020). Quantitative determination of human serum testosterone via isotope dilution ultra-performance liquid chromatography tandem mass spectrometry. *Mol Med Rep*, *22*(2), 1576-1582. https://doi.org/10.3892/mmr.2020.11235

Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., Piltonen, T., & Norman, R. J. (2018). Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod*, *33*(9), 1602-1618. https://doi.org/10.1093/humrep/dey256

Travison, T. G., Vesper, H. W., Orwoll, E., Wu, F., Kaufman, J. M., Wang, Y., Lapauw, B., Fiers, T., Matsumoto, A. M., & Bhasin, S. (2017). Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe. *J Clin Endocrinol Metab*, *102*(4), 1161-1173. https://doi.org/10.1210/jc.2016-2935

van der Veen, A., van Faassen, M., de Jong, W. H. A., van Beek, A. P., Dijck-Brouwer, D. A. J., & Kema, I. P. (2019). Development and validation of a LC-MS/MS method for the establishment of reference intervals and biological variation for five plasma steroid hormones. *Clin Biochem*, *68*, 15-23. https://doi.org/10.1016/j.clinbiochem.2019.03.013

Vermeulen, A., Verdonck, L., & Kaufman, J. M. (1999). A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab*, *84*(10), 3666-3672. https://doi.org/10.1210/jcem.84.10.6079

Vesper, H., Botelho, J., & Wang, Y. (2014). Challenges and improvements in testosterone and estradiol testing [Invited Review]. *Asian Journal of Andrology*, *16*(2), 178-184. https://doi.org/10.4103/1008-682x.122338

Viana, A., Jr., Daflon, A. C., Couto, A., Neves, D., de Araujo-Melo, M. H., & Capasso, R. (2017). Nocturnal Hypoxemia is Associated With Low Testosterone Levels in Overweight Males and Older Men With Normal Weight. *J Clin Sleep Med*, *13*(12), 1395-1401. https://doi.org/10.5664/jcsm.6832

Wang, A., Arver, S., Flanagan, J., Gyberg, V., Nasman, P., Ritsinger, V., & Mellbin, L. G. (2018). Dynamics of testosterone levels in patients with newly detected glucose abnormalities and acute myocardial infarction. *Diab Vasc Dis Res*, 1479164118802543. https://doi.org/10.1177/1479164118802543

Welker, K. M., Lassetter, B., Brandes, C. M., Prasad, S., Koop, D. R., & Mehta, P. H. (2016). A comparison of salivary testosterone measurement using immunoassays and tandem mass spectrometry. *Psychoneuroendocrinology*, *71*, 180-188. https://doi.org/10.1016/j.psyneuen.2016.05.022

Yun, Y.-M., Botelho, J. C., Chandler, D. W., Katayev, A., Roberts, W. L., Stanczyk, F. Z., Vesper, H. W., Nakamoto, J. M., Garibaldi, L., Clarke, N. J., & Fitzgerald, R. L. (2012). Performance Criteria for Testosterone Measurements Based on Biological Variation in Adult Males: Recommendations from the Partnership for the Accurate Testing of Hormones. *Clinical Chemistry*, *58*(12), 1703-1710. https://doi.org/10.1373/clinchem.2012.186569

Zakharov, M. N., Bhasin, S., Travison, T. G., Xue, R., Ulloor, J., Vasan, R. S., Carter, E., Wu, F., & Jasuja, R. (2015). A multi-step, dynamic allosteric model of testosterone's binding to sex hormone binding globulin. *Mol Cell Endocrinol*, *399*, 190-200.

https://doi.org/10.1016/j.mce.2014.09.001

Zitzmann, M., Nieschlag, E., Traish, A., & Kliesch, S. (2019). Testosterone Treatment in Men with Classical vs. Functional Hypogonadism: A 9-Year Registry. *Journal of the Endocrine Society*, *3*. https://doi.org/10.1210/js.2019-SUN-222

Policy Update History:

Approval Date	Effective Date; Summary of Changes
09/13/2024	01/01/2025: New policy.