# Hormone Replacement using Subcutaneous Pellet Implantation



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## DESCRIPTION

*Note: This policy is specifically related to subcutaneously implanted hormone pellets in the office setting. This policy does not apply to those undergoing treatments for gender transition.*

### Testosterone and Testosterone Levels

Testosterone is produced in genotypic males, primarily by the testes, in response to stimuli from the hypothalamic and pituitary glands. Low testosterone is caused by deficient production of the hormone and is also known as androgen deficiency. Primary androgen deficiency results from failure of testosterone production at the testicular level in the presence of normal hypothalamic and pituitary function. Secondary androgen deficiency results from failure of the pituitary gland to produce androgen-stimulating hormones (luteinizing hormone, follicle-stimulating hormone). It can be caused by dysfunction at the hypothalamic or pituitary level.

Testosterone replacement therapy is the primary treatment for androgen deficiency in men. Testosterone replacement is intended to counter the adverse effects of low testosterone levels with clinical signs and symptoms of hypogonadism. A variety of testosterone preparations are available for clinical use.

**Adverse Events of Testosterone Therapy**
There is a long list of potential adverse effects that could occur with testosterone replacement, to include but not limited to:

- Acne
- Adverse changes in lipid profile
- Cardiovascular events
- Erythrocytosis and increases in hematocrit
- Gynecomastia
- Liver toxicity
- Prostate-related events, including development or worsening of prostate cancer, prostatic hypertrophy, increases in PSA levels, and symptoms of prostatism
- Precipitation or worsening of sleep apnea
- Suppression of spermatogenesis
- Worsening of genotypic XY pattern baldness

**Hypogonadism**
Hypogonadism is the clinical syndrome associated with androgen deficiency. The signs and symptoms of hypogonadism depend on the age of onset. In prepubertal genotypic males, the hallmark of androgen deficiency is the failure to develop secondary genotypic XY individuals sex characteristics. In adults, the signs and symptoms are nonspecific, with the most specific symptoms related to sexual functioning such as decreased libido and erectile dysfunction. Symptoms are dependent on age, the severity of androgen deficiency, duration of androgen deficiency, sensitivity to androgen, and comorbid illness. Symptoms and signs other than sexual dysfunction include loss of body hair, hot flashes or sweats, decreased energy, depression, sleep disturbance, reduced muscle mass, and strength, and/or increased body fat. All can occur in the absence of androgen deficiency and, therefore, the diagnosis of hypogonadism can be challenging. A 2014 systematic review by Zarotsky et al (2014) reported on risk factors, comorbidities, and consequences of genotypical male hypogonadism and identified multiple comorbid conditions consistently risk factors for hypogonadism, including advanced age, obesity, metabolic syndrome, and poor general health status. Multiple other conditions, including diabetes, coronary heart disease, hypertension, stroke, and peripheral artery disease, correlated with the presence of hypogonadism, although these were not identified as risk factors.

Testosterone levels decrease with age, beginning in the fourth or fifth decade of a person's life, and this decrease is sometimes referred to as genotypical male "andropause." In the European Male Aging Study of 3220 men, there was a decline in serum testosterone levels of 0.4% per year between the ages of 40 and 70. Because this decline is gradual and modest, the clinical impact is uncertain. While there are also

parallel decreases in androgen-dependent factors with age, such as sexual function, lean body mass, and bone mineral density, the degree to which these changes are due to decreasing testosterone has not been determined with certainty.

Because of the decline in testosterone levels with age, more elderly genotypic XY individuals will have lower levels than younger men. Using a cutoff of 325 ng/dL as the lower limit of normal testosterone levels, Travison et al (2007) estimated based on a prospective cohort of 890 men that the rate of low testosterone is 20% for men in their 60s; 30% for men in their 70s; and 50% for men in their 80s. In this study, other factors were associated with decreased testosterone, such as obesity and severe emotional stress.

A much lower percentage of men have a combination of low testosterone levels and definite symptoms of hypogonadism. In the European Male Aging Study, this was estimated to be present in 2.3% of men when using a cutoff of at least 3 symptoms potentially related to androgen deficiency.

Another factor that makes the diagnosis of hypogonadism challenging is the measurement of testosterone levels. Testosterone levels fluctuate substantially due to various factors. There is a diurnal variation, which is more pronounced in younger men, with peak levels occurring in the early morning. This makes the timing of measurement important and requires repeated measurement before making a determination that testosterone is consistently low. Also, there is a wide range of levels seen in healthy men and assigning the proper age-appropriate cutoff is controversial. Some men exhibit clear symptoms of hypogonadism with testosterone levels that are in the low-normal range, while other men with low levels do not experience any symptoms.

More specific symptoms of hypogonadism, as classified by the Endocrine Society, include the following):

- Incomplete or delayed sexual development
- Decreased libido
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of axillar and/or pubic body hair
- Very small (<5 mL) or shrinking testes
- Height loss due to vertebral fractures, low trauma fractures, low bone density
- Hot flushes, sweats

The role of testosterone therapy in men with sexual dysfunction with low, borderline normal, and normal testosterone levels is not well defined.

**Androgen Deficiency and Chronic Steroid Treatment**

Individuals treated with chronic steroid therapy have lower levels of testosterone compared with age-matched patients not on steroids. This effect of steroids is thought to suppress the hypothalamic-pituitary axis as well as testosterone production in the testes.

This hormonal suppression contributes to the increase in abdominal fat and a decrease in BMD seen in patients treated chronically with steroids.

**Androgen Deficiency and HIV Infection**
There is a high prevalence of androgen deficiency in patients with HIV infection who are on antiviral treatment, with up to 25% of this population having low testosterone levels. Men with low levels of testosterone have worse outcomes of HIV disease, including faster disease progression, greater loss of muscle mass, and larger declines in physical functioning.

**Diagnosis of Androgen Deficiency**
An established diagnosis of hypogonadism with androgen deficiency includes appropriate evaluation and diagnostic workup of a genotypical male who presents with symptoms of hypogonadism. Clinical practice guidelines recommend measuring serum testosterone only in men with consistent clinical manifestations of hypogonadism. Screening in asymptomatic populations is not recommended. Measurement of serum total testosterone is initially used; serum-free testosterone levels can be measured when total testosterone is in the low-normal range, and alterations of serum hormone-binding globulin are suspected. Once a persistently low testosterone level has been established, diagnostic testing of the hypothalamic-pituitary axis should be performed to distinguish primary hypogonadism from secondary hypogonadism. When secondary hypogonadism is identified, the underlying etiology should be identified, and any reversible causes treated appropriately before consideration of testosterone replacement.

Genotypical males on chronic steroid treatment would be receiving ongoing treatment for a chronic condition as opposed to episodic treatment for an acute condition or acute flare of a chronic condition. The length of acute episodic steroid treatment may vary from several days to several months, but, in most cases, will be less than 4 to 6 weeks. Persistently low testosterone levels refer to serum levels below the lower limit of normal on at least 2 occasions when measured in the early morning (>8:00 A.M.). The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society has recommended a lower limit for normal levels of 300 ng/dL for total testosterone. Joint guidelines from several European and American specialty societies have recommended that replacement therapy be considered at serum total testosterone levels less than 350 ng/dL.

**Menopause**
Menopause is a normal, natural event that occurs with aging. The ovaries progressively fail to produce estrogen and other hormones. Menopause marks the permanent end of fertility. Many physical changes occur during the transition from the reproductive years through menopause and beyond. Most of these changes are normal consequences of both menopause and aging. Each individual experiences menopause in a unique way. For many individuals, menopause is asymptomatic and associated with little disruption of normal life and well-being. However, some individuals experience severe symptoms that adversely affect their quality of life.

There is a long list of physical changes that may occur during this time, which may be related to menopause or aging – or both. Some of these are changes in menstrual periods, hot flashes, sleep disturbances, night sweats, vaginal dryness and decreased sex drive. Several prescription drugs are available to help relieve menopause-related symptoms. Hormone therapy (HT) is the most effective intervention for management of these quality-of-life issues. HT may be defined as estrogen therapy alone or a combination of estrogen and a progestational agent in individuals with a uterus. The addition of a progestational agent is to protect the uterus from estrogen stimulation. Endometrial cancer has been shown to be increased with the use of unopposed estrogen.
In addition to falling estrogen levels, the body's production of another hormone, androgen, declines with age possibly contributing to decreased sexual desire. The ovaries and adrenal glands secrete androgen, primarily as testosterone. Implantation of pellets containing, estrogen, or testosterone in combination with estrogen or estradiol may be custom compounded by pharmacists according to physician specifications for the management of the individual's menopause-related symptoms.

While implantable estradiol pellets have been suggested as treatment for symptoms of menopause, there are **no** United States Food and Drug Administration (FDA)-approved, commercially available formulations of implantable estradiol pellets available in the United States. These formulations of estradiol have been shown to produce unpredictable and fluctuating serum concentrations of estrogen. The FDA's Fertility and Maternal Health Drugs Advisory Committee unanimously agreed to terminate compassionate investigative new drug (IND) programs for estrogen pellets as a last-resort treatment of menopausal disorder. The Committee noted "the risk of bleeding and infection, the lack of information on release rates, difficulty in reversibility of the drug, increased feasibility of over-dosage of the drug, and increased risk of non-compliance with safety measures [such as] the addition of progestin."

**Administration**
A depot formulation is a subcutaneous hormone pellet. The individual pellets are smaller than a grain of rice and are placed subcutaneously in the buttocks, abdominal wall, or thigh under local anesthesia in a physician's office. They provide a slow continuous release of hormone into the bloodstream. They are replaced every 3 to 6 months. Limitations include the need for minor surgical procedures, and local reactions at the implantation site (e.g., infections, fibrosis).

The following PICO was used to select literature to inform this review.

**Populations**
The relevant populations of interest are individuals with one of the following:

- Androgen deficiency with one of the following:
  - HIV infection
  - Chronic steroid treatment
  - Clinical symptoms of hypogonadism

    - Type 2 diabetes
- Older genotypic XY individuals with low testosterone levels without definite hypogonadism
- Testosterone for pain management in genotypical XX individuals

**Interventions**
The therapy being considered is testosterone replacement therapy. Testosterone replacement therapy is the primary treatment for androgen deficiency in genotypical males. Testosterone replacement is intended to counter the adverse effects of low testosterone levels. Estrogen is also considered part of hormone replacement therapy.

There are numerous U.S. Food and Drug Administration-approved testosterone formulations available for replacement therapy. For the purpose of this medical policy subcutaneous pellets are the only form discussed.

- Subcutaneous Pellets - subcutaneous testosterone pellets are also a depot formulation. The pellets are placed in the buttocks, abdominal wall, or thigh under local anesthesia. They are replaced every 3 to 6 months. Limitations include the need for minor surgical procedures, and local reactions at the implantation site (e.g., infections, fibrosis).

Testosterone and estrogen replacement therapy is provided by endocrinologists and primary care providers in an outpatient clinical setting.

**Comparators**
Comparators of interest include no testosterone replacement.

**Outcomes**
The general outcomes of interest are overall survival (OS), symptoms, morbid events, functional outcomes, and quality of life.

**Androgen Deficiency and Clinical Symptoms of Hypogonadism**
A large number of systematic reviews that assess only RCTs or RCTs and non-RCTs have been published over the last 2 decades and reported on outcomes such as sexual function, body composition, and bone mineral density (BMD) while individual RCTs have evaluated the impact of testosterone on depression and cognition. These are not detailed here because they are outdated and/or include results of non-RCTs. A more recent systematic review that only included data from RCTs with low bias is discussed next.

(2014-2018) The National Institutes of Health, sponsored 7 double-blind, placebo-controlled randomized trials that evaluated whether testosterone treatment of elderly men with low serum testosterone concentrations and symptoms and objective evidence of impaired mobility and/or diminished libido and/or reduced vitality would be efficacious in the following:

- improving mobility (Physical Function Trial)

- sexual function (Sexual Function Trial)
- fatigue (Vitality Trial)
- cognitive function (Cognitive Function Trial)
- hemoglobin (Anemia Trial)
- bone density (Bone Trial)
- coronary artery plaque volume (Cardiovascular Trial).

The major consideration in participant selection in these trials was a requirement of serum testosterone low enough to ensure that the men were unequivocally testosterone deficient, but not so low as to preclude sufficient enrollment or eventual generalizability of the results. Men were randomized to 12 months of testosterone gel (1%) or to placebo gel. General eligibility criteria for all trials age 65 years or older with serum testosterone levels averaging less than 275 ng/dL. Exclusion criteria were a history of prostate cancer, at high risk of prostate cancer, International Prostate Symptom Score (IPSS) greater than 19, a condition known to cause hypogonadism, or at high cardiovascular risk. There were also trial-specific eligibility criteria. The Sexual Function Trial required decreased libido and a partner willing to have intercourse twice a month. The Physical Function Trial required difficulty walking or climbing stairs and gait speed of less than 1.2 m/s on the 6-minute walk test. The Vitality Trial required low vitality (self-report and indicated by the score on a validated test). Briefly the conclusions noted, testosterone treatment resulted in substantial benefit for sexual function, anemia, and bone density outcomes but had a small impact on physical function and vitality and no effect on cognition. Although testosterone treatment was associated with an increase in coronary artery noncalcified plaque volume, the number of cardiovascular or prostate adverse events were comparable with the placebo arm. The major limitation of these trials is that the results apply only to men ages 65 years and older with confirmed testosterone concentrations less than 275 ng/dL and durability of treatment effect beyond a year has not been demonstrated.

(2018) The Endocrine Society commissioned a systematic review and meta-analysis, conducted by Ponce et al., to determine whether testosterone replacement therapy (1) improves sexual function, physical function, fatigue, mood, cognition, anemia, and BMD in men with hypogonadism and (2) is associated with an increased risk of lower urinary tract symptoms and erythrocytosis in men with hypogonadism.
The systematic review evaluated only placebo-controlled randomized trials (4 RCTs; N=1779 patients) that assigned men with symptomatic hypogonadism with total testosterone level less than 300 ng/dL at the screening for at least 12 weeks compared with placebo in adult men. Results reported that testosterone replacement therapy was associated with a small but statistically significant improvement in libido, erectile function, sexual activity, and sexual satisfaction compared with placebo but no differences in energy levels or mood. Compared with placebo, testosterone treatment was associated with a significantly higher frequency of erythrocytosis but there was no significant difference in the change in lower urinary tract symptoms. Strengths of this review were the inclusion of only RCTs that were low-risk of bias, participants who met criteria for the diagnosis of hypogonadism (testosterone level ≤300 ng/dL, and presence of ≥1 symptoms or signs of hypogonadism), and reported outcomes were deemed clinically relevant and important to patients and ascertained using validated instruments.

Limitations included the heterogeneity of instruments used to ascertain outcomes across trials, hypogonadism of multiple etiologies, and lack of individual patient data meta-analysis to ascertain the relation between symptoms improvement and testosterone levels. Further, none of the trials selected in the systematic review were long enough or large enough to have sufficient statistical power to ascertain safety outcomes (prostate cancer, cardiovascular events, bone fractures).

**Section Summary: Androgen Deficiency and Clinical Symptoms of Hypogonadism**
For men with low testosterone levels and sexual dysfunction, evidence from RCTs and meta-analyses has demonstrated a beneficial effect on increased libido. Other sexual symptoms (eg, erectile dysfunction) are also likely to be improved but the evidence is less strong. For non-sexual symptoms, there is evidence that lean body mass increased, body fat decreased, and BMD increased with testosterone therapy. However, the impact of these changes on functional status and fractures is less clear. For outcomes such as decreased energy, depression, quality of life, and cognition, the evidence is limited and inconsistent in reporting the benefits of replacement therapy.

**Androgen Deficiency and Chronic Steroid Treatment**
(2006) Bhasin et al. completed the systematic review which identified two placebo-controlled randomized trials of testosterone replacement in patients on chronic steroid treatment for asthma or chronic obstructive pulmonary disease. The trials were limited by small sample sizes and short duration of follow-ups. Pooled analysis of the two trials showed a significant increase in lean body mass of 2.3 kg (95% CI, 2.0 to 3.6 kg) and a significant decrease in fat mass of 3.1 kg (95% CI, -2.8 to -3.5 kg). There was also a significant improvement in lumbar bone density of 4% (95% CI, 2% to 7%), although there was no significant improvement in BMD of the femoral neck.

**Section Summary: Androgen Deficiency and Chronic Steroid Treatment**
A meta-analysis of 2 RCTs in men receiving chronic steroid treatment found a significant increase in lean body mass and a significant decrease in fat mass in patients receiving testosterone therapy vs placebo. Thus, the evidence would suggest that testosterone is likely to ameliorate adverse events related to chronic steroid use on these parameters.

**Androgen Deficiency and HIV Infection**
(2006) Bhasin et al. completed a systematic review of testosterone replacement in HIV-infected men with weight loss was performed. They identified 8 trials of testosterone replacement in HIV-infected patients with weight loss. The trials were of variable quality and heterogeneous in their methodologies. A combined analysis of changes in body weight, fat-free mass, and lean body mass was performed. There was an estimated increase of 1.1 kg in body weight (95% CI, 0.2 to 2.0 kg), 1.4 kg in fat-free mass (95% CI, 0.7 to 2.1 kg), and 1.3 kg in lean body mass (95% CI, 0.4 to 2.2 kg) associated with testosterone replacement. Reviewers also assessed the outcomes of muscle strength and depression. Three trials reported on changes in muscle strength, with 2 of 3 reporting significant improvements with testosterone therapy. Four trials reported on changes in depression, with combined analysis showing a modest improvement in depression scores

for testosterone-treated patients. There were no significant changes in parameters of HIV infection (e.g., T lymphocyte or viral load for patients treated with testosterone).

**Section Summary: Androgen Deficiency and HIV Infection**
RCTs of patients with HIV infection and weight loss, included in a systematic review, found that testosterone replacement was associated with an increase in body weight and lean body mass and a decrease in body fat. Findings from these trials would suggest that testosterone replacement is likely to ameliorate the weight loss associated with HIV infection.

**Androgen Deficiency and Type 2 Diabetes**
(2021) Wittert et al. reported on an RCT, included in the meta-analysis by Zhang et al. (2018), that studied 1007 men aged 50 to 74 years, with a waist circumference of 95 cm or higher, a serum testosterone concentration of 14.0 nmol/L or lower but without pathological hypogonadism, and impaired glucose tolerance (oral glucose tolerance test [OGTT] 2-h glucose 7.8–11.0 mmol/L) or newly diagnosed type 2 diabetes (provided OGTT 2-h glucose ≤15.0 mmol/L) enrolled in a lifestyle program randomized to testosterone undecanoate (1000 mg) (n=504) or placebo (n=503) at baseline, 6 weeks, and then every 3 months for 2 years. Although the study was multinational, the majority of patients (>70%) were enrolled from Australia and New Zealand. The primary outcomes at 2 years were type 2 diabetes (defined as 2-h OGTT glucose ≥11.1 mmol/L) and mean change from baseline in 2-h OGTT glucose. The proportion of patients who developed diabetes was lower in the testosterone versus placebo group (12% [55 of 443] versus 21% [87 of 413] respectively; relative risk [RR]= 0.59, 95% CI 0.43 to 0.80; p=.0007). The mean change from baseline 2-h glucose was also greater in the testosterone versus placebo group (-1.70± 2.47 versus -0.95± 2.78 respectively; mean difference= -0.75; 95% CI -1.10 to -0.40; p<.0001). The treatment effect was independent of baseline serum testosterone. Treatment with testosterone was not associated with excess cardiovascular or prostate cancer adverse events. However, there were increases in pre-specified safety triggers. The proportion of patients with safety triggers was 1% versus 22% (>54% hematocrit levels) and 19% versus 23% (an increase of ≥0.75 μg/mL in prostate-specific antigen) in the placebo versus testosterone group respectively.

(2018) Zhang et al. published a systematic review and meta-analysis evaluating the effects of testosterone supplement treatment in hypogonadal men with type 2 diabetes. Eight RCTs with a total of 596 participants were included (all but 3 of which are also included in Cai et al [2014] below). Meta-analysis showed that testosterone supplement treatment can significantly improve glycemic control by reducing homeostatic model assessment of insulin resistance (mean difference [MD] -0.79; 95% CI -1.23 to -0.34), fasting glucose (MD -0.98; 95% CI -1.13 to -0.54), fasting insulin (MD -2.47; 95% CI -3.99 to -0.95), and HbA1c % (MD -0.45; 95% CI -0.73 to -0.16). Also, results showed a decline in cholesterol (MD -0.29; 95% CI -0.38 to -0.19) and triglyceride (MD -0.37; 95% CI -0.59 to -0.15). Study limitations include lack of generalizability due to the racial and ethnic homogeneity of study populations, adjusted estimates were not performed due to insufficient data, and by the variation in testosterone regimens between studies.

In an RCT not included in the Zhang et al (2018) meta-analysis, Hackett et al. (2014) randomized 211 patients with type 2 diabetes and hypogonadism to parenteral testosterone (testosterone undecanoate 1000 mg at weeks 0, 6, and 18) or to placebo; they were followed for 30 weeks. For the trial's primary outcome (change in HbA1c level), testosterone treatment was associated with a significant reduction in HbA1c levels at 6 weeks of therapy (from 7.74% to 7.50%). At 18 weeks of therapy, the MD between treatment and control group, after adjusting for covariates, was -0.20 (95% CI, -0.34 to -0.05; p=.007). There were significant reductions in waist circumference, weight, and body mass index in men without depression. Hackett et al (2016) reported on a secondary study outcome, sexual function outcome's Sexual function was assessed with the 15-item International Index of Erectile Function. In men with mild hypogonadism, there were no significant differences in sexual function scores in the testosterone and placebo groups. In men with severe hypogonadism, at 30 weeks, there was a significant improvement in 3 of 4 International Index of Erectile Function sexual function domains compared with placebo. In the testosterone group, 116 adverse events were reported, 2 of which (injection pain) were definitely treatment-related and 19 of which were possibly treatment-related. There were 4 serious adverse events (2 in each group) but none was treatment-related. Trialists did not specify the nonserious adverse events.

(2016) Magnussen et al. reported on the findings of a small RCT evaluating 39 patients with controlled type 2 diabetes. Men ages 50 to 70 years with bioavailable testosterone levels less than 7.3 nmol/L were randomized to testosterone gel (n=20) or to placebo (n=19) for 24 weeks. Treatment with testosterone improved body composition (increase lean body mass and decrease fat mass), but not glycemic control, peripheral insulin sensitivity, endogenous glucose production, or substrate metabolism.

(2014) Cai et al. reported on the results of a systematic review and meta-analysis of RCTs that evaluated the effect of testosterone therapy on metabolic parameters in patients with type 2 diabetes and hypogonadism. Five RCTs (total n=351 subjects) identified met eligibility criteria, 3 of which were double-blind, placebo-controlled trials and 2 of which were open-label and single-blind, no-treatment controlled trials. In pooled analysis, testosterone was associated with reduced fasting plasma glucose levels (MD = -1.10; 95% CI, -1.88 to -0.31), fasting insulin levels (MD = -2.73; 95% CI, -3.63 to -1.84), HbA1c level (MD = -0.87; 95% CI, -1.32 to -0.42), and triglyceride levels (MD = -0.35; 95% CI, -0.62 to -0.07). Reviewers noted that both trials were limited by relatively few participants and discussion of methods.

One of the larger RCTs in the Cai et al (2014) meta-an alysis, conducted by Jones et al (2011), enrolled 220 patients with type 2 diabetes and/or metabolic syndrome and hypogonadism. Treatment in the testosterone group was with daily transdermal testosterone 60 mg. The primary outcome was the change in insulin resistance, as measured by the homeostasis model of insulin resistance, and secondary outcomes were changes in body composition, glycemic control, lipid levels, and sexual dysfunction. There was a 16% reduction in the homeostasis model of insulin resistance at the 6-month

follow-up (p<.02), and this difference persisted at the 12-month follow-up. Other outcomes were reported at the 6-month follow-up. There were statistically significant improvements for the overall group in the International Index of Erectile Function scores for the testosterone group, but no significant improvement in the HbA1c or fasting glucose levels. There were no differences for the overall group on measures of body composition or lipid levels. On subgroup analysis, there was an improvement for patients with metabolic syndrome in their mean low-density lipoprotein levels.

**Section Summary: Androgen Deficiency and Type 2 Diabetes**
Several RCTs have assessed testosterone replacement in patients with hypogonadism and type 2 diabetes. A systematic review of these trials noted methodologic limitations (e.g., lack of blinding, limited discussion of methods). Pooled analyses found testosterone replacement led to modest improvements in indices of glucose control (e.g., hemoglobin A1c levels, insulin sensitivity). There is a lack of trials linking these surrogates to clinical outcomes such as major adverse cardiovascular events. The benefits may be outweighed by the increased risk of adverse events of treatment in the diabetic population.

**Older Genotypic XY Individuals with Low Testosterone Levels without Definite Hypogonadism**
A few RCTs have evaluated the impact of testosterone replacement in elderly men with low testosterone levels, without definite evidence of hypogonadism. Most trials have been small and included only a limited range of outcomes. The largest RCTs are discussed next.

(2020) Mok et al. published the results of a randomized, double-blind, placebo-controlled study that enrolled 45 men aged at least 40 years without pathologic hypogonadism but with androgen deficiency-like energy and/or sexual symptoms to either daily testosterone or placebo gel treatment for 6 weeks. The trial included 3 phases including a cross-over study design for the first 2 phases followed by a third mandatory extension phase in which participants chose which previous treatment they preferred to repeat while remaining masked to their original treatment. Primary endpoints were energy and sexual symptoms as assessed by a visual analog scale called lead symptom score. Results showed that 6 weeks of treatment with testosterone did not improve energy or sexual symptoms more than placebo in symptomatic men without pathologic hypogonadism.

(2018) Traustadottir et al. performed a double-blind, randomized, placebo-controlled, parallel-group trial to determine the effects of testosterone supplementation on oxygen consumption (VO2) peak during incremental cycle ergometry for older men with low testosterone. Patients were randomized to either the testosterone group (n=69) or placebo group (n=60). Men in the testosterone group maintained the same VO2 peak from baseline (24.2 ± 5.2 mL/kg/min); however, the VO2 peak fell significantly from baseline (23.6±5.6 mL/kg/min) for the placebo group (average 3-year decrease, 0.88 mL/kg/min; 95% CI -1.39 to 0.38 mL/kg/min; p=.035). There was a significant change in the difference in VO2 peak between groups (average 3-year difference, 0.91 mL/kg/min; 95% CI 0.010 to 0.122 mL/kg/min; p=.008). A limitation of the study was the

participants who completed measures of aerobic capacity across the time points were limited to one site.

(2009) Legros et al. reported on a large multicenter RCT, from Europe, enrolled 322 patients who were 50 years or older, with mild-to-moderate symptoms of hypogonadism and low testosterone levels. Patients were randomized to daily testosterone 80, 160, or 240 mg or to placebo, and the primary outcome was the change in the Aging Males Symptom scale at 6 months. There were no statistically significant differences in the total Aging Males Symptom score between groups at 6 months, although the scores in the testosterone group showed greater numeric improvement. There was a statistically significant difference in the Aging Males Symptom sexual domain subscore for the 160-mg testosterone group, but not for the 80- and the 240-mg groups. There were no statistically significant differences in adverse events between groups, including the change in prostate-specific antigen (PSA) level.

(2008) Emmelot-Vonk et al. completed a trial by enrolled 237 men between the ages of 60 and 80 years who had low testosterone levels but were otherwise healthy. Patients were randomized to oral testosterone 80 mg or to placebo and followed for 6 months. A range of outcome measures was reported, including functional mobility, body composition, muscle strength, cognitive function, BMD, metabolic parameters, and quality of life. Safety outcomes were also included: PSA, prostate volume, renal function, liver function, and hematocrit levels. For most outcome measures, there was no improvement in the testosterone group compared with placebo therapy. There was an increase in lean body mass and a decrease in the percent body fat. However, these changes were not accompanied by improvements in functional capacity or muscle strength. There were no significant changes in cognitive function, BMD, or quality of life. There was a worsening metabolic profile, though not statistically significant (p=.07), with 47.8% of men in the testosterone group meeting the definition for metabolic syndrome at the end of the study compared with 35.5% of men in the placebo group. There was a significant, but small, increase in hematocrit concentration for men in the testosterone group, and an increase in creatinine levels that was of borderline significance. Otherwise, there were no group differences in safety outcomes.

Several smaller RCTs have been published, ranging in size from 13 to 131 patients. The most consistent finding reported in these trials was an increase in lean body mass (4 studies) and a decrease in body fat (3 studies). The impact on strength was mixed, with 2 studies reporting an improvement in the testosterone group and 2 studies reporting no difference between groups. An increase in hemoglobin level and/or hematocrit concentration was reported in 1 study, and an increase in BMD was reported in another. None of these RCTs reported on functional status, quality of life, or sexual performance.

**Section Summary: Older Genotypic XY Individuals Men with Low Testosterone Levels without Definite Hypogonadism**

Several RCTs have been published, and most have been small and reported on a limited range of clinical outcomes. For most outcomes reported, there was no significant benefit

reported for testosterone replacement. Some studies have reported improvements in lean body mass and decreased body fat, and one RCT reported improvement in sexual function. However, these trials did not report improvements in functional status or muscle strength. The adverse event profile of testosterone therapy is not well-defined, and there have been concerns about increased adverse prostate-related outcomes and cardiovascular outcomes. This uncertainty in the adverse event profile creates challenges in determining the risk-benefit profile of treatment in otherwise healthy men.

**Testosterone for Pain Management in Genotypic XC Individuals**

(2019) Pogatzki-Zahn et al. noted that the role of sex hormones on post-surgical pain perception is basically unclear. These researchers examined the role of endogenous gonadal hormones for pain and hyperalgesia in human volunteers after experimental incision. A 4-mm incision was made in the volar forearm of 15 female volunteers both in the follicular and the luteal phase (random block design). Somatosensory profiles were assessed at baseline and 1 to 72 hours after incision by quantitative sensory testing (QST), compared between both cycle phases, and related to individual plasma levels of gonadal hormones. Sensory testing at baseline revealed significantly lower pain thresholds (25 versus 46 mN, $p < 0.005$) and increased pain ratings to pinprick (0.96 versus 0.47, $p < 0.0001$) in the luteal phase; similarly, 1 hour after incision, pain intensity to incision (38 versus 21/100, $p < 0.005$), pinprick hyperalgesia by rating ($p < 0.05$), and area of secondary hyperalgesia ($p < 0.001$) were enhanced in the luteal phase. Multiple regression analysis revealed that pinprick pain sensitivity at baseline was significantly predicted by progesterone (partial $r = 0.67$, $p < 0.001$), follicle-stimulating hormone (FSH) (partial $r = 0.61$, $p < 0.005$), and negatively by testosterone (partial $r = -0.44$, $p < 0.05$). Likewise, incision-induced pain and pinprick hyperalgesia (rating and area) were significantly predicted by progesterone (partial $r = 0.70$, $r = 0.46$, and $r = 0.47$, respectively; $p < 0.05$ to 0.0001) and in part by FSH; the contribution of estrogen, however, was fully occluded by progesterone for all measures. The authors concluded that pinprick pain and incision-induced pain and mechanical hyperalgesia were greater in the luteal phase and predicted by progesterone, suggesting a major role for progesterone. Other hormones involved were testosterone (protective) and in part FSH.

(2015) In a case-series study, Dubick et al. examined the feasibility and safety of a novel method for the management of chronic lower back pain (LBP). Injections of recombinant human growth hormone (rhGH) and testosterone to the painful and dysfunctional areas in individuals with chronic LBP were used. In addition, subjects received manual therapies and exercise addressing physical impairments such as motor control, strength, endurance, pain, and loss of movement. Pain ratings and self-rated functional outcomes were assessed. This trial involved consecutive patients with chronic LBP who received the intervention of injections of recombinant human growth hormone and testosterone and attended chiropractic and/or physical therapy. Outcomes were measured at 12 months from the time of injection. A total of 60 consecutive patients attending a pain management practice for chronic LBP were recruited for the experimental treatment. Most subjects were private pay. Subjects who provided informed consent and were determined not to have radicular pain received diagnostic blocks. Those who responded

favorably to the diagnostic blocks received injections of recombinant human growth hormone and testosterone in the areas treated with the blocks. Subjects also received manipulation- and impairment-based exercises. Outcomes were assessed at 12 months through pain ratings with the Mankowski Pain Scale and the Oswestry Disability Index (ODI). Of the 60 patients recruited, 49 provided informed consent, and 39 completed all aspects of the study. Those patients receiving the intervention reported a significant decrease in pain ratings ($p < 0.01$) and a significant improvement in self-rated ODI scores ($p < 0.01$). In addition, in the ODI results, 41 % of the patients demonstrated a 50 % or greater change in their disability score. Of the subjects who withdrew from the study, 1 was due to the pain created by the injections and 9 were for non-study factors. The authors concluded that the intervention appeared to be safe, and the results provided a reasonable expectation that the intervention would be beneficial for a population of individuals with chronic non-radicular LBP. Moreover, these researchers stated that due to the design of the study, causality could not be inferred, but these findings did indicate that further study of the intervention may be needed. These researchers stated that the results of this case series support the development of randomized controlled trials (RCTs) comparing the use of placebo injections versus rhGH and testosterone injection therapy, with and without impairment-specific rehabilitation. This was a small ($n = 39$ subjects who completed the study); and its findings were confounded by the combined use of rhGH, testosterone, manual therapies, and exercise.

(2014) Calabrese et al stated that diabetic neuropathy is associated with neuropathic pain in about 50 % of diabetic subjects. Clinical management of neuropathic pain is complex and so far, unsatisfactory. These investigators analyzed the effects of the testosterone metabolites, dihydrotestosterone (DHT), and 3α-diol, on nociceptive and allodynia thresholds and on molecular and functional parameters related to pain modulation in the dorsal horns of the spinal cord and in the dorsal root ganglia of rats rendered diabetic by streptozotocin injection. Furthermore, the levels of DHT and 3α-diol were analyzed in the spinal cord. Diabetes resulted in a significant decrease in DHT levels in the spinal cord that was reverted by DHT or 3α-diol treatments. In addition, 3α-diol treatment resulted in a significant increase in 3α-diol in the spinal cord compared with control values. Both steroids showed analgesic properties on diabetic neuropathic pain, affecting different pain parameters and possibly by different mechanisms of action. Indeed, DHT counteracted the effect of diabetes on the mechanical nociceptive threshold, pre- and post-synaptic components, glutamate release, astrocyte immunoreactivity, and expression of interleukin-1β (IL1β), while 3α-diol was effective on tactile allodynia threshold, glutamate release, astrocyte immunoreactivity and the expression of substance P, toll-like receptor 4, tumor necrosis factor-α, transforming growth factor β-1, IL1β, and translocator protein. The authors concluded that these findings indicated that testosterone metabolites are potential agents for the treatment of diabetic neuropathic pain.
(2011) Aloisi et al noted that in male patients suffering from chronic pain, opioid administration induces severe hypogonadism, leading to impaired physical and psychological conditions such as fatigue, anemia and depression. Hormone replacement therapy is rarely considered for these hypogonadic patients, notwithstanding the various pharmacological solutions available. To treat hypogonadism and to evaluate the

consequent endocrine, physical and psychological changes in male chronic pain patients treated with morphine (epidural route), these researchers tested the administration of testosterone via a gel formulation for 1 year. Hormonal (total testosterone, estradiol, free testosterone, DHT, cortisol), pain (VAS and other pain questionnaires), andrological (Ageing Males' Symptoms Scale-AMS) and psychological (POMS, CES-D and SF-36) parameters were evaluated at baseline (T0) and after 3, 6 and 12 months (T3, T6, T12 respectively). The daily administration of testosterone increased total and free testosterone and DHT at T3, and the levels remained high until T12. Pain rating indexes (QUID) progressively improved from T3 to T12 while the other pain parameters (VAS, Area%) remained unchanged. The AMS sexual dimension and SF-36 Mental Index displayed a significant improvement over time. The authors concluded that these findings suggested that a constant, long-term supply of testosterone could induce a general improvement of the male chronic pain patient's quality of life (QOL), an important clinical aspect of pain management. These researchers stated that their results strongly suggested that this therapy can positively modulate the dimensions of pain. This effect allowed them to propose the use of testosterone in clinics as an adjuvant, in combination with opioid therapy. These preliminary findings need to be validated by well-designed studies.

**Testosterone and Cardiovascular Events**

The clinical significance of many of these potential adverse events is unclear. Several meta-analyses have studied adverse events expected to be more common. This review of adverse events will include both randomized and nonrandomized studies, with emphasis on systematic reviews and meta-analyses of the available studies.

(2016) Albert and Morley reported the findings of a systematic review that included 45 trials with 5328 subjects with mean age of 63.3 years and a mean follow-up of 10.6 months. Over the duration of available follow-up, testosterone treatment was not associated with increased risk of cardiovascular events (RR=1.10; 95% CI, 0.86 to 1.41; p=.45). However, there was an increase event rate during the first 12 months (RR=1.79; 95% CI, 1.13 to 2.83; p=.012), predominantly among those 65 years or older (RR=2.90; 95% CI, 1.35 to 6.21; p=.006).

(2015) Corona et al. published an overview of previously published meta-analyses on the association between testosterone replacement therapy and cardiovascular risk. Reviewers included the 3 meta-analyses described below, as well as 2 others, all of which focused on RCT evidence. Reviewers reported that only 1 of the 5 meta-analyses supported an association between testosterone therapy and an increased cardiovascular risk. They stated that, in the single positive meta-analysis, cases of peripheral edema and self-reported syncope were included in the category of cardiovascular events, which might have overstated the number of clinically significant events. The other 4 meta-analyses did not find significant differences between testosterone and placebo groups in the incidence of overall cardiovascular events or specific events including cardiovascular death, fatal and nonfatal myocardial infarctions (MI), and cerebrovascular events.

(2015) Etminan et al. completed a case-control study performed within a cohort of 934283 men ages 45 to 80 years. It identified 30066 cases of MI and matched each case with 4 controls. There was no evidence of increased current testosterone replacement therapy use in case patients (RR=1.01; 95% CI, 0.89 to 1.16). There was also no association between past testosterone replacement therapy use and MI or evidence of different risk level by type of preparation. A small increase in risk was reported for first-time testosterone replacement therapy users (RR=1.41; 95% CI, 1.06 to 1.87).

(2014) Baillargeon et al. completed a retrospective cohort study by evaluating administrative claims data from Medicare to assess the relation between testosterone administered *intramuscularly* and the risk of MI. The study included 6355 Medicare beneficiaries who received at least 1 testosterone injection between 1997 and 2005 and who were matched in a 1:3 ratio to 19,065 testosterone nonusers based on a composite MI prognostic score. After adjustment for demographic and clinical covariates, testosterone therapy was not associated with an increased risk of MI (adjusted hazard ratio, 0.84; 95% CI, 0.69 to 1.01). Testosterone therapy was associated with a reduced risk of MI in men with an MI prognostic score in the highest quartile (hazard ratio, 0.69; 95% CI, 0.53 to 0.92), while men in the lower 3 quartiles showed no difference in MI risk with testosterone therapy.

(2014) Finkle et al. conducted a large retrospective cohort study using administrative claims data to assess the relation between testosterone therapy and nonfatal MI. The authors generated a cohort of 55593 men who filled their first prescription for 1 of several testosterone prescriptions between 2008 and 2010 from the Truven Health Market Scan Commercial Claims and Encounters Database, which includes diagnoses, procedures, and prescriptions for all enrollees of contributing health plans. Testosterone recipients were compared with a population of men who filled their first prescription for a phosphodiesterase type 5 inhibitor (sildenafil or tadalafil; N =167279) during the same time period. For testosterone recipients, the rate ratio of MI in the post- compared with the pre-testosterone period was 1.36 (95% CI, 1.03 to 1.81). Compared with subjects in the phosphodiesterase type 5 inhibitor group, the rate ratio for MI risk for testosterone recipients was 1.90 (95% CI, 1.04 to 3.49). After stratifying by age, for testosterone recipients younger than age 55 years, the rate ratio for MI in the post-testosterone period was 0.95 (95% CI, 0.54 to 1.67); for testosterone recipients ages 75 and older, the rate ratio for MI in the post-testosterone period was 3.43 (95% CI, 1.54 to 7.56; p=.03 for trend). No similar trend was seen for phosphodiesterase type 5 inhibitor recipients. Although this study suggested an association between testosterone use and nonfatal MI, it was limited by its retrospective design and the potential for confounding by measured and unmeasured variables.

(2013) Vigen et al. completed a large retrospective comparative cohort study which evaluated the risk of cardiovascular events in patients treated with testosterone replacement therapy. This study used data from the Veterans Administration Clinical Assessment Reporting and Tracking Program to identify all male patients who had both undergone coronary angiography and had a total testosterone level checked between 2005

and 2011. There were 8709 patients with a low testosterone level, defined as less than 300 ng/dL. The population had high levels of comorbidity, with 80% of patients having coronary artery disease, 50% diabetes, and 20% prior to MI. There were 1223 patients treated with testosterone and 7486 who were not. After a mean follow-up of 27.5 months, the primary outcome of all-cause mortality, MI, or stroke was more frequent in the group treated with testosterone (hazard ratio, 1.29; 95% CI, 1.04 to 1.58; p=.02).

(2010) Fernandez-Balsells et al published a systematic review of randomized and nonrandomized comparative studies. They included 51 studies and examined the outcomes of mortality, cardiovascular events, cardiovascular risk factors, prostate events, and erythrocytosis. Patients treated with testosterone had increased hematocrit concentrations (weighted mean difference, 3.2%; 95% CI, 1.4% to 5.0%), and decreased high-density lipoprotein levels (weighted mean difference, 0.5 mg/dL; 95% CI, 0.13 to 0.85 mg/dL). No significant differences were reported in mortality, cardiovascular events, or prostate-related events.

(2007) Haddad et al. completed a systematic review of placebo-controlled randomized trials and examined the rates of adverse cardiovascular events and changes in cardiovascular risk factors. This review included 30 trials (total n=1642 men). Total adverse cardiovascular events were numerically more frequent in testosterone-treated patients, but the difference compared with placebo was not statistically significant (OR=1.8; 95% CI, 0.8 to 4.2). There were small changes in blood pressure, lipid levels, and glucose, but none of these changes was statistically significant.

(2005) Calof et al. performed a meta-analysis of placebo-controlled randomized trials. Nineteen studies were selected (total n=1084 patients) and assessed the outcomes of mortality, prostate-related events, changes in hematocrit concentration, and sleep apnea. Patients treated with testosterone were more likely to have a hematocrit greater than 50% (OR=3.7; 95% CI, 1.8 to 7.5). There were no significant differences in mortality, cardiovascular events, or sleep apnea.

**Testosterone Effects on the Prostate Gland**
Several meta-analyses have specifically evaluated the relation between testosterone and prostate-related events.

(2016) Kohn et al. completed a systematic review by identified 14 RCTs on testosterone therapy in aging men and assessed lower urinary tract symptoms with the IPSS. In a pooled analysis, there was no statistically significant difference in change in IPSS among men treated with testosterone vs placebo (p=.11). Similarly, another systematic review, Kathrins et al (2016) identified 35 prospective studies and found that most trials did not demonstrate a correlation between testosterone therapy and enlarged prostate volume, de novo lower urinary tract symptoms, or worsening lower urinary tract symptoms.

Cui et al (2014) conducted a systematic review of RCTs that reported on the effect of testosterone replacement therapy on prostate cancer risk. This analysis included 22 RCTs

(total n=2351 patients), 11 of which reported short-term (<12 months) outcomes and 11 of which reported long-term (12-36 months) outcomes. Five studies evaluated injectable testosterone, 1 evaluated oral testosterone, and 5 studies evaluated transdermal testosterone over the short-term; there was no significant association between any administration method and prostate cancer, prostate biopsy, or prostate nodules. However, for the studies evaluating transdermal testosterone, there was a significant association between testosterone treatment and change in PSA level (SMD=0.33; 95% CI, 0.21 to 0.45; p<.000). There was no association between testosterone therapy and abnormal PSA levels. For long-term administration, 3 studies evaluated injectable testosterone, 2 studies evaluated oral testosterone, and 6 studies evaluated transdermally administered testosterone. There was no significant association between testosterone administration by any method and prostate cancer, prostate biopsy, or prostate nodules. No significant association was found between testosterone administration over the long-term and change in PSA level.

**Testosterone and Venous Thromboembolism**

(2018) Houghton et al. published a systematic review and meta-analysis to determine if there is an association between exogenous testosterone (any route) and venous thromboembolism. Eleven studies (6 RCTs, 5 observational studies) with a total of 1251876 (RCT, n=2236; observational, n=1249640) patients were included. Meta-analysis of all studies found no significant association between venous thromboembolism and testosterone therapy (OR 1.41, 95% CI 0.96–2.07); there was also no significant association when stratified by study design: RCT (OR 2.05, 95% CI 0.78-5.39), cohort studies (OR 1.06, 95% CI 0.85–1.33), and case-control studies (OR 1.34, 95% CI 0.78–2.28). The analysis was limited by high heterogeneity among the included studies (I2 =84.4%).

(2015) Baillargeon et al completed a large case-control study by evaluated the risk of venous thromboembolism associated with testosterone replacement therapy. This study assessed 30572 men ages 40 years and older. Subjects had a diagnosis of venous thromboembolism and were on an anticoagulant drug. Cases were matched with 3 controls on age, time of onset, location, diagnosis of hypogonadism, and the presence of a prothrombotic condition. There was no increased risk of testosterone replacement therapy in the venous thromboembolism group (OR=0.91; 95% CI, 0.38 to 2.16). The lack of an association persisted when different time frames of testosterone replacement therapy exposure were examined.

**Summary of Evidence**

For individuals who have androgen deficiency and clinical symptoms of hypogonadism who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. For men with low testosterone levels and sexual dysfunction, the evidence has been fairly consistent in demonstrating a beneficial effect on increased libido. Other sexual function symptoms (e.g., erectile dysfunction) are also likely to be improved but the evidence is less strong. For other symptoms, there is

evidence that lean body mass is increased, body fat is decreased, and bone mineral density is increased with testosterone therapy. However, the impact of these changes on functional status and fractures is less clear. For outcomes such as decreased energy, depression, quality of life, and cognition, the evidence is limited and inconsistent in reporting benefits of replacement therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have androgen deficiency and HIV infection who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. A limited number of trials have included patients with HIV infection and associated weight loss. These trials have reported improvements in body weight, lean body mass, and a decrease in body fat, which indicates that testosterone replacement is likely to ameliorate weight loss associated with HIV infection. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have androgen deficiency on chronic steroid treatment who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. A limited number of trials have included patients with androgen deficiency in chronic steroid treatment. These trials have reported improvements in body weight, lean body mass, and a decrease in body fat, which are likely to ameliorate the effects of chronic steroids on these parameters. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have androgen deficiency and type 2 diabetes who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. The available RCTs have reported that testosterone replacement leads to modest improvements in glucose control (e.g., hemoglobin A1c levels, insulin sensitivity). There is a lack of trials reporting on clinical outcomes, and the small benefits may be outweighed by the adverse events of treatment. Current professional guidelines reflect the controversy regarding the balance of risks and benefits. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals (older men) with low testosterone levels without definite hypogonadism who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. The available RCTs are mostly small and have reported on a limited range of clinical outcomes. For most outcomes, there was no benefit for testosterone replacement. Some studies have reported improvements in lean body mass and decreased body fat, and a recent RCT found improved sexual function. However, these studies did not report improvements in functional status or muscle strength. Although the adverse event profile of testosterone therapy is not well-defined, there are concerns about increased adverse prostate-related outcomes and cardiovascular

outcomes. This uncertainty in the adverse event profile creates challenges in determining the risk-benefit profile of treatment in otherwise healthy men. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For genotypic XX individuals who receive testosterone replacement therapy for pain management, the evidence includes RCT and case series studies. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. Larger more well-defined studies are needed. comparing the use of testosterone pellets versus injections to determine safety and efficacy. Some studies suggested that testosterone can positively modulate the dimensions of pain. This effect allowed them to propose the use of testosterone in clinics as an adjuvant, in combination with opioid therapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

At the current time, there is lack of medical and scientific evidence to support the efficacy and safety of customized subcutaneous hormone replacement regimes utilizing bioidentical hormones. Well-designed and controlled clinical trials are needed to provide evidence of improved net health outcomes with compounded bioidentical hormone replacement, subcutaneously inserted over conventional hormone therapies. The FDA issued a safety communication in 2015, warning against the use of testosterone products for low testosterone due to aging.

**Professional Guidelines and Position Statements**

**The American College of Obstetricians and Gynecologists (ACOG)**
(2012; Reaffirmed 2020) The Committee on Gynecologic Practice and the American Society for Reproductive Medicine Practice Committee made the following conclusions and recommendations in the Compounded Bioidentical Menopausal Hormone Therapy article:

- Evidence is lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal hormone therapy.
- Customized compounded hormones pose additional risks. These preparations have variable purity and potency and lack efficacy and safety data.
- Conventional hormone therapy is preferred over compounded hormone therapy given the available data.
- Despite claims to the contrary, evidence is inadequate to support increased efficacy or safety for individualized hormone therapy regimens based on salivary, serum, or urinary testing.

(*Accessed February 2022*)

**American Diabetes Association**
(2022) The American Diabetes Association (ADA) Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes recommends the following:

- In men with diabetes who have symptoms or signs of hypogonadism, such as decreased sexual desire (libido) or activity, or erectile dysfunction, consider screening with a morning serum testosterone level. B
    - Mean levels of testosterone are lower in men with diabetes compared with age matched men without diabetes, but obesity is a major confounder.
    - Testosterone replacement in men with symptomatic hypogonadism may have benefits including improved sexual function, well-being, muscle mass and strength, and bone density.
    - In men with diabetes who have symptoms or signs of low testosterone (hypogonadism), a morning total testosterone level should be measured using an accurate and reliable assay.
    - In men who have total testosterone levels close to the lower limit, it is reasonable to determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, sex hormone binding globulin, and albumin concentrations. Please see the Endocrine Society clinical practice guideline for detailed recommendations.
    - Further tests (such as luteinizing hormone and follicle-stimulating hormone levels) may be needed to further evaluate the patient.
    - Testosterone replacement in older men with hypogonadism has been associated with increased coronary artery plaque volume, with no conclusive evidence that testosterone supplementation is associated with increased cardiovascular risk in hypogonadal men.

  (*Accessed February 2022*)

**The American Urology Association (AUA)**
(2018) Practice Guidelines for Evaluation and Management of Testosterone Deficiency

| Recommendation | SOR | LOE |
|---|---|---|
| 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 | 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 | Grade A |
| Further research is needed to understand the role of free testosterone level in the diagnosis of men with testosterone deficiency. | _____ | _____ |
| 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 | Grade B |

| | | |
|---|---|---|
| In patients with low testosterone, clinicians should measure serum luteinizing hormone levels. | Strong | Grade A |
| Serum prolactin levels should be measured in patients with low testosterone levels combined with low or low/normal luteinizing hormone levels. | Strong | Grade A |
| Serum estradiol should be measured in testosterone deficient patients who present with breast symptoms or gynecomastia prior to the commencement of testosterone therapy | Expert Opinion | ———— |
| Clinicians should adjust testosterone therapy dosing to achieve a total testosterone level in the middle tertial of the normal reference range. | Conditional | Grade C |
| Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive. | Strong | Grade A |
| Commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible. | Conditional | Grade C |
| Patients should be informed that testosterone therapy may result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms. | Moderate | Grade B |
| Patients should be informed that the evidence is inconclusive whether testosterone therapy improves cognitive function, measures of diabetes, energy, fatigue, lipid profiles, and quality of life measures. | Moderate | Grade B |
| Prior to offering testosterone therapy, clinicians should measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia. | Strong | Grade A |
| PSA should be measured in men over 40 years of age prior to commencement of testosterone therapy to exclude a prostate cancer diagnosis. | Clinical Principle | ———— |
| Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. | Strong | Grade B |
| The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. | Strong | Grade A |

(*Accessed February 2022*)

**The Endocrine Society**

(2018) The Endocrine Society has a clinical practice guideline for testosterone therapy in men with hypogonadism with the following conclusions:

- We recommend making a diagnosis of hypogonadism only in men with symptoms and signs consistent with testosterone (T) deficiency and unequivocally and consistently low serum T concentrations.
- We recommend measuring fasting morning total T concentrations using an accurate and reliable assay as the initial diagnostic test.
- We recommend confirming the diagnosis by repeating the measurement of morning fasting total T concentrations.
- In men whose total T is near the lower limit of normal or who have a condition that alters sex hormone–binding globulin, we recommend obtaining a free T concentration using either equilibrium dialysis or estimating it using an accurate formula.
- In men determined to have androgen deficiency, we recommend additional diagnostic evaluation to ascertain the cause of androgen deficiency. We recommend T therapy for men with symptomatic T deficiency to induce and maintain secondary sex characteristics and correct symptoms of hypogonadism after discussing the potential benefits and risks of therapy and of monitoring therapy and involving the patient in decision making.
- We recommend against starting T therapy in patients who are planning fertility in the near term or have any of the following conditions: breast or prostate cancer, a palpable prostate nodule or induration, prostate-specific antigen level > 4 ng/mL, prostate-specific antigen > 3 ng/mL in men at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer) without further urological evaluation, elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia. (SOR: Recommend, QOE: Low)
- Suggest that when clinicians institute T therapy, they aim at achieving T concentrations in the mid-normal range during treatment with any of the approved formulations, taking into consideration patient preference, pharmacokinetics, formulation-specific adverse effects, treatment burden, and cost.
- Clinicians should monitor men receiving T therapy using a standardized plan that includes evaluating symptoms, adverse effects, and compliance; measuring serum T and hematocrit concentrations; and evaluating prostate cancer risk during the first year after initiating T therapy.
- Suggest that clinicians consider short-term testosterone therapy in HIV-infected men with low testosterone concentrations and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain.
- In hypogonadal men 55 to 69 years old, who are being considered for testosterone therapy and have a life expectancy >10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate

monitoring and engaging the patient in shared decision making regarding prostate cancer monitoring. For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone. (SOR: Suggest, QOE: Very low)

- In hypogonadal men being considered for testosterone therapy who are 40 to 69 years old and at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer), we suggest discussing prostate cancer risk with the patient and offering monitoring options." (SOR: Suggest QOE: Very low)
- In men with type 2 diabetes mellitus who have low testosterone concentrations, we recommend against testosterone therapy as a means of improving glycemic control. (SOR: Recommend, QOE: Low)
- In hypogonadal men who have started testosterone therapy, we recommend evaluating the patient after treatment initiation to assess whether the patient has responded to treatment, is suffering any adverse effects, and is complying with the treatment regimen. (Ungraded Good Practice Statement)
- Monitoring includes measuring testosterone and hematocrit at 3 to 6 months (depending upon the formulation) and measuring testosterone and hematocrit at 12 months and annually after initiating testosterone therapy.

(*Accessed February 2022*)

(January 2022) In an article for Hypogonadism in Men posted by the Endocrine Society it noted the following testosterone facts for men

- Low testosterone comes with age — Testosterone or "T" levels naturally decrease by 1% each year after age 30, though don't severely deplete, even in advanced age.
- T production may be disrupted by disorders of the testicles, pituitary gland, or brain.
- T levels change from hour to hour — highest in the morning; lowest at night
- T levels can temporarily lower due to too much exercise, poor nutrition, severe illness, and with certain medications.
- Normal T levels in adult men should be between 300–1,000 ng/dL (nanograms per deciliter), depending on age and lab used.
- Testosterone must be measured more than once for accurate assessment.

(*Accessed February 2022*)

**The European Menopause and Andropause Society (EMAS)**

(2015) A position statement was published by the European Menopause and Andropause Society (EMAS) on testosterone replacement therapy in the aging male with the following relevant recommendations:

- Testing for testosterone deficiency should be only performed in men with symptoms of androgen deficiency; universal testosterone testing in aging males is not recommended.

- Symptoms compatible with androgen deficiency involve loss of libido, erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality and depressed mood.
- A general policy of offering TRT to all aging men with low testosterone concentrations is not recommended.
- Physicians should consider offering TRT, on an individual basis, to aging men with low testosterone concentrations on more than one occasion and clinically significant symptoms of androgen deficiency.
- Potential benefit of TRT should outweigh the cost, inconvenience and risks of therapy for aging males.
- There is no consensus on the beneficial effects of TRT with regard to obesity, metabolic syndrome, type 2 diabetes mellitus, sexual function and osteoporosis
- Testosterone replacement therapy (TRT) should be offered to individuals if a combination of testosterone deficiency symptoms and low testosterone are present.
- Specific populations, such as older men with low testosterone concentrations and type 2 diabetes mellitus might benefit from TRT.
- TRT is absolutely contra-indicated in cases of metastatic prostate, or breast cancer, unevaluated prostate nodule or induration, PSA > 4 ng/ml, hematocrit >50%, severe lower urinary tract symptoms and/or uncontrolled congestive heart failure.
- If TRT is prescribed, serum testosterone concentrations should be therapeutically raised into a range that is mid-normal for healthy, young men.
- Patients receiving TRT should undergo regular testing for adverse events; a critical risk-versus-benefit estimation on whether to continue TRT should be made 6 months after treatment initiation.
- Risks and benefits of TRT should be very carefully weighed up in testosterone deficient aging men with or without pre-existing heart disease, until evidence from large randomized prospective trials regarding cardiovascular safety of TRT becomes available.

(*Accessed February 2022*)

**Regulatory Status**

**The United States Food and Drug Administration**

**-Bioidentical Hormones**

Many marketed products that are called “bioidentical hormones” are compounded drugs, which are not FDA-approved. FDA does not have evidence that compounded “bioidentical hormones” are safe and effective, or safer or more effective than FDA-approved hormone therapy.

- The FDA has approved drugs containing hormones that are identical to the hormones made naturally by genotypic XX individuals *in their reproductive years*.
- The FDA recommends that women use hormone therapies that are FDA-approved. FDA-approved hormone therapies are evaluated for safety and effectiveness.

**-Testosterone**
FDA approval for the use of testosterone subcutaneous implantation is currently only for genotypical males.

- The FDA cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions confirmed by laboratory tests.
    - Testosterone is FDA-approved as replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause hypogonadism. However, the FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established.
- The FDA requires manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone.
- The communication also stated: "FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use. These studies included aging men treated with testosterone. Some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not."

# PRIOR APPROVAL

Not applicable.

# POLICY

*Note: This policy is specifically related to subcutaneously implanted hormone pellets in the office setting. This policy does not apply to those undergoing treatments for gender transition.*

**Related Medical Policies:**

- 05.01.45 Testosterone Agents –Topical/Buccal/Nasal/Oral/Injection – Drug Policy

**Testosterone Pellets**
The use of testosterone pellets (i.e.,Testopel®) is considered **medically necessary** when **the following criteria** has been met**:**

- The individual is a genotypical male; **and**
- Has persistently low testosterone levels as evidenced by two early morning fasting serum total testosterone levels that are below 300 ng/dL on both days:
    - (*Note: Exception to this criteria point would be the bilateral orchiectomy which is not applicable*).

**And has one of the following** diagnoses (*see A – E*):

A. Hypogonadotropic hypogonadism (also called secondary hypogonadism) (congenital or acquired) due to **one of the following**:
    - Idiopathic gonadotropin; **or**

- Luteinizing hormone-releasing hormone (LHRH) deficiency; **or**
- Pituitary-hypothalamic injury from tumors, trauma, or radiation.

**and** has the presence of **one of the following** symptoms of hypogonadism:

- Incomplete or delayed sexual development; **or**
- Decreased libido; **or**
- Decreased spontaneous erections; **or**
- Breast discomfort, gynecomastia; **or**
- Loss of axillar and/or pubic body hair; **or**
- Very small (< 5 mL) or shrinking testes; **or**
- Height loss due to vertebral fractures, low trauma fractures, low bone density; **or**
- Hot flushes, sweats.

B. Primary hypogonadism (congenital or acquired) with testicular failure due to **one of the following** conditions:

- Bilateral torsion; **or**
- Chemotherapy; **or**
- Cryptorchidism; **or**
- Klinefelter Syndrome; **or**
- Orchiectomy (also called orchidectomy) (*Note: Documentation of low serum testosterone is not required for bilateral orchiectomy*); **or**
- Orchitis; **or**
- Toxic damage from alcohol or heavy metals; **or**
- Vanishing testis syndrome.

**and** has the presence of **one of the following** symptoms of hypogonadism:

- Incomplete or delayed sexual development; **or**
- Decreased libido; **or**
- Decreased spontaneous erections; **or**
- Breast discomfort, gynecomastia; **or**
- Loss of axillar and/or pubic body hair; **or**
- Very small (< 5 mL) or shrinking testes; **or**
- Height loss due to vertebral fractures, low trauma fractures, low bone density; **or**
- Hot flushes, sweats.

C. Chronic steroid treatment; **or**

D. Clearly delayed puberty when 13 years old or greater; **or**

E. Human immunodeficiency virus (HIV) *with* associated weight loss.

**Investigational**

**Estrogen Pellets**

Subcutaneous hormone pellets containing *estrogen alone or estrogen combinations* are considered **investigational** for all indications including, but not limited to the following because the evidence is insufficient in determining the effects of the technology the net health outcomes:

- Bioidentical hormone formulations

- Customized subcutaneous pellet hormone replacement regimes utilizing bioidentical hormones
- Symptoms associated with menopause

**Testosterone Pellets**
The use of subcutaneous hormone pellets containing *testosterone* are considered **investigational** when criteria above has not been met and in all other indications including but not limited the following because the evidence is insufficient in determining the effects of the technology the net health outcomes:

- Absence of clinical signs and symptoms of hypogonadism
- Age-related hypogonadism/late-onset hypogonadism
- Athletic performance enhancement
- Customized subcutaneous hormone replacement regimes utilizing bioidentical hormones.
- Depression
- Menopause
- Sexual dysfunction (i.e., erectile dysfunction or decreased libido)
- The use of testosterone pellets (i.e., Testopel®), in genotypic XX individuals

**Policy Guidelines**
*Note: The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society and the American Urology Association has recommended a lower limit for normal levels of 300 ng/dL for total testosterone –Joint guidelines from several European and American specialty societies have recommended that replacement therapy be considered at serum total testosterone levels less than 350 ng/dL. For the purpose of this review Wellmark uses the recommendations from the Endocrine Society and the American Urology Association.*

**Definitions**

- *Androgen*: A general term for any genotypic XY sex hormone.
- *Endogenous*: Developing or originating within the body.
- *Hypogonadism*: An inadequate gonadal function, marked by deficiencies in the secretion of gonadal hormones and spermatogenesis.
- *Orchiectomy*: Excision of one or both testes, done when a testis is seriously injured or diseased.
- *Subcutaneous:* Under the skin.

**Dosing**
Dosage recommendations per the FDA label.
The suggested dosage for androgens varies depending on the age, and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions. The dosage guideline for the testosterone pellets for replacement therapy in androgen deficient genotypical males is 150 mg to 450 mg subcutaneously every 3 to 6 months. Various dosage regimens have been used to induce

pubertal changes in hypogonadal genotypical males; some experts have advocated lower doses initially, gradually increasing the dose as puberty progresses, with or without a decrease in maintenance levels. Other experts emphasize that higher dosages are needed to induce pubertal changes and lower dosages can be used for maintenance after puberty. The chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose.

Dosages in delayed puberty generally are in the lower range of that listed above and, for a limited duration, for example 4 to 6 months.

The number of pellets to be implanted depends upon the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally. The usual dosage is as follows: implant two 75 mg pellets for each 25 mg testosterone propionate required weekly. Thus, when a patient requires injections of 75 mg per week, it is usually necessary to implant 450 mg (6 pellets). With injections of 50 mg per week, implantation of 300 mg (4 pellets) may suffice for approximately three months. With lower requirements by injection, correspondingly lower amounts may be implanted. It has been found that approximately one-third of the material is absorbed in the first month, one-fourth in the second month and one-sixth in the third month. Adequate effect of the pellets ordinarily continues for three to four months, sometimes as long as six months.

# PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 11980 Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)
- J3490 Unclassified drugs (*when utilized for subcutaneous estradiol and/or testosterone hormone pellets*)
- S0189 Testosterone pellet, 75 mg

# SELECTED REFERENCES


- North American Menopause Society. Bioidentical Hormone Therapy.
- American College of Obstetricians and Gynecologists. ACOG Committee Opinion #532, November 2005 (Reaffirmed 2012): Compounded Bioidentical Menopausal Hormone Therapy.
- Institute for Clinical Systems Improvement (ICSI). Health Care Guideline: Menopause and Hormone Therapy (HT): Collaborative Decision-Making and Management. Ninth Edition, October 2008.
- Gallenberg, Mary. Mayo Foundation for Medical Education and Research (MFMER). Bioidentical hormones: Are they safer? December 15, 2011.

- Goodman NF, Cobin RH, Ginzburg SB, Katz IA, Woode DE. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause. Endocr Pract. November/December 2011; 17(Suppl 6).
- Position Statement: The 2012 Hormone Therapy Position Statement of the North American Menopause Society. Menopause. January 17, 2012; 19(3): pp. 257-271.
- FDA Consumer Health Information. Bio-Identicals: Sorting Myths from Facts. April 8, 2008.
- National Institutes of Health (NIH). Menopausal Hormone Therapy Information. Last reviewed September 15, 2011.
- Ruiz AD, Daniels KR, Barner JC, Carson JJ, Frei CR. Effectiveness of compounded bioidentical hormone replacement therapy: an observational cohort study. BMC Womens Health. 2011 Jun 8; 11: 27.
- Conaway E. Bioidentical hormones: an evidence-based review for primary care providers. J Am Osteopath Assoc. 2011 Mar;111(3):153-64.
- Sood R, Shuster L, Smith R, Vincent A, Jatoi A. Counseling postmenopausal women about bioidentical hormones: ten discussion points for practicing physicians. J Am Board Fam Med. 2011 Mar-Apr; 42(2):202-10.
- U.S. Food and Drug Administration. Compounded menopausal hormone therapy questions and answers.
- Wierman ME, Wiebke A, Basson R, et al. Androgen Therapy in Women: A Reappraisal: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2014:99;3489-3510.
- Boothby LA, Doering PL, Kipersztok S. Bioidentical hormone therapy: a review. Menopause 2004; 11:356.
- Takahashi K, Manabe A, Okada M, et al. Efficacy and safety of oral estridol for managing postmenopausal symptoms. Maturitas 2000; 34:169.
- Xu L, Freeman G, Cowling BJ, Schooling CM (2013). Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med, 11, 108.
- Fda.gov,. "FDA Drug Safety Communication: FDA Cautions About Using Testosterone Products For Low Testosterone Due To Aging; Requires Labeling Change To Inform Of Possible Increased Risk Of Heart Attack And Stroke With Use". N.p., 2015. Web. 8 May 2015.
- Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. J Androl. 2008;159:507-514.
- Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. N Engl J Med. Feb 18 2016;374(7):611-624. PMID 26886521
- Dimopoulou C, Ceausu I, Depypere H, et al. EMAS position statement: Testosterone replacement therapy in the aging male. Maturitas. Feb 2016;84:94-99. PMID 26614257

- Morales A, Bebb RA, Manjoo P, et al. Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline. CMAJ. Dec 8 2015;187(18):1369-1377. PMID 26504097
- Crowley, W., Pitteloud, N., et al. (2016) Diagnosis nad treatment of delayed puberty. UptoDate.
- FDA.gov Womens Health Topics: Menopause. 12-27-2017.
- Albert SG, Morley JE. Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review. Clin Endocrinol (Oxf). Sep 2016;85(3):436-443. PMID 27124404
- Magnussen LV, Glintborg D, Hermann P, et al. Effect of testosterone on insulin sensitivity, oxidative metabolism and body composition in aging men with type 2 diabetes on metformin monotherapy. Diabetes Obes Metab. Oct 2016;18(10):980-989. PMID 27265844
- Corona G, Rastrelli G, Morgentaler A, et al. Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores. Eur Urol. Apr 20 2017. PMID 28434676
- Snyder,P., Matsumoto, A., Schmader, K., Martin, K. Overview of testosterone deficiency in older men. UptoDate Jan 2018.
- Testosterone and aging: Clinical research directions, Liverman CT, Blazer DG (Eds), National Academies Press, Washington DC 2004.
- Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010; 95:2536.
- Bhasin et al.(2018) Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism, Volume 103, Issue 5, 1 May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229
- McClintock, T., Valovske, M., Kwon, N. et al. (2019) Testosterone replacement therapy associated with an increased risk of urolithiasis. World Journal of Urology 37(12) 2737-2746.
- Kaminetsky JC, McCullough A, Hwang K, et al. A 52-Week Study of Dose Adjusted Subcutaneous Testosterone Enanthate in Oil Self-Administered via Disposable Auto-Injector. J Urol 2019; 201:587.
- Mohler ER 3rd, Ellenberg SS, Lewis CE, et al. The Effect of Testosterone on Cardiovascular Biomarkers in the Testosterone Trials. J Clin Endocrinol Metab 2018; 103:681.
- Corona G, Torres LO, Maggi M. Testosterone Therapy: What We Have Learned From Trials. The journal of sexual medicine. 2020;17(3):447-460. doi:10.1016/j.jsxm.2019.11.270.
- Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. May 01 2018; 103(5): 1715-1744. PMID 29562364

- Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. Jun 2010; 95(6): 2536-59. PMID 20525905
- Zarotsky V, Huang MY, Carman W, et al. Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. Andrology. Nov 2014; 2(6): 819-34. PMID 25269643
- Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab. Jul 2008; 93(7): 2737-45. PMID 18270261
- Travison TG, Araujo AB, Kupelian V, et al. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. J Clin Endocrinol Metab. Feb 2007; 92(2): 549-55. PMID 17148559
- Cunningham GR, Toma SM. Clinical review: Why is androgen replacement in males controversial?. J Clin Endocrinol Metab. Jan 2011; 96(1): 38-52. PMID 20881265
- FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. https://www.fda.gov/Drugs/DrugSafety/ucm436259.htm.
- Bolona ER, Uraga MV, Haddad RM, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. Jan 2007; 82(1): 20-8. PMID 17285782
- Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. J Urol. Aug 2000; 164(2): 371-5. PMID 10893588
- Corona G, Rastrelli G, Morgentaler A, et al. Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores. Eur Urol. Dec 2017; 72(6): 1000-1011. PMID 28434676
- Neto WK, Gama EF, Rocha LY, et al. Effects of testosterone on lean mass gain in elderly men: systematic review with meta-analysis of controlled and randomized studies. Age (Dordr). Feb 2015; 37(1): 9742. PMID 25637335
- Bhasin S, Calof OM, Storer TW, et al. Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab. Mar 2006; 2(3): 146-59. PMID 16932274
- Tracz MJ, Sideras K, Bolona ER, et al. Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. J Clin Endocrinol Metab. Jun 2006; 91(6): 2011-6. PMID 16720668
- Amiaz R, Pope HG, Mahne T, et al. Testosterone gel replacement improves sexual function in depressed men taking serotonergic antidepressants: a randomized, placebo-controlled clinical trial. J Sex Marital Ther. 2011; 37(4): 243-54. PMID 21707327
- Shores MM, Kivlahan DR, Sadak TI, et al. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with

subthreshold depression (dysthymia or minor depression). J Clin Psychiatry. Jul 2009; 70(7): 1009-16. PMID 19653976
- Seidman SN, Orr G, Raviv G, et al. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized, placebo-controlled clinical trial. J Clin Psychopharmacol. Jun 2009; 29(3): 216-21. PMID 19440073
- Borst SE, Yarrow JF, Fernandez C, et al. Cognitive effects of testosterone and finasteride administration in older hypogonadal men. Clin Interv Aging. 2014; 9: 1327-33. PMID 25143719
- Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, et al. The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: A systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Endocrinol Metab. Mar 17 2018. PMID 29562341
- Snyder PJ, Ellenberg SS, Cunningham GR, et al. The Testosterone Trials: Seven coordinated trials of testosterone treatment in elderly men. Clin Trials. Jun 2014; 11(3): 362-375. PMID 24686158
- Snyder PJ, Bhasin S, Cunningham GR, et al. Lessons From the Testosterone Trials. Endocr Rev. Jun 01 2018; 39(3): 369-386. PMID 29522088
- Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. Jun 2006; 91(6): 1995-2010. PMID 16720669
- Zhang J, Yang B, Xiao W, et al. Effects of testosterone supplement treatment in hypogonadal adult males with T2DM: a meta-analysis and systematic review. World J Urol. Aug 2018; 36(8): 1315-1326. PMID 29511802
- Cai X, Tian Y, Wu T, et al. Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Asian J Androl. Jan-Feb 2014; 16(1): 146-52. PMID 24369149
- Jones TH, Arver S, Behre HM, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care. Apr 2011; 34(4): 828-37. PMID 21386088
- Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol. Jan 2021; 9(1): 32-45. PMID 33338415
- Hackett G, Cole N, Bhartia M, et al. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. J Sex Med. Mar 2014; 11(3): 840-56. PMID 24308723
- Hackett G, Cole N, Saghir A, et al. Testosterone undecanoate improves sexual function in men with type 2 diabetes and severe hypogonadism: results from a 30-week randomized placebo-controlled study. BJU Int. Nov 2016; 118(5): 804-813. PMID 27124889
- Magnussen LV, Glintborg D, Hermann P, et al. Effect of testosterone on insulin sensitivity, oxidative metabolism and body composition in aging men with type 2

diabetes on metformin monotherapy. Diabetes Obes Metab. Oct 2016; 18(10): 980-9. PMID 27265844
- Mok SF, Fennell C, Savkovic S, et al. Testosterone for Androgen Deficiency-Like Symptoms in Men Without Pathologic Hypogonadism: A Randomized, Placebo-Controlled Cross-over With Masked Choice Extension Clinical Trial. J Gerontol A Biol Sci Med Sci. Sep 16 2020; 75(9): 1723-1731. PMID 31425577
- Traustadottir T, Harman SM, Tsitouras P, et al. Long-Term Testosterone Supplementation in Older Men Attenuates Age-Related Decline in Aerobic Capacity. J Clin Endocrinol Metab. Aug 01 2018; 103(8): 2861-2869. PMID 29846604
- Legros JJ, Meuleman EJ, Elbers JM, et al. Oral testosterone replacement in symptomatic late-onset hypogonadism: effects on rating scales and general safety in a randomized, placebo-controlled study. Eur J Endocrinol. May 2009; 160(5): 821-31. PMID 19211706
- Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA. Jan 02 2008; 299(1): 39-52. PMID 18167405
- Kenny AM, Kleppinger A, Annis K, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. Jun 2010; 58(6): 1134-43. PMID 20722847
- Kenny AM, Prestwood KM, Gruman CA, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. May 2001; 56(5): M266-72. PMID 11320105
- Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab. Aug 1999; 84(8): 2647-53. PMID 10443654
- Sih R, Morley JE, Kaiser FE, et al. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab. Jun 1997; 82(6): 1661-7. PMID 9177359
- Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab. Oct 1992; 75(4): 1092-8. PMID 1400877
- Albert SG, Morley JE. Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review. Clin Endocrinol (Oxf). Sep 2016; 85(3): 436-43. PMID 27124404
- Corona G G, Rastrelli G, Maseroli E, et al. Testosterone Replacement Therapy and Cardiovascular Risk: A Review. World J Mens Health. Dec 2015; 33(3): 130-42. PMID 26770933
- Fernandez-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. Jun 2010; 95(6): 2560-75. PMID 20525906
- Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized,

placebo-controlled trials. J Gerontol A Biol Sci Med Sci. Nov 2005; 60(11): 1451-7. PMID 16339333
- Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. Jan 2007; 82(1): 29-39. PMID 17285783
- Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014; 9(1): e85805. PMID 24489673
- Baillargeon J, Urban RJ, Kuo YF, et al. Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy. Ann Pharmacother. Sep 2014; 48(9): 1138-1144. PMID 24989174
- Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. Nov 06 2013; 310(17): 1829-36. PMID 24193080
- Etminan M, Skeldon SC, Goldenberg SL, et al. Testosterone therapy and risk of myocardial infarction: a pharmacoepidemiologic study. Pharmacotherapy. Jan 2015; 35(1): 72-8. PMID 25582846
- Cui Y, Zhang Y. The effect of androgen-replacement therapy on prostate growth: a systematic review and meta-analysis. Eur Urol. Nov 2013; 64(5): 811-22. PMID 23567065
- Cui Y, Zong H, Yan H, et al. The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. Jun 2014; 17(2): 132-43. PMID 24445948
- Kohn TP, Mata DA, Ramasamy R, et al. Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis. Eur Urol. Jun 2016; 69(6): 1083-90. PMID 26874809
- Kathrins M, Doersch K, Nimeh T, et al. The Relationship Between Testosterone-Replacement Therapy and Lower Urinary Tract Symptoms: A Systematic Review. Urology. Feb 2016; 88: 22-32. PMID 26616095
- Houghton DE, Alsawas M, Barrioneuvo P, et al. Testosterone therapy and venous thromboembolism: A systematic review and meta-analysis. Thromb Res. Dec 2018; 172: 94-103. PMID 30396049
- Baillargeon J, Urban RJ, Morgentaler A, et al. Risk of Venous Thromboembolism in Men Receiving Testosterone Therapy. Mayo Clin Proc. Aug 2015; 90(8): 1038-45. PMID 26205547
- Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and Management of Testosterone Deficiency: AUA Guideline. J Urol. Aug 2018; 200(2): 423-432. PMID 29601923
- American Diabetes Association. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes. Diabetes Care. Jan 2022
- Smith RP, Kaunitz AM. Dysmenorrhea in adult women: Treatment. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2021.

- Kroshinsky D. Erythema nodosum. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2020.
- Aloisi AM, Ceccarelli I, Carlucci M, et al. Hormone replacement therapy in morphine-induced hypogonadic male chronic pain patients. Reprod Biol Endocrinol. 2011;9:26.
- Calabrese D, Giatti S, Romano S, et al. Diabetic neuropathic pain: A role for testosterone metabolites. J Endocrinol. 2014;221(1):1-13.
- Dubick MN, Ravin TH, Michel Y, Morrisette DC. Use of localized human growth hormone and testosterone injections in addition to manual therapy and exercise for lower back pain: A case series with 12-month follow-up. J Pain Res. 2015;8:295-302.
- Pogatzki-Zahn EM, Drescher C, Englbrecht JS, et al. Progesterone relates to enhanced incisional acute pain and pinprick hyperalgesia in the luteal phase of female volunteers. Pain. 2019;160(8):1781-1793.
- The Endocrine Society. Hypogonadism in Men. January 23,2022. Patient resources. Available at https://www.endocrine.org/patient-engagement/endocrine-library/hypogonadism


# POLICY HISTORY

| Date | Reason | Action |
|---|---|---|
| February 2022 | Annual Review | Policy Revised |
| February 2021 | Annual Review | Policy Revised |
| February 2020 | Annual Review | Policy Revised |
| February 2019 | Annual Review | Policy Revised |
| February 2018 | Annual Review | Policy Revised |
| February 2017 | Annual Review | Policy Revised |
| February 2016 | Annual Review | Policy Revised |
| March 2015 | Annual Review | Policy Revised |
| April 2014 | Annual Review | Policy Revised |
| May 2013 | Annual Review | Policy Revised |
| June 2012 | | New Policy |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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