Approved by the AUA Board of Directors
February 2018
Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

EVALUATION AND MANAGEMENT OF TESTOSTERONE DEFICIENCY: AUA GUIDELINE

John P. Mulhall, MD; Landon W. Trost, MD; Robert E. Brannigan, MD; Emily G. Kurtz, MD; J. Bruce Redmon, MD; Kelly A. Chiles, MD MSc; Deborah J. Lightner, MD; Martin M. Miner, MD; M. Hassan Murad, MD, MPH; Christian J. Nelson, PhD; Elizabeth A. Platz, ScD, MPH; Lakshmi V. Ramanathan, PhD; Ronald W. Lewis, MD

Executive Summary

Testosterone testing and prescriptions have nearly tripled in recent years; however, it is clear from clinical practice that there are many men using testosterone without a clear indication.[1-3] Some studies estimate that up to 25% of men who receive testosterone therapy do not have their testosterone tested prior to initiation of treatment.[2, 3] Of men who are treated with testosterone, nearly half do not have their testosterone levels checked after therapy commences.[2, 3] While up to a third of men who are placed on testosterone therapy do not meet the criteria to be diagnosed as testosterone deficient,[2, 3] there are a large percentage of men in need of testosterone therapy who fail to receive it due to clinician concerns, mainly surrounding prostate cancer development and cardiovascular events, although current evidence fails to definitively support these concerns. Given the clinical and commercial testosterone landscape, the American Urological Association (AUA) identified a need to produce an evidence-based document that informs clinicians on the proper assessment and management of patients with testosterone deficiency. The AUA and the Testosterone Panel were committed to creating a Guideline that ensures that men in need of testosterone therapy are treated effectively and safely.

Methodology

A systematic review utilized research from the Mayo Clinic Evidence Based Practice Center and additional supplementation by the authors. Literature searches included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. Controlled vocabulary supplemented with keywords was used to search for studies according to each defined question. This search included articles published between January 1, 1980 – February 6, 2017 and yielded 15,217 references, 546 (enrolling approximately 350,000 men) of which were used to support guideline statements. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

Guideline Statements

Diagnosis of Testosterone Deficiency

1. Clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone. (Moderate Recommendation; Evidence Level: Grade B)
2. The diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. (Strong Recommendation; Evidence Level: Grade A)
3. The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs.(Moderate Recommendation; Evidence Level: Grade B)
4. Clinicians should consider measuring total testosterone in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use even in the absence of symptoms or signs associated with testosterone deficiency. (Moderate Recommendation; Evidence Level: Grade B)
5. The use of validated questionnaires is not currently recommended to either define which patients are candidates for testosterone therapy or to monitor symptom response in patients on testosterone therapy. (Conditional Recommendation; Evidence Level: Grade C)

Adjunctive Testing

6. In patients with low testosterone, clinicians should measure serum luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)
7. Serum prolactin levels should be measured in patients with low testosterone levels combined with low or low/ normal luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)
8. Patients with persistently high prolactin levels of unknown etiology should undergo evaluation for endocrine disorders. (Strong Recommendation; Evidence Level: Grade A)
9. 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)
10. Men with testosterone deficiency who are interested in fertility should have a reproductive health evaluation performed prior to treatment. (Moderate Recommendation; Evidence Level: Grade B)
11. Prior to offering testosterone therapy, clinicians should measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia. (Strong Recommendation; Evidence Level: Grade A)
12. 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)

Counseling Regarding Treatment of Testosterone Deficiency

13. Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease. (Strong Recommendation; Evidence Level: Grade B)

14. 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 Recommendation; Evidence Level: Grade B)
15. 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 Recommendation; Evidence Level: Grade B)
16. The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. (Strong Recommendation; Evidence Level: Grade A)
17. Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. (Strong Recommendation; Evidence Level: Grade B)
18. Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy. (Expert Opinion)
19. Patients should be informed that there is no definitive evidence linking testosterone therapy to a higher incidence of venothrombolic events. (Moderate Recommendation; Evidence Level: Grade C)
20. Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). (Moderate Recommendation; Evidence Level: Grade B)
21. All men with testosterone deficiency should be counseled regarding lifestyle modifications as a treatment strategy. (Conditional Recommendation; Evidence Level: Grade B)

Treatment of Testosterone Deficiency

22. Clinicians should adjust testosterone therapy dosing to achieve a total testosterone level in the middle tertile of the normal reference range. (Conditional Recommendation; Evidence Level: Grade C)
23. Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive. (Strong Recommendation; Evidence Level: Grade A)
24. Testosterone therapy should not be commenced for a period of three to six months in patients with a history of a cardiovascular events. (Expert Opinion)
25. Clinicians should not prescribe alkylated oral testosterone. (Moderate Recommendation; Evidence Level: Grade B)
26. Clinicians should discuss the risk of transference with patients using testosterone gels/creams. (Strong Recommendation; Evidence Level: Grade A)
27. Clinicians may use aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators, or a combination thereof in men with testosterone deficiency desiring to maintain fertility. (Conditional Recommendation; Evidence Level: Grade C)
28. Commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible. (Conditional Recommendation; Evidence Level: Grade C)

Follow-up of Men on Testosterone Therapy

29. Clinicians should measure an initial follow-up total testosterone level after an appropriate interval to ensure that target testosterone levels have been achieved. (Expert Opinion)
30. Testosterone levels should be measured every 6-12 months while on testosterone therapy. (Expert Opinion)
31. Clinicians should discuss the cessation of testosterone therapy three to six months after commencement of treatment in patients who experience normalization of total testosterone levels but fail to achieve symptom or sign improvement. (Clinical Principle)

INTRODUCTION

Purpose

Testosterone testing and prescriptions have nearly tripled in recent years; however, it is clear from clinical practice that there are many men using testosterone without a clear indication.[1-3] Some studies estimate that up to 25% of men who receive testosterone therapy do not have their testosterone tested prior to initiation of treatment, and nearly half do not have their testosterone levels checked after therapy commences.[2,3] While up to a third of men who are placed on testosterone therapy do not meet the criteria to be diagnosed as testosterone deficient,[2, 3] there are a large percentage of men in need of testosterone therapy who fail to receive it due to clinician concerns, mainly surrounding prostate cancer development and cardiovascular events, although current evidence fails to definitively support these concerns.

The explosion in the use of testosterone in the past decade is multifactorial in its etiology, including the increased use of direct-to-consumer advertising, which has resulted in greater patient knowledge and demand; relaxation of the indications for testosterone prescribing by clinicians; and the establishment of clinical care centers devoted to men's health, testosterone treatment, and anti-aging strategies.

Given the growing concern and need for proper testosterone therapy, the AUA identified a need to produce an evidence-based document that informs clinicians on the proper evaluation and management of testosterone deficient patients. The goals of this document are to (i) guide clinicians in how to assess patients for testosterone deficiency and manage them with testosterone products, and (ii) educate clinicians in key areas of testosterone in which many clinicians are deficient (e.g., interpreting the testosterone literature, understanding testosterone laboratory testing). Ultimately, the AUA and the Testosterone Panel were committed to creating a Guideline that ensures that men in need of testosterone therapy are treated effectively and safely.

Definitions and Index Patient

The Panel chose to cease use of the term hypogonadism, a term introduced decades ago to signify low testosterone levels associated with infertility. Hypogonadism has more recently been used interchangeably with the idea of low testosterone production alone. To be scientifically accurate, the Panel chose the term *testosterone deficiency*. Testosterone deficiency does not imply simply a state of low testosterone *production*, but rather to be testosterone deficient is to have low testosterone levels *combined* with symptoms or signs that are associated with low serum total testosterone (henceforth referred to as 'low testosterone'). Thus, a patient is considered testosterone deficient and a candidate for testosterone therapy *only* when he meets *both* criteria. The challenge for clinicians is that the symptoms that have been associated with low testosterone levels are very non-specific and can be manifestations of other conditions (e.g., chronic fatigue, chronic stress, a depressed state).

It was decided that a cut-off value was critical to define testosterone deficiency and that this cut-off be based on at least two total testosterone levels drawn in an early morning fashion at the same laboratory using the same assay. The cut-off of 300 ng/dL was chosen based on the mean total testosterone levels cited in the best available literature with a view to maximizing the potential benefit from prescribing testosterone while minimizing the risks of such treatment.

The Panel explicitly uses the term *testosterone therapy* rather than testosterone replacement therapy or testosterone supplementation to be in keeping with the beliefs of the current thought leaders in the field. Testosterone therapy refers to all forms of treatment that are aimed at increasing serum testosterone, including exogenous testosterone as well as alternative strategies, such as selective estrogen receptor modulators (SERMs), human chorionic gonadotropin (hCG) or aromatase inhibitors (AIs).

The Panel defines success as achievement of therapeutic testosterone levels to the normal physiologic range of 450 -600 ng/dL (middle tertile of the reference range for most labs) accompanied by symptom/sign improvement/resolution.

The index patient for this guideline is the adult male with testosterone deficiency as defined above; however, the Panel included recommendations for three other patient types who are of great interest and concern for the practicing urologist: the patient with cardiovascular disease (CVD) or who has risk factors for CVD; men with testosterone deficiency who are interested in preserving their fertility; and men with testosterone deficiency who are at risk for or have prostate cancer.

Methodology

The guideline panel developed *a priori* 15 key questions from which guideline statements were derived. The questions were developed based clinical challenges

faced by urologists in daily practice. A systematic review of the published literature was conducted to answer these key questions and provide the evidence base for the guideline. The searches included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. Controlled vocabulary supplemented with keywords was used to search for studies according to each defined question. This search included articles published between January 1, 1980 – February 6, 2017.

The search yielded 15,217 references, 546 (enrolling approximately 350,000 men) of which were used to support guideline statements. Of the outcomes included in the protocol of this systematic review, data were available on quality of life (QoL), sexual function, cardiovascular events, anemia, bone health, insulin resistance, cardiovascular risk factors, mood, cognitive function, body composition, and numerous adverse events. Minimal data were found regarding outcomes of frailty, risk of venous thromboembolism, hyperestrogenemia, sleep apnea, prostate biopsy, recurrence of treated prostate cancer, and incidence of breast cancer. Randomized controlled trials (RCTs) were sought for effectiveness questions, whereas both randomized and non-randomized studies were sought for adverse events and questions of association and risk factors. Random effects meta-analyses were performed when deemed appropriate. Evidence tables (for included studies) and evidence profiles (showing estimates of effect for the outcomes of interest) were generated and presented to the Panel.

Included Interventions. Direct testosterone therapies included the following: oral agents, transdermal agents (gels, creams, patches), buccal agents, trans-nasal agents, intramuscular (IM) agents (short- and long-acting), and subcutaneous (SQ) pellets**.** Alternative testosterone therapies included SERMs, hCG, and AIs.

Determination of Evidence Strength*.* The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only individual study quality but consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 1). ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/ burdens is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *is likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence		

risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances, and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, the Panel provides guidance in the form of *Clinical Principles* or *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged. A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

For additional information on the challenges associated with reviewing the literature on testosterone deficiency, refer to Appendix A.

Name Brand Pharmaceutical Agents

The AUA has a policy that all pharmaceutical and biological agents are referred to only by their chemical compound formulation in guidelines, white papers, and best practice statements and not by their brand or generic name. This allows the AUA to eliminate any notion of allegiance to industry in general, or to any product in particular. Additionally, identifying drugs solely by their chemical compound formulation allows guidelines to remain current, despite the dynamic nature of the marketplace.

The AUA has made an exception for this guideline. For most pharmaceutical products, the usage, dosage, and application is consistent across brands, and identification by chemical compound is sufficient to communicate to the reader when to use a given medication. The testosterone therapeutic space is relatively unique. While all products contain the same medication (testosterone), each product and modality has distinct pharmacokinetic and application attributes based on the excipient agents and the permeator components.

For example, there are several testosterone gels available in 1%, 1.62%, and 2% formulations, each are marketed under a different brand or generic name. Within this modality family alone, there are three different application sites, including upper body, thigh, and axilla, with four different dosing ranges for each gel.

Identifying injectable drugs can be likewise confusing. While there are three injectable drugs, two of them are short-acting and one is long-acting. Finally, testosterone pellets are also available in branded form, with no generic agents currently available.

To merely refer to injectable or gel testosterone formulations without differentiation does not impart complete and accurate information to the reader. Considering the inherent confusion surrounding testosterone therapy in the current prescribing landscape, the AUA believes it is imperative to be as explicit as possible and present the reader the most complete information, which will optimize the efficacy and safety of testosterone therapy.

Please refer to Table 2 for more information on pharmaceutical products discussed in this guideline. A detailed profile of the therapeutic agents discussed in this guideline can be found in Appendix B.

Prevalence

The prevalence of testosterone deficiency in the American male population is difficult to quantify. A review by Millar et al.[4] searched MEDLINE and Embase databases from January 1966 to July 2014 for studies that compared clinical indication of low testosterone along with a measurement of serum testosterone in men. Among the 40 studies (N=37,565; age 43-82 years) that met the inclusion criteria, the prevalence of low testosterone, defined as the lower normal limit of the assay used, ranged from 2-77%.[4] The authors commented on the discrepant testosterone thresholds used to define low testosterone as well as conflicting approaches to measuring testosterone: total testosterone was used in 29 studies, range 200–433 ng/dL; bioavailable testosterone was used in 9 studies, range 69.4–198.4 ng/dL; and free testosterone was used in 4 studies, range 4.6–7.0 ng/dL.

Other population based studies have attempted to measure prevalence, but have not used standard methodology, which makes arriving at a definitive number of testosterone deficiency difficult. Across the prevalence literature, the cut-off values used to define low testosterone vary widely, heterogeneity exists in the populations studied, the forms of testosterone used to measure testosterone (total and/or free) are not consistent, and the assays utilized to measure

testosterone differ. Given these inconsistences, prevalence of low testosterone has varied dramatically among studies, with statistics reporting 2 – 50%.[5-8] A summary of findings from four large-scale contemporary prevalence studies can be found in Table 3.

Testosterone Measurement

Testosterone is the predominant androgen in males and is involved in a multitude of physiological and biochemical processes throughout the body. It is bound to albumin (50%, loosely-bound), sex hormone-binding globulin ([SHBG], 44%, tightly-bound), corticotropin-binding globulin (4%, loosely-bound), and approximately 2% circulates as free testosterone.[9] The free and loosely-bound testosterone fractions combined are known as bioavailable testosterone.

Testosterone assays are plagued by variability in results. This variability is expressed as a coefficient of variation (CV), which is a measure of precision.[10] In order to express this precision of assay test results, two measures of the CV are typically reported: the inter-assay CV and the intra-assay CV. *Inter-assay* CV measures the agreement between tests using the same method of measurement on identical samples, in the same laboratory, by the same operator using the same equipment within a short interval of time. *Intra-assay* CV is the degree of variation between repeated measurements of the same sample under different conditions. These parameters are calculated by analyzing normal and abnormal control specimens that have known values of the substance being measured.

The differences in testosterone methodologies have led to considerable effort by a variety of parties including the Centers for Disease Control (CDC) and the College of American Pathologists towards harmonization of assays. Part of this effort includes the availability of serum-based reference material from pooled sera available from the National Institute for Standards and Technology for testosterone and a hormone standardization program using liquid chromatography/ mass spectrometry (LCMS) offered by CDC. Laboratories that perform testosterone assays that have a CV that falls within ±6.4 % of samples tested by the CDC (with testosterone values ranging from 2.5-1,000 ng/dL) are certified. The names of these laboratories are available on the CDC website.[11-14]

An overview of the assays available to aid in the diagnosis of testosterone deficiency is available in Table 4.

Reference Ranges

Well-established reference ranges constitute the essential basis for identifying whether the circulating levels of a particular analyte, testosterone in this case, are normal or low. Due to the challenges in testosterone methodology, there is considerable variability in testosterone reference ranges.[13] The specific reference ranges used to diagnose testosterone deficiency are discussed in more depth later in this document. However, practicing clinicians who review testosterone lab results will commonly face the dilemma of whether to use the reference ranges published by their specific lab or the absolute measure itself. As an example, a total testosterone value of 250 ng/dL may be considered low based on the current guideline but be marked within the normal range by the laboratory. This situation commonly occurs as reference laboratories often define a normal value as ranging within the 5^{th} (or 2.5^{th}) and 95^{th} (or 97.5^{th}) percentiles of a sampled population. However, as the testosterone literature uses absolute values to define low testosterone, the absolute value is ultimately the most important factor to determine whether patients may expect to achieve benefits with testosterone therapy. In cases of discrepancy between laboratory reference ranges and this guideline, clinicians are recommended to utilize the absolute value with the understanding that all labs (including CDC-certified LCMS) include some degree of variability. Clinicians wishing to identify laboratories meeting CDC standards are encouraged to refer to the list of sites currently meeting CDC requirements listed on the CDC Hormone Standardization Program.

Table 2: Dosing Profiles of Available Testosterone Formulations (as of 2018)

Drug Name	Brand Name	Delivery System	Dose	Starting Dose	Dose Range	Application Site	Monitoring
Topical							
1% gel	Testim®	5g Tube	50mg/tube	50mg	50-100mg	Shoulders, upper arms	T within 4 weeks
1% gel	Vogelxo®	5g Tube 5g Packet 5g Pump	50mg/tube 50mg packet 12.25mg/actuation	50mg 50mg 4 actuations	50-100mg	Shoulders, upper arms	T within 4 weeks
1% gel	Androgel®	Packet Pump	50mg 12.25mg/actuation	50mg 4 actuations	50-100mg	Shoulders, upper arms	T within 4 weeks
1.62% gel	Androgel®	Packet Pump	40.5mg 20.25mg/actuation	40.5mg packet 2 actuations	20.25-81mg	Shoulders, upper arms	T within 4 weeks
2% gel pump	Fortesta®	Pump	10mg/actuation	4 actuations	10-70mg	Thigh	T within 4 weeks
2% solution	Axiron®	Pump	30mg/actuation	2 actuations	30-120mg	Axilla	T within 4 weeks
Patch	Androderm®	Patch	2 or 4mg/patch	4mg	2-6mg	Back, abdomen, upper arms or thighs	T within 4 weeks
Oral							
Buccal system	Striant®	Buccal systems	30mg/patch	1 buccal patch every 12 hours	NA	Upper gum (above incisor); rotate sides	T within 4 weeks
Intranasal							
Nasal Gel	Natesto®	Pump Bottle	11 mg	1 pump each nostril every 8 hours	NA		T within 4 weeks
Intramuscular							
T cypionate	*	Injection (1 and 10mL vials)		100 mg	50-200mg every 7 -14 days	Gluteal muscle or lateral upper thigh	After cycle 4

T: testosterone

*Available under multiple brand names

Table 2: Dosing Profiles of Available Testosterone Formulations (as of 2018)

Drug Name	Brand Name	Delivery System	Dose	Starting Dose	Dose Range	Application Site	Monitoring
T enanthate	*	Injection (5mL vials)		100 mg	50-200mg every 7-14 days	Gluteal muscle or lateral upper thigh	After cycle 4
T undecanoate	Aveed®	Injection– (750mg/3mL)	750mg (single dose)	750mg injection at weeks 0, 4, and every 10 weeks thereafter	750mg	Gluteal muscle	After cycle 4
Pellets							
Testosterone	Testopel®	Pellet	75mg/pellet	10 pellets	6-12 pellets every 3 to 4 months	Subcutaneous (buttock, flank)	2 and 12 weeks after each insertion

T: testosterone

*Available under multiple brand names

Table 3: Prevalence of Testosterone Deficiency

Author/Study	Number of Patients	Description of Population	Definition of Testosterone Deficiency	Method of Testosterone Deficiency Measurement	Prevalence of Testosterone Deficiency
Harman et al. 2000[5] *Baltimore Longitudinal Aging Study (BLAS)*	890	Generally healthy, middle class, 87% white Age range: 20-91 years (mean 63.8) Mean BMI: 25.6	TT <325 ng/dL or a FTI <0.153 Only one TT or FTI value needed to be in the deficient range to be considered testosterone deficient	Early morning samples from each subject's most recent and previous 3 visits as well as those from 10, 15, 20, 25, and 30 years prior were analyzed (3,565 samples total with a mean of 4 samples per patient). TT: RIA SHBG: RIA FT: FTI	50-59 years: 12% 60-69 years: 19% 70-79 years: 28% >80 years: 49%
Araujo et al. 2004[6] *Massachusetts Male Aging Study (MMAS)*	T1: 1,709 T2: 1,156	Patients were evenly divided among 40-49 years, 50-59 years, and 60-70 years; 95% white	TT<200 ng/dL combined with three or more symptoms (reduced libido, ED, depression, lethargy, inability to concentrate, sleep disturbance, irritability, and depressed mood), or a total testosterone level between 200-400 ng/dL with three or more symptoms and a free testosterone level < 8.9 ng/dL	Patients were evaluated at 2 time points (T1: 1987-1989; T2: 1995-1997) separated by a mean of 8.8 years, all testing was done on single samples taken in the morning. TT: RIA SHBG: RIA FT: Sodergard equation assessment of patient symptoms	T1 40-49 years: 4.1% 50-59 years: 4.5% 60-70 years: 9.4% T2 40-49 years: 7.1% 50-59 years: 11.5% 60-70 years: 22.8%
Mulligan et al. 2006[7] *Hypogonadism in Males (HIM)*	2,098	All men ≥45 years (mean 60.5) undergoing routine evaluation by their primary care physicians, 82% white Mean BMI: 29.7	TT <300 ng/dL, or men who were previously diagnosed with testosterone deficiency and who were currently using testosterone therapy	All draws were performed between 8a.m. and noon. TT: RIA SHBG: RIA FT: equilibrium dialysis Bioavailable T: Ammonium sulfate precipitation	38.7% of study population Mean testosterone level 245 ng/dL 17% increase in testosterone deficiency per decade of life

BMI: body mass index, ED: erectile dysfunction, FT: free testosterone, FTI: free testosterone index, GCMS: gas chromatography mass spectrometry, RIA: radioimmunoassay, SHBG: Sex hormone-binding globulin, TT: total testosterone

Table 3: Prevalence of Testosterone Deficiency

Author/Study	Number of Patients	Description of Population	Definition of Testosterone Deficiency	Method of Testosterone Deficiency Measurement	Prevalence of Testosterone Deficiency
Wu et al. 2010[8] *European Male Aging Study (EMAS)*	3,219	Age range: 40-79 years (mean 57.9)	TT <317 ng/dL along with the three sexual symptoms (sexual function [e.g., decreased frequency of morning erections, decreased frequency of sexual thoughts, ED, physical symptoms [e.g., inability to perform vigorous activity, inability to walk more than 1 km, inability to bend, kneel or stoop], and psychological symptoms [e.g., loss of energy, sadness, fatigue]	Men evaluated by primary care physicians had a single lab draw prior to 10a.m. and were administered a series of questionnaires. TT: GCMS SHBG: Immunoassay FT: Vermeulen equation	2.1% of study population

BMI: body mass index, ED: erectile dysfunction, FT: free testosterone, FTI: free testosterone index, GCMS: gas chromatography mass spectrometry, RIA: radioimmunoassay, SHBG: Sex hormone-binding globulin, TT: total testosterone

Table 4: Assays for the Diagnosis of Testosterone Deficiency

Assay	Units	Co-efficient of Variation	Advantages	Disadvantages
Total Testosterone				
Immuno-assay (including radio-immunoassay and enzyme immunoassay)	ng/dL	Intra-assay: -14% to +19% CV most pronounced at lower T values (40% in samples with TT <100 ng/dL)	• Rapid • High throughput • Reference range data available	• Reduced accuracy at low/high T levels • Interfering factors (heterophile antibodies in patients' serum) • Significant inter-assay variability
LCMS	ng/dL	±6.4% (to maintain CDC approval status)	• Gold standard • Excellent sensitivity and specificity at low T concentrations (<40)	• Not FDA approved • Labor intensive • Low throughput
Salivary	pmol/L	Intra-assay: 13% Inter-assay: 13%	• Simplicity • Patient access • Correlates with calculated free serum testosterone	• Not FDA approved • Extensive sample preparation requiring high skill • Concerns about specimen (saliva) stability
Free Testosterone				
Equilibrium Dialysis	pg/dL	Intra-assay: 10.0% Inter-assay: 6.8%	• Gold standard • Excellent sensitivity and specificity	• Labor intensive • Low throughput
Calculation methods (Law of Mass Action Equations after Nanjee & Wheeler, Sodergard, or Vermeulen)	pg/mL	Inter-assay: 18-30%.	• Rapid • Simple • Has correlated in some series (but not all) well with equilibrium dialysis	• Relies on TT and SHBG assay accuracy • Accuracy relies on equilibrium dissociation constants for binding of SHBG and albumin to testosterone • High inter-assay variability •
Direct (Ultracentrifugation, Analog)	pg/mL	Inter-assay: 8.9% Intra-assay: 10.3%.	• Method shows promise but additional studies required to measure assay performance across the range of free testosterone values	• Technically challenging • Low throughput

CV: coefficient of variation, E2: estradiol, LCMS: liquid chromatography/tandem mass spectrometry, SHBG: sex hormone-binding globulin, T: testosterone, TT: total testosterone

Table 4: Assays for the Diagnosis of Testosterone Deficiency

Assay	Units	Co-efficient of Variation	Advantages	Disadvantages
Bioavailable Testosterone				
Ammonium Sulfate precipitation	ng/dL	Intra-assay: 7.2% Inter-assay: 7.9%	• Excellent sensitivity and specificity	• Time/labor intensive • Technically challenging • Low throughput • Tracer contamination
Estradiol				
Immunoassay	pg/mL	Inter-assay 30 % observed compared to LCMS Most pronounced at lower E2 values <18 pg/dl)	• Rapid • High throughput • Reference range data available	• Reduced accuracy at low E2 levels • Interferences • Significant inter-assay variability
LCMS	pg/mL	Inter-assay <7%	• Gold standard • Excellent sensitivity and specificity	• Not FDA approved • Labor intensive • Low throughput
Sex Hormone-Binding Globulin				
Immunoassay (including radio-immunoassay and enzyme immunoassay)	nmol/L	Intra-assay: 6.7 % Inter-assay: 8.2 %	• Rapid • High throughput	• Interfering factors (heterophile antibodies in patient's serum)
Luteinizing Hormone				
Immunoassay	IU/L	Intra-assay: <4% Inter-assay: <9%	• Rapid • High throughput	• Interfering factors (heterophile antibodies in patient's serum)
Prolactin				
Immunoassay	ng/mL	Intra-assay: <4% Inter-assay: <5 %	• Rapid • High throughput	• Interfering factors (heterophile antibodies in patient's serum) • Several dilutions required at very high levels of prolactin for accurate measurement

CV: coefficient of variation, E2: estradiol, LCMS: liquid chromatography/tandem mass spectrometry, SHBG: sex hormone-binding globulin, T: testosterone, TT: total testosterone

Table 4: Assays for the Diagnosis of Testosterone Deficiency

Assay	Units	Co-efficient of Variation	Advantages	Disadvantages
PSA				
Immunoassay	ng/mL	Intra-assay: <5% Inter-assay: <8%	• Rapid • High throughput • WHO standardization to minimize variation between assays	• Despite standardization, variation does exist between assays performed on different instruments.
LCMS	ng/mL	CV: 2-6%	• Excellent sensitivity and specificity	• Not FDA approved • Labor intensive • Low throughput

CV: coefficient of variation, E2: estradiol, LCMS: liquid chromatography/tandem mass spectrometry, SHBG: sex hormone-binding globulin, T: testosterone, TT: total testosterone

GUIDELINE STATEMENTS

Diagnosis of Testosterone Deficiency

1. **Clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone. (Moderate Recommendation; Evidence Level: Grade B)**

Given the relative non-specificity of symptoms associated with low testosterone, a need exists to define a total testosterone threshold to guide clinicians in the diagnosis and management of the testosterone deficient male. The Panel believes that total testosterone <300 ng/dL is the proper threshold value to define low testosterone. This will increase clinicians' confidence regarding the risk-benefit ratio of testosterone therapy, explicitly place a higher value on maximizing true benefit, and reduce clinically inefficacious testosterone therapy. To support this threshold, a series of RCTs of testosterone therapy were evaluated, all of which used a cutoff of total testosterone <350 ng/dL as inclusion criterion. Across these studies, the median baseline total testosterone was 249 ng/dL, with interquartile ranges of 233 - 283 ng/dL.

A number of medical societies (e.g., American Society of Andrology, Endocrine Society, European Association of Urology, European Academy of Andrology, International Society of Andrology, International Society for the Study of the Aging Male) have used various thresholds to define low total testosterone, ranging from 230-350 ng/dL. Large-scale population studies that have attempted to quantify the prevalence of testosterone deficiency have also established 250-350 ng/dL (concurrent with certain symptoms and signs) as the threshold for the diagnosis of testosterone deficiency.[4-8]

Establishing total testosterone thresholds for a diagnosis of testosterone deficiency is challenging considering the heterogeneity that exists in the testosterone deficiency literature. There is a great deal of variability across studies with respect to the forms of testosterone measured (total versus free), the assays utilized to measure testosterone, the time of day when the sample is obtained, and the number of testosterone measurements taken. The most accurate testosterone measurements are obtained in the early morning and on more than one occasion, which is not uniform across testosterone trials.

The Panel recommends that clinicians use the same laboratory with the same method/instrumentation for serial total testosterone measurement. Where possible, clinicians should use LCMS to measure total testosterone levels to maximize accuracy and limit CV between tests in men undergoing testing, particularly in men with very low total testosterone levels. The Panel recognizes that not all laboratories use LCMS technology, and immunoassays may be the only measurement tool available to clinicians.

Some authorities have advocated that free testosterone should be the primary measure used to define testosterone deficiency. This is based on the concept that the free testosterone fraction is believed to be the most biologically active component. Although direct measurement of free testosterone has a generally good correlation with equilibrium dialysis, it is not reliable because of high CV. Given that the direct method for free testosterone measurement is also time-consuming and labor intensive, calculation derived free testosterone measurement is more commonly used, however there is considerable variation in total testosterone assays as well as the clinical conditions that affect serum albumin and SHBG, all of which impact this measurement.

The Panel does not recommend using free testosterone measurements as the primary diagnostic method for testosterone deficiency. Total and free testosterone are not to be considered interchangeable measures as there is no clear data that point to consistent thresholds between the two measures below which deficiency symptoms are observed and above which therapeutic benefits occur.[15, 16] An analysis of 3,219 men (mean age 58 years) who had a single morning testosterone measurement suggested that using a free testosterone level added no value to the diagnosis of testosterone deficiency when the total testosterone level was <231 ng/dL. When total testosterone was between 230-317 ng/dL, free testosterone measurement may be helpful in diagnosis.[8] Free testosterone also has a place in the diagnosis of testosterone deficiency in highly symptomatic patients with total testosterone levels in the low/normal or equivocal range.[17]

The Panel recognizes that in clinical practice there are men who have total testosterone levels >300 ng/dL who are highly symptomatic and who have anecdotally experienced symptom/sign improvement with testosterone therapy. The Panel urges clinicians to use their clinical judgment in the management of such patients. One strategy is to further evaluate patients using adjunctive tests, which might strengthen an argument for a short-term trial of testosterone therapy. Such tests are discussed in Appendix C.

2. **The diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. (Strong Recommendation; Evidence Level: Grade A)**

There are inherent challenges in testosterone measurement due to the health status of patients at the time of testing, circadian rhythms in testosterone production, intra-individual variability, and inconsistencies in the assays themselves. To ensure accuracy and precision, it is necessary to obtain *at least two* serum total testosterone measurements in an early morning fashion to diagnose patients with low testosterone. If a patient's first test is <300 ng/dL and the second test is normal, then the clinician should use his or her judgment to determine if a third test is to be used as a control.

At this time, there is no definitive evidence indicating what the optimal time interval should be between the two separate tests. Likewise, while some literature suggests that food ingestion might affect testosterone levels, the evidence is particularly weak, and the Panel does not recommend that clinicians insist on fasting prior to testing.

***Circadian Rhythm*.** Among men with traditional (10p.m. to 6a.m.) sleep patterns, peak testosterone values occur around 3-8a.m., with 32-39% of the diurnal total decline occurring within the first 30 minutes of waking.[18-23] Older men experience diurnal blunting and more stability in testosterone levels throughout the day, while younger men undergo greater variation. Total testosterone values obtained at 4p.m. in men aged 30-40 years were 20-25% lower than measurements takes at 8a.m., while men aged 70 years experienced only a 10% decline between the two time points.[23]

Intra-individual Testosterone Variability. Intra-individual testosterone variability is significant. Repeat measures can fluctuate 65-153% between tests, depending upon the assay utilized,[24] however using 2 or 3 measures can reduce this variability by 30-43%, respectively. To minimize these effects, two morning draws for testosterone are recommended before any clinical intervention.

Acute Illness. Acute illnesses should be considered when measuring testosterone levels, the presence of which can affect the accuracy of the test and lead to artificially decreased testosterone measurements. In a small study of young men with acute respiratory infections, mean total testosterone levels declined by 10%, with some cohorts experiencing reductions of up to 30%.[25]

3. **The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs.(Moderate Recommendation; Evidence Level: Grade B)**

Total testosterone <300 ng/dL alone does not define testosterone deficiency. The diagnosis of testosterone deficiency must include the presence of symptoms and/or signs associated with low testosterone in combination with documented low total testosterone levels. Clinicians should make note of any patient-reported symptoms, particularly those listed in Table 5 and conduct a physical examination to assess patients for signs related to low testosterone. Making a diagnosis of testosterone deficiency in the absence of signs and/or symptoms increases the likelihood of making a false diagnosis and reduces the potential benefit of testosterone therapy. Clinicians should refrain from measuring testosterone levels in patients who are asymptomatic, do not exhibit signs related to low testosterone, or do not have any comorbid conditions that are associated with low testosterone.

A challenge in making the diagnosis of testosterone deficiency is that many of the symptoms reported by patients are non-specific and might be related to conditions other than low testosterone. Patients complaining of changes in mood (e.g., irritability, depression), decreased ability to focus, decreased intellectual function, perceived decrease in strength and physical function, loss of muscle mass (sarcopenia), increased fat mass (especially centrally-located visceral fat), erectile dysfunction ([ED], including absence of nocturnal/early morning erections), or decreased sex drive may exhibit these symptoms secondary to chronic stress, chronic fatigue, or depression rather than due to low testosterone levels.

Fatigue (especially afternoon fatigue) may be associated with low testosterone levels, but it is a symptom that is non-specific and can be attributed to other conditions. A meta-analysis of 4 observational studies involving 4,426 men, showed that men with low testosterone levels had a higher prevalence of fatigue than men with normal testosterone levels (OR=1.46; CI 1.16, 1.98).[26-29] While significant heterogeneity was not detected in this analysis, the thresholds used to define low testosterone varied among the studies. Those that used <350ng/dL as a cut-off to define low testosterone did not detect a significant association between

reported fatigue and testosterone level (p=0.547),[29] but studies that used a lower cut-off found this correlation to be stronger.[26-28] A study of 203 men with documented type 2 diabetes (mean age 61.4 years) found that patients who had total testosterone <231 ng/dL (n=73) were significantly more likely (p=0.02) to report fatigue on the Androgen Deficiency in the Aging Male (ADAM) questionnaire than men who had total testosterone >231 ng/dL (n=130).[28] Similarly, a cross-sectional analysis of 355 diabetic men found that 68% of men (49/71) who had total testosterone <231 ng/dL and 64% of men (70/109) with testosterone 231-346 ng/dL reported fatigue on the ADAM questionnaire, while only half of men with total levels >346 ng/dL reported fatigue.[27]

Men who have been diagnosed with ***depression*** are more likely to have low testosterone than men who are not depressed (OR=1.81; CI: 1.48, 2.32)[30-34] however, a meta-analysis of 7 observational studies that compared the prevalence of depression between men with low testosterone men and with normal testosterone did not detect a significant difference between the two groups (OR=1.23; CI: 0.92,1.63).[1, 35-40] This is partly due to the subjective nature of depressive symptoms and the fact that the symptoms of depression can overlap with those associated with other conditions. Studies whose primary endpoint was to measure the association between depression and low testosterone found that men with low testosterone have a significantly higher incidence of depression as well as a shorter time to onset of depression. This is particularly pronounced in older men with low testosterone, who are 3-times more likely to have increased risk of depression when compared to men with normal testosterone (HR=3.2; CI 1.7, 5.9). After adjustment for age and comorbidities, low testosterone levels remained a statistically significant predictor of the age of onset of depression (HR=2.1, CI 1.3, 3.2; p=0.002).[39]

ED (organic in nature) is a symptom that may be associated with low testosterone. The Panel recognizes that ED is often correlated with medical conditions that are themselves associated with low testosterone (e.g., low sex drive, diabetes, obesity) and that the presence of these comorbidities makes it difficult to isolate the association between low testosterone and ED or definitively state that low testosterone is an independent predictor of ED. The scientific literature examining the relationship between ED and low testosterone is further limited by the variability in, or absence of, the definition of ED, incomplete vascular comorbidity information, as well as variability in the thresholds used to define low testosterone. Despite the methodological limitations, individual studies have shown a link between low testosterone levels and ED. The Panel recognizes ED as a symptom associated with low testosterone levels and clinicians are advised to measure total testosterone in all such patients.

Point estimates that measure the difference in testosterone levels between men with and without ED may appear statistically significant, but these estimates are not always clinically meaningful. Pooled analysis of 29 studies indicates that men with ED have lower testosterone levels than men without ED (mean difference = -47ng/dL; CI: -69, -25.52);[37, 41-68] however, this difference, while significant, is negligible and does not provide the clinician with clinically relevant discrimination between these populations.

There does appear to be a trend towards lower total testosterone and a diagnosis of ED. The European Male Aging Study (EMAS)[8] studied 3,369 men (mean age 59 years) and culled data on their sexual, physical, and psychological symptoms along with morning total testosterone measurements. Adjusted logistical regression showed an inverse relationship between total testosterone and the presence of ED, with a probability of experiencing ED increasing as total testosterone levels decreased. Specifically, the odds ratio for developing ED in men with total testosterone <317ng/dL was 1.64 (CI: 0.93, 2.80) compared to 1.94 (CI: 1.20, 1.83) in men with total testosterone <231ng/dL. An analysis of 625 men in the Massachusetts Male Aging Study (MMAS)[6] used a single question to define ED and also showed an increase in ED risk as total testosterone levels decreased. However, after accounting for confounding variables (e.g., age, body mass index [BMI], comorbidities, depression), the study found that testosterone levels had no effect on the likelihood of having ED (OR=0.99; CI: 0.11, 1.11).

Other symptoms that may be associated with low testosterone include gynecomastia, history of infertility/ difficulty conceiving, visual field changes (bitemporal hemianopsia), and anosmia.

Clinicians should conduct a ***targeted physical exam*** to examine patients for signs that are associated with low testosterone. This assessment should include evaluation of general body habitus; virilization status (examination of body hair patterns and amounts in androgen dependent areas); BMI or waist circumference; evaluation for gynecomastia; testicular evaluation; and presence of varicoceles.

Men who are ***obese*** (BMI ≥30) or who have ***increased waist circumference*** (>40 inches) should have their testosterone levels checked.[69] Although obesity is a confounding factor and is often associated with other conditions (e.g. diabetes), obesity is also associated with low testosterone levels. Obese men are almost five times more likely to have low testosterone than men who are not obese (OR=4.89; CI: 2.35, 10.17).[43, 70-73] Unadjusted baseline measurements of 1,687 middle-aged men who were classified as normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9) or obese (BMI >30) showed that nearly a third of overweight/obese subjects had low total testosterone (<300 ng/dL) compared to 6.4% of men who were of normal weight.[71] Another study in younger men (aged 19-24 years) with ED indicated that there was a statistically significant difference ($p<0.001$) in the prevalence of low testosterone between men who were stratified to BMI <27 (non-obese) and BMI >27 (obese).[43] A study in 225 men found that BMI was associated with low testosterone; specifically, there was a 2.2 fold increase in the odds of low testosterone for every 5-point increase in BMI.[74]

Recent studies have explored the association between ***varicocele*** and low testosterone levels, and while there is no definitive evidence that varicocele presence is a cause of low testosterone, accumulating data suggest that ligation surgery might increase serum testosterone levels. A systematic review found that varicocele ligation results in significant improvement in testosterone levels in some men, with a mean improvement of approximately 100 ng/dL. At this time, identification of the optimal patient (based on age, varicocele grade, baseline testosterone level) has not been defined.[75]

Gynecomastia is a benign enlargement of the male breast tissue that can occur at times of male androgen/ estrogen change (alteration in testosterone/estradiol [E2] ratio), infancy, adolescence, or old age, and may be a sign of low serum testosterone. Male breast growth can be classified as pharmacological (associated with risperidone, cimetidine, anti-androgens, digoxin, clomiphene, methadone, marijuana, chlorpromazine), physiological (occurring in the neonatal period and at puberty), and pathological (in association with testosterone deficiency, testicular tumors, hyperprolactinemia, Klinefelter syndrome [KS], HIV disease, or cirrhosis). Histologically, the male breast contains both glandular and fatty tissue, and although gynecomastia may result from proliferation in either or both, proliferation of only the fatty tissue is termed pseudogynecomastia. Only 1% of male breast enlargement is caused by malignancy,[76] however with any enlargement of the male breast, the possibility of carcinoma should be considered.

Table 5: Symptoms and Signs Associated with Testosterone Deficiency

Physical Symptoms and Signs
Reduced energy
Reduced endurance
Diminished work performance
Diminished physical performance
Loss of body hair
Reduced beard growth
Fatigue
Reduced lean muscle mass
Obesity
Cognitive Symptoms and Signs
Depressive symptoms
Cognitive dysfunction
Reduced motivation
Poor concentration
Poor memory
Irritability
Sexual Symptoms and Signs
Reduced sex drive
Reduced erectile function

4. **Clinicians should consider measuring total testosterone in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use even in the absence of symptoms or signs associated with testosterone deficiency. (Moderate Recommendation; Evidence Level: Grade B)**

Anemia. It is believed that as many as one-third of older men have unexplained anemia[77] and data from observational studies indicate that there is a significant association between low testosterone levels and reduced hemoglobin (Hb) levels. As such, all patients who have a history of unexplained anemia should have their testosterone tested. A meta-analysis of 10 studies showed that men with baseline low testosterone levels had significantly lower Hb values than men with normal testosterone (mean Hb difference: -0.65 mg/dL; CI -0.95, -0.36).[26, 78-87] The significance of the relationship was independent of thresholds used to define low testosterone among the studies (196 ng/dL - 300 ng/ dL) or study population, which included patients with

spinal cord injury, diabetes, renal failure, and heart disease.

A linear regression model run on cross-sectional data from EMAS that controlled for age, BMI, smoking status, and other comorbidities found that men who had moderate (231 ng/dL-317 ng/dL) and severe (<231 ng/dL) testosterone deficiency had significantly lower Hb as compared to testosterone replete patients.[8]

Bone Density Loss. While it has been estimated that more than one third of men over the age of 50 years with testosterone deficiency have bone density loss,[88, 89] the evidence linking low testosterone levels to osteopenia/osteoporosis in older men is not definitive. Aging is associated with reduced bone mineral density (BMD), which can lead to risk of fractures.[90] Given the larger implications for men's health, particularly in elderly patients, the Panel recommends that men who present with low-trauma bone fractures (LTBF) have their testosterone measured. Clinicians might also consider obtaining a bone densitometry (DEXA) scan to establish a baseline measurement (Appendix C). Although a meta-analysis of 3 observational studies in elderly men (aged 60-74 years) showed no significant difference in BMD in patients who had low testosterone levels compared to those who had normal levels (mean difference -0.19 g/cm^2, CI: -0.44, 0.05),[26, 90, 91] serum E2 levels were found to be associated to BMD.[88, 90] One study of 162 men aged 65-88 years who had total testosterone levels <300 ng/dL did find that low testosterone levels were a significant independent predictor of BMD loss after controlling for age, weight, height, and BMI ($p<0.05$).[91] The association between low testosterone and BMD might extend to younger men as well. A retrospective review of 399 men (mean age 37 years) with a mean total testosterone of 308 ng/dL found that 35% of patients had BMD at osteopenic levels and 3% had osteoporosis. BMD increased in patients treated with testosterone therapy leading the authors to conclude that younger testosterone deficient men may benefit from having routine DEXA scans performed, particularly those with concomitant low E2 and low BMI.[89]

Diabetes. Patients who have diabetes have been shown to have significantly lower testosterone levels than men who are not diabetic, and the American Association of Clinical Endocrinologists (AACE) recommends that men with type 2 diabetes be evaluated for testosterone deficiency.[69] A meta-analysis of 52 studies that compared testosterone levels in diabetic men and non-diabetic men showed a significant reduction in testosterone values in men who had diabetes (mean difference -73.57 ng/dL; CI: -84.20, -62.67).[20, 54, 64, 92-137] The patient populations across studies had a high degree of heterogeneity and contained testosterone measurements taken at baseline that were unadjusted, which is problematic in diabetes analysis given that obesity is a potentially confounding factor. Another meta-analysis of 37 studies[138] found that diabetic men had significantly lower testosterone values than those who did not have diabetes; individual studies with adjusted point estimates also support this outcome.[97, 133, 139] A multivariate logistic regression model from one study of 1,089 men who had total testosterone <300 ng/dL and type 2 diabetes identified diabetic neuropathy as an independent risk factor for low testosterone.[94] Corona et al. likewise found that the prevalence of low testosterone levels (defined as total testosterone of <300 ng/dL) was 24.5% in diabetic men as compared to 12.6% in the rest of the sample ($p<0.0001$), a difference that remained significance after adjustment for age and BMI.[107]

Chemotherapy. A meta-analysis of 5 studies that examined the effects of chemotherapy on testosterone levels indicates that men with a history of chemotherapy have significantly reduced serum testosterone when compared to men who do not have such a history (mean difference -109.22 ng/dL; CI: -209, -8.69).[140-144] Although some of studies included in the analysis did not show a significant difference in testosterone levels in chemotherapy patients as compared to controls, the age of the patients might have been a contributing factor. One study involving 1183 testicular cancer survivors (mean age 44 years) who underwent either surgery, radiotherapy, or two different chemotherapy protocols found that the odds of a testosterone deficiency diagnosis after treatment was over 7-times greater in the low-dose chemotherapy group (cisplatin 850 mg) and over 4-times greater in the high-dose chemotherapy group (cisplatin >850 mg) as compared to the controls (adjusted OR=7.9 and adjusted OR=4.8, respectively).[142]

Testicular Radiation Therapy. Men who have had exposure of their testes during radiation therapy, either through direct or scatter radiation, are possibly at risk for low testosterone and the Panel recommends total testosterone measurement in such patients. While Leydig cells are less radiosensitive than germ cells, radiation exposure to the testis can impair testosterone production. Two studies[145, 146] included in the evidence report that was developed in the support of this guideline suggest a link between radiation (in rectal cancer and prostate cancer patients) and low testosterone levels, however the studies are limited by

heterogeneity in study populations, heterogeneity in radiation delivery, and the presence of confounders such as chemotherapy exposure. Conversely, a recent study exposing patient testes to radiation (3 patients 17Gy and 4 patients 24Gy) demonstrated normal testosterone levels up to 3 years after radiation exposure.[147]

HIV. Men who are seropositive for HIV have been shown to have a higher rate of testosterone deficiency than the general population.[37] Cohort studies in HIV infected men have estimated that the rate of testosterone deficiency in this group ranges from 17-38%,[37, 148, 149] while population-based studies have estimated the rate of testosterone deficiency much lower.[6, 37, 87] It was once thought that gonadal dysfunction in HIV infected men is caused by virus-induced reduction in Leydig cells, but in the post-antiretroviral therapy era, it is postulated that the etiology of testosterone deficiency can be attributed to malnutrition, cytokine activity, opportunistic infections/ acute illnesses, or the HIV medications themselves.[37, 148] HIV infected men who are testosterone deficient have also been shown to have concomitant elevated HbA1c levels (p=0.016) and are at higher risk for CVD (p=0.004) when compared to HIV+ patients who have normal testosterone levels.[148] Patients who are seropositive for HIV should have their testosterone levels measured given the co-morbidity risks as well as evidence culled from placebo-controlled randomized trials that indicates that HIV+ men respond favorably to testosterone replacement therapy[150-152] in absolute terms; QoL indicators; and muscle strength, size, and volume.

Chronic Narcotic Use. Men who have a history of chronic narcotic use are at an increased risk of opioid-induced androgen deficiency, which is characterized by low testosterone levels.[42] A meta-analysis of 7 studies showed that men who were on opioid treatment for non -cancer related pain for at least 30 days had a significant reduction in testosterone levels (-117.11 ng/ dL; CI -176.17, -58.04)[42, 153-158] when compared to patients who were opioid-free.

Male Infertility. Testosterone deficiency is prevalent in men presenting for an infertility evaluation.[159] The testes contain germ cells that produce spermatozoa and Leydig cells that produce testosterone; any pathology of the testes can result in infertility and testosterone deficiency, conditions that frequently co-exist. A survey of 120 patients who were treated for infertility at the University of Illinois-Chicago found that the incidence of testosterone deficiency was 45% in men with non-obstructive azoospermia, 42.9% in men with oligospermia, and 16.7% in men with obstructive azoospermia.[159]

Pituitary Disorders. Pituitary dysfunction may be a significant cause of testosterone deficiency. The pituitary gland sits in the sella turcica below the cerebrum and plays a critical role in testosterone physiology by producing luteinizing hormone (LH), which targets the Leydig cells in the testes stimulating them to produce testosterone. Serum testosterone and the downstream hormone E2 are involved in the feedback mechanism to the hypothalamus and pituitary to suppress LH production. In homeostasis, LH levels are typically low. With worsening Leydig cell function, there is a reduction in the feedback mechanism resulting in elevation of LH levels (hypergonadotropic hypogonadism). In conditions where LH is not produced in normal amounts (hypogonadotropic hypogonadism), testosterone deficiency may also result. The most common clinical causes of pituitary-associated hypogonadotropic hypogonadism include prolactinoma, pituitary radiation, pituitary removal, hemochromatosis/iron overload and certain parasellar processes. Functioning prolactinomas result in hyperprolactinemia, suppressing LH production and leading to low testosterone levels. The contemporary management of functioning prolactin secreting tumors is the use of medications, such as bromocriptine and cabergoline. Large pituitary tumors, functioning or non-functioning, may require surgical extirpation because of mass effect. Radiation to the brain that exposes the pituitary gland can also result in pituitary dysfunction and low testosterone. The hypothalamic-pituitary unit is highly radiosensitive. Thus, pituitary dysfunction can develop after radiation therapy for sellar, parasellar, and extrasellar neoplasms (e.g., craniopharyngiomas, meningiomas, germinomas, chordomas, hemangio-pericytomas, pituicytomas, gliomas), head and neck tumors, and following total body irradiation for systemic malignancies. Depending upon the radiation dose, delivery modality, and underlying tumor type, LH deficiency rates in patients whose pituitary gland has been exposed to radiation is 10-96%.[160]

Chronic Corticosteroid Use. Men who have a history of chronic corticosteroid use have been shown to be at risk for low testosterone levels. An analysis of 3 studies with highly homogeneous populations showed that corticosteroid users had a significant reduction in testosterone levels when compared to men who were not on steroid therapy (-85.22 ng/dL; 95 CI: -105.17, -65.27).[161-163] In particular, men who are on long-term corticosteroid therapy are more likely to have a

diagnosis of low testosterone (OR=1.82; CI: 1.15, 2.86).[161, 250] In one study, 36 long-standing rheumatoid arthritis (RA) patients (mean duration of disease 17 years) aged 38-75 years were followed for 6 months to determine the effect of prednisone on testosterone levels. At the end of follow-up, RA patients who were on 5-10 mg of prednisone/day had a mean testosterone level of 356 ng/dL, which was a statistically significant difference from testosterone levels measured in healthy controls (409 ng/dL; $p<0.05$).[162] However, another study in 99 men with RA returned conflicting results: 74 men taking 5 mg/day of prednisone (with a cumulative dose of 8,633 mg) had an average total testosterone of 461 ng/dL, which was lower than those men who were not on steroid treatment (n=25; 545 ng/dL), but the difference was not statistically significant ($p<0.06$).[163]

5. **The use of validated questionnaires is not currently recommended to either define which patients are candidates for testosterone therapy or monitor symptom response in patients on testosterone therapy. (Conditional Recommendation; Evidence Level: Grade C)**

Screening questionnaires are not an appropriate tool to identify candidates for testosterone therapy. Their role in diagnosing testosterone deficiency is unclear, and they should not be used at the expense of a full patient evaluation, including laboratory testosterone measurement.

Several validated questionnaires are used as screening tools to identify men at high risk for testosterone deficiency, but there is an absence of concordance among the questionnaires as to what symptoms are related to low testosterone or to what extent these symptoms improve with treatment. The validation studies for each questionnaire use a distinct total testosterone cut-off for defining low testosterone; however, total testosterone has been shown to correlate poorly with most questions.[164, 165]

The validated instruments include ADAM, Quantitative ADAM, Aging Male Survey (AMS), MMAS, and the ANDROTEST.[10, 166, 167] Specificities and sensitivities vary greatly amongst these tests making them ill-suited for screening or for use as a surrogate for testosterone laboratory testing. Higher sensitivities and lower specificities have been reported for the AMS and ADAM, with a sensitivity/specificity of 81%/19% and 97%/39%, respectively, for each questionnaire; while the MMAS and ANDROTEST exhibit lower sensitivities and higher specificities, with a sensitivity/specificity of 60%/53% and 71%/65%, respectively.[10]

Adjunctive Testing

6. **In patients with low testosterone, clinicians should measure serum luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)**

LH, which is routinely measured by immunoassay, may help to establish the etiology of testosterone deficiency and can be an important factor in determining if adjunctive tests should be ordered (Appendix C). A low or low/normal LH level points to a secondary (central) hypothalamic-pituitary defect, (hypogonadotropic hypogonadism), while an elevated LH level indicates a primary testicular defect (hypergonadotropic hypogonadism).[168] In men with hypogonadotropic hypogonadism, the yield from adjunctive tests (e.g., prolactin measurement, pituitary imaging, iron studies) is increased. However, the literature at this time fails to define the LH level below which such adjunctive testing is warranted.

Hypogonadotropic hypogonadism can result from a number of conditions, including congenital abnormalities (e.g. Kallman syndrome), as well as pituitary or suprasellar tumors, pituitary infiltrative disorders (e.g., hemochromatosis, tuberculosis, sarcoidosis, histiocytosis), medications (i.e. chronic narcotic exposure), hyperprolactinemia, prior head trauma, pituitary apoplexy, and severe chronic illness. In the event that a patient may have hypogonadotropic hypogonadism, adjunctive tests should be ordered.

Hypergonadotropic hypogonadism, which is not a contraindication to begin testosterone therapy, can result from a number of conditions, including congenital abnormalities (KS being the most common), iatrogenic causes (e.g., bilateral orchiectomy, testicular radiation, chemotherapy), testicular trauma, infection, or autoimmune damage. In some cases, the etiology is obvious (e.g. iatrogenic causes), in others, a karyotype may be warranted to establish a diagnosis of KS (47, XXY).[169] In other cases, it may not be possible to establish a definitive etiology.

Testosterone deficient patients with low or low/normal LH levels can be considered candidates for SERM use as a treatment for testosterone deficiency, particularly those wishing to preserve their fertility.[170] However, an LH level below which SERM response is optimized is not firmly established.

7. Serum prolactin levels should be measured in patients with low testosterone levels combined with low or low/normal luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)

In patients who have low total testosterone and low or low/normal LH levels (hypogonadotropic hypogonadism), serum prolactin should be measured to screen for hyperprolactinemia (Appendix C).[168, 169] If a patient has elevated prolactin levels, prolactin measurement should be repeated to ensure that the initial elevation was not spurious. Men with total testosterone levels of <150 ng/dL in combination with a low or low/normal LH should undergo a pituitary MRI regardless of prolactin levels, as non-secreting adenomas may be identified.[171]

8. **Patients with persistently high prolactin levels of unknown etiology should undergo evaluation for endocrine disorders. (Strong Recommendation; Evidence Level: Grade A)**

Hyperprolactinemia is an uncommon condition[172, 173] but it is a well-established cause of secondary (central) testosterone deficiency and can lead to infertility, decreased libido, sexual dysfunction, and gynecomastia. Medications, most commonly dopamine antagonists (but also anti-psychotics, anti-emetics, proton pump inhibitors, calcium channel blockers, opiates, and selective serotonin reuptake inhibitors) may cause hyperprolactinemia.[173] Chronic medical conditions, such as hypothyroidism, renal failure, and cirrhosis are associated with hyperprolactinemia as well.[174]

Persistently elevated prolactin levels can indicate the presence of pituitary tumors such as prolactinomas,[175] the most common functioning pituitary tumor. Current literature fails to support any specific level of prolactin elevation that is predictive of prolactinomas, however any persistent elevation in prolactin level may be associated. While prolactin levels generally parallel tumor size, most are typically associated with prolactin levels above 250 mg/L,[175] although levels can exceed 1,000 mg/L.[176] Milder elevations in prolactin can be seen with prolactinomas as well as with other pituitary or parasellar tumors or infiltrative processes.[176, 177]

Patients should be referred to an endocrinologist for further evaluation if the etiology for hyperprolactinemia cannot be established. An evaluation for a prolactinoma in such patients is imperative because these benign tumors can be effectively managed using medications, such as bromocriptine or carbergoline. Furthermore, the identification of other pituitary tumors or processes may have important clinical implications for the patient beyond testosterone deficiency.[178]

9. 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)

Given the enzymatic conversion of testosterone to E2 by aromatase, it is not uncommon for E2 levels to increase while patients are on testosterone therapy.[179] Men who present with breast symptoms should have their E2 measured (Appendix C) and those with elevated E2 measurements (>40 pg/mL), should be referred to an endocrinologist. For men who develop gynecomastia/breast symptoms while on treatment (e.g., breast pain, breast tenderness, nipple tenderness), a period of monitoring based on clinical judgment should be considered, as breast symptoms sometimes abate.

Clinicians should be aware that symptomatic gynecomastia or other breast symptoms are an uncommon side effect in men on testosterone therapy. In randomized, placebo-controlled trials involving testosterone therapy this has been a rarely reported adverse event. Among all of the studies included in the evidence report for this guideline, only 3 returned gynecomastia events.[180-182] In one multi-center study across 16 sites, 227 men (19-68 years, untreated for low testosterone in the preceding four weeks) were given either 50mg of testosterone gel (n=73), 100 mg of testosterone gel (n=78), or a testosterone patch (n=76). After 180 days of treatment, only 1 patient in the 50mg gel arm, 3 patients in the 100mg gel arm, and no patients in the testosterone patch arm were found to have gynecomastia. Of these four men, two were known to have pre-existing gynecomastia.[180]

Another multi-center study compared the effectiveness and risks of transdermal and IM testosterone in 66 men aged 22-65 years old. At the end of the 24-week trial, there was only 1 new case of gynecomastia in the transdermal group; 4/9 pre-existing cases either resolved or improved. In the IM testosterone group, there were no new cases of gynecomastia, and one patient with pre-existing gynecomastia had gynecomastia resolution.[181]

Finally, a randomized trial of 76 men (mean age 50.6 years), who had at least 1 ejaculatory dysfunction symptom and at least 2 testosterone tests <300 ng/dL,

were put on 2% transdermal testosterone (60 mg daily) solution for 16 weeks. There was only 1 reported case of gynecomastia in the treatment arm (n=35) at follow up compared to no cases in the placebo group (n=35).[182]

10. Men with testosterone deficiency who are interested in fertility should have a reproductive health evaluation performed prior to treatment. (Moderate Recommendation; Evidence Level: Grade B)

Men diagnosed with testosterone deficiency who are interested in preserving their current fertility should undergo testicular exam to evaluate testicular size, consistency, and descent and have their serum follicle-stimulating hormone (FSH) measured to assess their underlying reproductive health status (Appendix C).[183] Most of the testis is composed of reproductive tissue, such as germ cells and Sertoli cells, and it is common for men with reduced testicular volume to also have impaired sperm production.[184]

FSH, a pituitary gonadotropin, targets the Sertoli cells within the testes and is a key regulator of spermatogenesis.[185, 186] Based on the hypothalamic-pituitary-gonadal feedback mechanisms, normal spermatogenesis is typically associated with an FSH level in the low/normal range.[169] Elevated FSH levels in the setting of testosterone deficiency (hypergonadatropic hypogonadism) is typically indicative of impaired spermatogenesis, and in such patients, clinicians should consider fertility testing, such as semen analysis.[169] Patients who have severe oligospermia (sperm concentration <5 million sperm per mL) or non-obstructive azoospermia should be offered reproductive genetics testing consisting of karyotype testing and Y-chromosome analysis for microdeletions.[183] The management of such patients is best conducted by a reproductive urologist.

11. Prior to offering testosterone therapy, clinicians should measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia. (Strong Recommendation; Evidence Level: Grade A)

Polycythemia, sometimes called erythrocytosis, is generally defined as a hematocrit (Hct) >52%. It is categorized into primary (life-long), often related to genetic disorders; and secondary (acquired), which is attributed to polycythemia vera, living at high altitude, hypoxia (e.g., chronic obstructive pulmonary disease, obstructive sleep apnea, tobacco use), paraneoplastic syndromes, and testosterone therapy.[187] [188]

Prior to commencing testosterone therapy, all patients should undergo a baseline measurement of Hb/Hct (Appendix C). If the Hct exceeds 50%, clinicians should consider withholding testosterone therapy until the etiology of the high Hct is explained.[187] While on testosterone therapy, a Hct ≥54% warrants intervention. In men with elevated Hct and high on-treatment testosterone levels, dose adjustment should be attempted as first-line management. In men with elevated Hct and low/normal on-treatment testosterone levels, measuring a SHBG level and a free testosterone level using a reliable assay is suggested. If SHBG levels are low/free testosterone levels are high, dose adjustment of the testosterone therapy should be considered. Finally, men with elevated Hct and on-treatment low/normal total and free testosterone levels should be referred to a hematologist for further evaluation and possible coordination of phlebotomy.

Androgens have a stimulating effect on erythropoiesis and elevation of Hb/Hct is the most frequent adverse event related to testosterone therapy.[189-191] During testosterone therapy, levels of Hb/Hct generally rise for the first six months, and then tend to plateau.[192, 193]

Among 5 randomized, placebo-controlled trials that evaluated Hb and Hct levels in men (mean baseline testosterone <300 ng/dL) using either gel, solution, or IM testosterone therapy for 12 weeks to 1 year, a significant increase in the incidence of elevated Hct was observed in those using testosterone (OR=6.46; CI: 1.86, 22.40) compared to those on placebo.[194-201] The calculated odds ratio belies the number of polycythemia events in absolute terms; 19 events in 1,094 patients occurred in the treatment arm as compared to 1 event in 1,093 patients in the placebo group.

While the incidence of polycythemia for one particular modality of testosterone compared to another cannot be determined, trials have indicated that injectable testosterone is associated with the greatest treatment-induced increases in Hb/Hct. In the current meta-analysis of RCTs, long-acting IM testosterone resulted in a mean increase in Hb levels of 1.4 mg/dL compared to 1.6 mg/dL with short-acting IM testosterone, 0.9 mg/dL with transdermal preparations, and 0.7 mg/dL with topical patches.[150, 182, 194-196, 201-218] This is likely due to the high and sometimes supra-physiological levels of testosterone that occur in the early days after injection.[219] A retrospective comparative series involving 175 men with testosterone deficiency who used different modalities of testosterone therapy reported that 19% of men receiving IM testosterone

experienced polycythemia compared to 12.5% with testosterone pellets and 5.4% with gels.[220]

It is unclear if the risk of polycythemia is greater in men with comorbid disorders that predispose to hypoxia, such as chronic obstructive pulmonary disease or obstructive sleep apnea.[188] It is also currently unknown if rates of polycythemia are associated only with short-acting injectable agents or occur with equal frequency when using the longer-acting testosterone undecanoate.[221]

12. 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)

In 2013, the AUA published the Early Detection of Prostate Cancer Guideline,[222] which makes no specific statements about PSA screening in men with testosterone deficiency or in men on testosterone therapy. It is the opinion of this Panel that serum PSA levels should be measured prior to the commencement of testosterone therapy in patients over 40 years of age in order to minimize the risk of prescribing testosterone therapy to men with occult prostate cancer.

PSA Response to Testosterone Therapy. PSA secretion is an androgen dependent phenomenon, and the rise of PSA levels in patients on testosterone therapy is primarily dependent upon baseline total testosterone levels. The literature indicates that men with lower baseline testosterone levels are more likely to experience PSA level increases. The Testim Registry in the United States followed PSA changes in men without prostate cancer who were on testosterone therapy. Participants (N=451) received 5-10g of 1% testosterone gel daily for 12 months. Patients were divided into 2 groups: A (n=197 with total testosterone <250ng/dL) and B (n=254 with total testosterone ≥250 ng/dL). In group A but not group B, baseline PSA levels correlated significantly with total testosterone levels (r=0.2; p<0.01). At the end of follow-up, PSA increased significantly in group A (21.9% change; 0.19±0.61 ng/mL; p=0.02) but not in group B (14.1% change; 0.28±1.18 ng/mL; p=0.06) with the greatest PSA change observed after one month of treatment.[223]

A meta-analysis of 9 RCTs that compared PSA changes in men who were treated with testosterone therapy to men who were on placebo showed that there was no difference in the risk of elevated PSA during or after the study period (OR=1.71; CI: 0.98, 3.00).[197-199, 216, 217, 224-230] While these RCTs were not powered to detect an increase in PSA as a primary or secondary endpoint, each trial measured PSA at baseline, intermittently throughout treatment, and at the end of study. Across all 9 studies, 2,601 men (mean range 55-74 years) with testosterone <350 ng/dL (mean range 225-303 ng/dL) were randomized to placebo (n=1,165) or treatment with transdermal or IM testosterone (n=1,414) for a period of 12 weeks to 3 years. Of the nine trials, six did not detect a statistically significant difference in PSA values between the treatment and placebo arm at the end of study, while small increases in PSA elevations, defined as the number of men who had PSA elevated to >4 ng/mL or PSA increases ≥0.75 ng/mL from baseline at any time point, were found in three studies.[227, 229, 230] A nested case-control study by Svartberg identified 2/19 men on treatment versus 1/19 men on placebo who had reportable increases of PSA during treatment (p <0.01), none of whom required cessation of testosterone therapy.[230] Kaufman et al. found that 17/234 men on testosterone therapy compared to 0/40 men on placebo had reportable PSA increases, with all 17 men discontinuing treatment. Seven of these men stopped therapy based upon a single elevated PSA value even though the second PSA test was not elevated. One subject from the testosterone group was diagnosed with prostate cancer, which was deemed possibly treatment related.[227] Finally, the Snyder Testosterone Trials reported that 23 men in the treatment arm (n=395) and 8 men in the placebo arm (n=395) had PSA increases >1.0 ng/dL during treatment, although p values were not reported. Only one man in the treatment group was diagnosed with prostate cancer during the study period; two more who had been on treatment and one on placebo were diagnosed in the following year.[229]

A 2005 meta-analysis by Calof et al.[190] pooled data from 19 RCTs to determine the number of all-cause prostate events in men who were on exogenous testosterone treatment compared to men who were on placebo. A total of 651 men (mean age 62.9 years) received oral, transdermal, or IM testosterone or placebo (n = 433) for a period of 12 weeks to 3 years. PSA levels at baseline did not differ between study arms (1.3 ng/mL) however, at the end of the study, more men in the testosterone group (57.1/1,000 patient years) reported PSA levels elevated to >4 ng/mL or PSA increases ≥1.5 ng/mL than in placebo-treated men (41.6/1000 patient years), a difference that was not significantly significant.

Elevated PSA Level Pre-Testosterone Therapy. For patients who have an elevated PSA at baseline, a second PSA test is recommended to rule out a spurious elevation. In patients who have two PSA levels at

baseline that raise suspicion for the presence of prostate cancer, a more formal evaluation, potentially including reflex testing (e.g., 4K or phi), and prostate biopsy with/without MRI, should be considered before initiating testosterone therapy.

PSA Testing in Men on Testosterone Therapy. Patients with testosterone deficiency who maintain testosterone levels in the normal range while on testosterone therapy should have their PSA levels tested, utilizing a shared decision-making approach, in accordance with the AUA's Early Detection of Prostate Cancer Guideline. Specifically, the AUA does not recommend routine PSA testing in men 40-54 years of age unless they are at higher risk (e.g., positive family history, African American race), at which point decisions regarding PSA testing should be individualized. In men 55-69 years of age, biennial PSA testing should be considered.

Counseling Regarding Treatment of Testosterone Deficiency

13. Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease. (Strong Recommendation; Evidence Level: Grade B)

Currently available literature has consistently shown that low testosterone levels are associated with an increased incidence of major adverse cardiac events (MACE), such as myocardial infarction, stroke, and possible cardiovascular-related mortality. Furthermore, low testosterone levels are also associated with an increased prevalence of certain atherosclerotic CVD (ASCVD) risk factors. Testosterone deficient patients should be informed that low testosterone levels place them at risk for these major cardiovascular events and clinicians should assess all testosterone deficient patients for ASCVD risk factors, both fixed (e.g., older age, male gender) and modifiable (e.g., dyslipidemia, hypertension, diabetes, current cigarette smoking). The presence of ASCVD risk factors is not a contraindication to starting testosterone therapy; however, the optimization of modifiable risk factors in such patients using lifestyle and medical management strategies is recommended and may be best addressed by the patient's primary care provider.

A meta-analysis of 7 observational studies indicated that men with low testosterone, as compared to men with normal testosterone, have an increased risk of myocardial infarction (OR=1.33; CI 1.12, 1.59);[1, 79, 231-235] a pooled analysis 12 studies demonstrated an increased risk cerebrovascular accidents (OR=1.41; CI: 1.12, 1.59);[79, 82, 231, 232, 234, 236-242] a meta-analysis of observational studies by Arujo et al. showed that men who reported lower (or low) testosterone levels had an increased risk of cardiac event-related death (RR = 1.25; CI: 0.97, 1.60) as well as all-cause mortality (RR=1.35; CI: 1.13, 1.62).[243]

Thirty-three studies that compared men with low testosterone to those with normal testosterone showed that testosterone deficient men were at significantly greater risk of having hypertension (OR=1.59; CI: 1.43, 1.77). [1, 7, 27, 28, 35, 40, 82, 231, 232, 234, 237, 239, 240, 244-263] Twenty-one studies indicated that men with low testosterone, as compared to men with normal testosterone levels, had significantly increased odds of having dyslipidemia (OR=1.34; CI: 1.12, 1.86). [7, 37, 40, 83, 231, 234, 237, 240, 247-250, 254-256, 258, 259, 262-265] 13 studies comparing the prevalence of obesity and 62 studies comparing BMI values showed that low testosterone patients are nearly twice as likely to be obese (OR=1.94; CI: 1.53, 2.47)[27, 28, 148, 248-250, 254, 256-258, 266-268] and have higher BMI (OR=1.97; CI: 1.62, 2.31).[1, 7, 26, 28, 38, 74, 78, 79, 81-86, 90, 101, 103, 107, 148, 233, 235, 237-242, 245, 247, 249, 251, 255, 257, 260, 262-265, 267-289] as compared to men with normal testosterone levels.

14. 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 Recommendation; Evidence Level: Grade B)

The main purpose of testosterone therapy is to return patients to normal physiological testosterone levels and provide relief of symptoms or signs. In trials, patients with low testosterone have demonstrated statistically significant improvements in erectile function, anemia, BMD, lean body mass, and depressive symptoms.

Erectile Function. ED is one of the primary reasons that men seek testosterone treatment. Two well-powered studies, Brock-Maggi (N=715)[197, 198] and Snyder (N= 790)[229] showed statistically significant mean improvements in the erectile function domain score of the International Index of Erectile Function (IIEF) of 2.64 and 2.80, respectively. In the pooled results of 6 trials,[197, 198, 229, 290-295] which included Brock-Maggi and Snyder, a mean 1.32 (CI: 0.38, 2.26) point improvement was seen in the Erectile Function Domain Score in men on testosterone therapy. These results are consistent with other meta-analyses,[296] yet methodological flaws in the study design may underestimate the true rate and magnitude of improvement in erectile function.

Study limitations included failure to report baseline erectile function, failure to identify a population of men with isolated ED, study population heterogeneity, and inconsistent inclusion criteria across studies. Study duration was also short, with only one study performed for 52 weeks.[229] This may underestimate the true benefits of therapy as long-term prospective data suggest ongoing and slowly progressive improvements in erectile function occurring up to three years after treatment initiation.[297]

While on testosterone therapy, patients with ED and testosterone deficiency often observe one or a combination of the following events: improved nocturnal erections, improved ease of attaining erections (even if non-functional), and improved ability to achieve a penetration hardness erection. While the Panel is unable to quantify what percentage of men with ED and testosterone deficiency experience clinically meaningful improvements in erectile function (in contrast to statistically significant improvements) or the ability to achieve a functional erection, it is clear that some men will have improvement in erectile function with testosterone therapy. At the present time, there are insufficient data available to predict which men with ED are most likely to respond to testosterone therapy.

Sex drive. Sex drive (sexual desire) is a complex aspect of sexual function and is difficult to objectively measure. The sexual desire domain of the IIEF is a commonly used standardized tool that can assess libido despite its limitations and narrow scope. A total of 3 RCTs demonstrated a non-significant mean improvement of 0.4 points (CI -0.6, 1.4) on the 10-point desire domain of the IIEF.[197, 198, 290, 292] However, a larger RCT evaluating the impact of testosterone therapy on the Derogatis Interview for Sexual Functioning in Men-II (DISF-M-II) score of sexual function reported that those men in the treatment arm of the sexual function sub-cohort were more likely to show improvement in desire when compared to those on placebo.[229] However, when the entire trial study population was measured for overall sexual function, which included measures of both desire and erectile function, improvements in 10/12 measures of sexual activity were relatively mild (+0.2 on testosterone versus -0.1 on placebo). These findings support the concept that sexual function represents a multidimensional condition that cannot be easily captured using subjective sexual function questionnaires. Improvements in sex drive were also assessed in another meta-analysis performed by Bolona et al.[298] Using a variety of measures, the authors demonstrated improvement with a pooled effect of 1.31 (31% increase in sex drive) among men treated with testosterone, with greater improvements noted among men with lower baseline testosterone levels.

Anemia. Patients with anemia, both unexplained and explained, can increase their Hb and/or Hct levels while on testosterone therapy. In the 14 unique RCTs that included measures of Hb/Hct,[3, 5, 7, 15-32] men on testosterone therapy compared to placebo demonstrated a mean 1.2 g/dL increase in Hb (3.2% increase in Hct).[77, 182, 194, 195, 204-206, 208, 210-214, 216-218, 299-303] Subset analyses based on duration of testosterone therapy showed that men treated for >3 months versus men treated for ≤3 months increased Hb by 1.2 compared to 0.2, respectively, although this failed to achieve statistical significance (p=0.22). In a trial with a 3-year follow-up, results demonstrated that mean Hct and Hb values increased significantly in the treatment arm ($p < 0.001$) but were unchanged in the placebo group.[299] In a subset analysis in men with baseline anemia, 52-54% (explained 52%, unexplained 54%) increased their Hb by 1.0 g/dL on testosterone therapy compared to 15-19% (explained 19%, unexplained 15%) on placebo.[77] At study completion, 58% of testosterone therapy patients were no longer considered anemic compared to 22% with placebo.

Bone Mineral Density. An increase in BMD is an important potential benefit of testosterone therapy for men who might be at risk for LTBF. Given the link between LTBF and morbidity and mortality in older men, evaluating bone density is an important step in the assessment of patients with testosterone deficiency. An analysis of 6 studies[15, 33-37] showed that BMD increased significantly (0.41 g/cm^2; CI 0.11, 0.72) in men on testosterone therapy compared to those on placebo.[230, 299, 304-307] Another RCT evaluated the effect of testosterone therapy in men with low baseline testosterone and osteoporosis/osteopenia who had a prior fracture.[308] At 24 months, men on testosterone therapy demonstrated an approximate 3-4% increase in BMD in the lumbar spine and femoral neck over those on placebo. Whether the changes in both these studies represent a clinically meaningful improvement is unclear. As with other symptoms, the duration of testosterone therapy likely has a significant impact on overall bone density benefits. One trial with three years of follow-up showed near linear, time-dependent improvements in BMD.[202] These findings are similar to other prospective, controlled data, which report an estimated 5% per year increase in BMD in men on testosterone therapy.[309] Declining bone density may

necessitate additional medical intervention, such as weight bearing exercise, calcium, vitamin D, or bisphosphonate medications. Furthermore, additional testing, such as parathyroid hormone, calcium, and vitamin D levels, may be required. If baseline DEXA demonstrate bone density loss, imaging should be repeated one to two years after testosterone initiation. DEXA should be repeated sooner should any LTBF occur. If normalized, subsequent serial imaging can be performed in two to five years.

Lean Body Mass. In men with testosterone deficiency, testosterone therapy results in increased lean muscle mass and reduced fat mass, but no overall changes in BMI. Based on analyses of 12 studies, lean body mass increased by a mean 1.9 kg with trial durations ranging from 12-156 weeks.[195, 199, 200, 203, 206, 217, 226, 230, 301, 302, 305, 310] Although there were an insufficient number of studies to confirm statistically significant differences between groups, benefits appeared to be dose- and duration-dependent. Studies reporting optimal testosterone levels yielded a mean 2.2 kg increase in lean body mass compared to a non-significant 0.8 kg increase when suboptimal levels of testosterone were achieved. Similarly, studies of ≤3 months' duration reported non-significant improvements (0.8 kg) compared to 2.1 kg with >3 months. Although fat mass was only indirectly assessed (via lean body mass), other meta-analyses have confirmed reductions in adiposity by an estimated 1.6-1.8 kg.[138, 311, 312] Meta-analyses have also consistently demonstrated increases in lean muscle mass with testosterone therapy but have reported inconsistent outcomes on overall BMI.[138, 311-314]

Depressive Symptoms. The impact of testosterone therapy on improving depressive symptoms has been reported in nine RCTs using various assessment measures, including the Hamilton Rating Scale for Depression, Beck's Depression Inventory, and Patient Health Questionnaire-9 questionnaires.[210, 213, 225, 230, 315-319] Overall, results demonstrated mild improvements in depressive indices with no impact on anxiety. Duration of studies and mode of administration did not appear to impact outcomes. Four trials included patients with either baseline major depression or dysthymia.[213, 316-318] Although results showed significant improvements in men receiving testosterone therapy (-0.63; CI -1.13, -0.13), results were not different when compared to those without baseline depression, suggesting improvements in mood regardless of baseline status. The rate of remission was also higher in a statistically significant manner among dysthymic men receiving testosterone therapy (53%) compared to placebo (19%).[317, 318]

15. 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 Recommendation; Evidence Level: Grade B)

Testosterone therapy has demonstrated indeterminate benefits for several symptoms that are associated with testosterone deficiency, including cognitive function, measures of diabetes, energy, fatigue, lipid profiles, and QoL measures. Despite the absence of definitive evidence, the Panel recommends that patients with these symptoms be counseled regarding the possibility of improvement on testosterone therapy.

Cognitive Function. A total of four RCTs assessed the impact of testosterone therapy on various measures of cognitive function.[225, 230, 315, 320] Mean age of participants in the trials ranged from 69-72.5 years, and two included men with no baseline cognitive impairments.[230, 315] Trial duration ranged from 24 weeks to 3 years. Overall, only one of the trials (N=22) demonstrated a significant improvement in a single measure of verbal memory, with no other changes in cognition noted.[225] In the largest RCT, men with subjective or objective memory impairments (severe impairments excluded) experienced no changes in visual memory, executive function, or spatial ability after one year of treatment.[320] Clinical experience and the medical literature demonstrate a link between the total absence of testosterone (castrate testosterone levels) and cognitive dysfunction, such as men on androgen deprivation therapy (ADT) for prostate cancer, which suggests there is a threshold effect in the link between testosterone deficiency with cognitive deficiency, with very low levels of testosterone being required to see cognitive changes.

Diabetes. Despite clinical experience that some men with testosterone deficiency and diabetes improve glycemic control with testosterone therapy, nine RCTs that assessed the impact of testosterone therapy on measures of diabetes demonstrated that there were no significant differences in HbA1c levels between those who were treated with testosterone and controls.[182, 199, 200, 206, 230, 302, 306, 321, 322] While these data overall suggest that testosterone therapy has minimal to no impact on measures of diabetes, other meta-analyses outside of the evidence report have reported conflicting results. Grossman et al.[323] performed a review of seven RCTs including men with diabetes or metabolic syndrome and

demonstrated no significant changes in HbA1c, consistent with the Panel's current findings. Another meta-analysis of RCTs performed by Cai[324] concluded that testosterone therapy in diabetic men improved fasting glucose levels (mean difference -1.1 points), fasting serum insulin levels (mean difference -2.73), and HbA1c (mean difference -0.87). Other meta-analyses that have included observational studies with less stringent inclusion criteria have demonstrated variable improvements in fasting glucose, insulin resistance, and HbA1c levels.[138, 325, 326]

Energy and Fatigue. Men who seek medical care for possible testosterone therapy often present with non-specific symptoms, such as low energy and fatigue, which can be manifestations of other conditions, such as chronic stress, chronic fatigue, and depression. There are conflicting results in the literature as to whether testosterone therapy has a significant impact on these symptoms. Three RCTs that evaluated the impact of testosterone therapy on patients who had low energy or fatigue demonstrated that there were minimal to no benefits in men with testosterone deficiency.[197, 225, 319] Brock et al. studied 636 men who were evaluated with a validated testosterone deficiency energy diary over a 16-week period.[197] Among those treated with testosterone, energy scores were not improved in a statistically significantly manner compared to placebo (+2.9 points; mean baseline score 50, transformed range 0-100). A second large RCT by Snyder et al.[319] used the Functional Assessment of Chronic Illness Therapy-Fatigue scales (range 0-52) in 474 men treated with testosterone for 12 months. Compared to placebo, no significant changes were noted with testosterone therapy, including when the data were evaluated as a continuous or dichotomous (≥4 point change) variable. However, when patients were requested to assess their global impression of change regarding energy level, men receiving testosterone were significantly more likely to rate changes as a little or much better compared to placebo (approximately 15% more in testosterone cohort). These findings highlight the limitations of standardized questionnaires in the assessment of energy. In both trials, scores in the placebo cohort increased by a relatively large amount (placebo: 6.7-7.4 points versus treatment: 8.0-10.6 points), highlighting the significant placebo effect.

Lipid Profiles. Several meta-analyses have evaluated the impact of testosterone therapy on lipid profiles. Overall, the effects of testosterone on lipid profiles are uncertain, with potential benefits limited to minor reductions in triglycerides and total cholesterol, if any. Using very lenient study selection criteria (all types of trials, including observational), Corona et al.[325] identified improvements in total cholesterol, triglycerides, and high-density lipoproteins (HDL). A similar meta-analysis of only RCTs demonstrated no changes in total cholesterol or triglycerides in men who were on testosterone as compared to those on placebo. When only RCTs of men with baseline total testosterone values <350 ng/dL were included, improvements were identified with total cholesterol (-10.9 mg/dL) and triglycerides (-7.0 mg/dL), but not HDL.[326] It is unlikely that these changes represent clinically meaningful differences. Using stricter criteria for inclusion (only RCTs), Cai et al.[324] demonstrated minor improvements in triglycerides (-13.5 mg/dL) among testosterone treated men in 4 RCTs of men with testosterone deficiency. No differences were identified in total cholesterol, low-density lipoproteins, or HDL. Older meta-analyses from 2007 and 2005 similarly demonstrated no impact of testosterone on lipid profiles.[312, 327]

Quality of Life. The impact of testosterone therapy on QoL in men with testosterone deficiency is challenging to quantify due to variable study methodology and inherent limitations with standardized questionnaires. Included studies had significant heterogeneity with the populations themselves, methods of assessment, study durations, baseline population characteristics, and number of participants, leading the Panel to conclude that there is currently insufficient evidence to determine if testosterone therapy impacts QoL in a meaningful way. Overall, seven studies reported no benefits on QoL in men using testosterone therapy compared to placebo,[199, 205, 212, 225, 226, 230, 303, 318] while five studies demonstrated improvements.[203, 317, 319, 328, 329]

16. The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. (Strong Recommendation; Evidence Level: Grade A)

While the vast majority of healthy men with normal testosterone levels will recover sperm production after cessation of exogenous testosterone,[330, 331] there are no high-quality reports detailing the recovery of spermatogenesis for either testosterone deficient or infertile males who have used exogenous testosterone.[332] Liu et al. analyzed data from 30 contraception studies in which semen analyses were assessed monthly in 1,549 healthy men placed on exogenous testosterone as a possible contraceptive.[331]

The probability of recovery of sperm concentration to >20 million/mL was 67% within 6 months, 90% within 12 months, 96% within 16 months, and 100% within 24 months. Patients who had shorter treatment duration, were on shorter-acting testosterone preparations, and had higher sperm concentrations and lower LH levels at baseline had better spermatogenesis recovery. Men were eligible for inclusion in the study if they had testosterone in the normal range, an unremarkable reproductive history and physical exam, and 2 semen samples with a sperm concentration of ≥20 million/mL. Given the reproductive profile of the study population, the spermatogenesis results might not be generalizable to patients with testosterone deficiency.[332]

A study of 66 males who presented with infertility while on exogenous testosterone therapy revealed several interesting findings.[333] The authors used a total motile sperm count (TMSC) of 5 million as the benchmark for spermatogenesis recovery. In this population, exogenous testosterone was stopped and combination high-dose hCG and SERM therapy was initiated. Patients had repeat semen testing at 6 and 12 months. The authors found that 65% of patients with azoospermia at presentation achieved a TMSC > 5 million at 12 months on salvage therapy compared to 92% of patients with cryptozospermia at presentation (rare sperm in the ejaculate), who achieved a TMSC > 5 million at 12 months. Increasing patient age and increasing duration of prior exogenous testosterone use both significantly reduced the likelihood of reaching the 5 million TMSC benchmark. While the lack of a baseline semen analysis before commencement of the initial exogenous testosterone therapy is a possible weakness of this study, the methodology mirrors the clinical scenario for a large percentage of men starting exogenous testosterone with no prior semen testing.

For men already on exogenous testosterone who are planning future reproduction, testosterone cessation should occur in advance of initiation of any effort to conceive. While two-thirds of males in the contraceptive studies recovered sperm in the ejaculate within 6 months of exogenous testosterone therapy cessation, 10% failed to do so until the second year.[331] Patients need to be made aware of the highly variable time course to recover sperm in the ejaculate and the variable degree to which spermatogenesis returns after stopping exogenous testosterone.[331, 333] Wenker et al. showed that some infertile men may never recover spermatogenesis after use of exogenous testosterone, and this important risk needs to be discussed with patients before starting treatment.[334] Intratesticular testosterone levels can be maintained by the simultaneous administration of low dose hCG with exogenous testosterone.[335] To date, a single study of 26 patients has assessed this combination therapy approach in terms of effects on semen parameters and found that the concurrent administration of low dose hCG and exogenous testosterone can preserve spermatogenesis in select patients.[336] In this study, no patient became azoospermic, and 35% of the patients conceived with their partner while on combination therapy.

Males with KS merit special mention. This is a relatively common condition that affects approximately 1:500 males and is characterized by hypergonadotropic hypogonadism. Patients with KS are often prescribed exogenous testosterone to treat signs and symptoms associated with low testosterone. In addition to exogenous testosterone monotherapy, a number of other regimens have been used to treat low testosterone in these men, including AI monotherapy, hCG monotherapy, SERM monotherapy, and various combinations of these classes of drugs.[337-339] Patients with KS frequently have low levels of testosterone production and high levels of aromatase activity, which leads to increased aromatization of testosterone to E2, resulting in decreased testosterone:E2 (T:E) ratios.[340] The aim of hormonal therapies in these individuals is to both optimize intrinsic testosterone production and decrease conversion of testosterone to E2. Decreasing E2 levels diminishes E2's negative feedback on LH production at the hypothalamus and pituitary gland.[340] Ramasamy et al. reported that both baseline and post-treatment T:E ratios have prognostic significance in azoospermic males with KS because at both of these time points, T:E ratios > 10:1 are associated with a higher likelihood of sperm retrieval on microscopic testicular sperm extraction.[338]

17. **Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. (Strong Recommendation; Evidence Level: Grade B)**

The relationship between testosterone therapy and the development of prostate cancer has been debated. The controversy surrounding prostate cancer and testosterone stems from the work of Dr. Charles Huggins who discovered that treating metastatic prostate cancer patients with ADT resulted in cancer remission,[341] suggesting that the presence of testosterone would lead to an increased likelihood of prostate cancer development. However, an analysis of

Huggins' original paper reveals that this assumption was based on a single patient who was cancer and androgen therapy naïve at study onset. The other men in the study already had metastatic disease at the time of testosterone initiation. Since Huggins' work, subsequent research has failed to definitively link testosterone therapy to a progression of prostate cancer in the untreated patient or recurrence in the treated patient.

While the FDA retains a warning regarding the potential risk of prostate cancer in patients who are prescribed testosterone products ("patients treated with androgens may be at increased risk for prostate cancer"), there is accumulating evidence against a link between testosterone therapy and prostate cancer development. A meta-analysis of 7 RCTs showed that there was no significant increase in the rate of a prostate cancer diagnosis in older, testosterone deficient men who were treated with testosterone compared to placebo (OR=1.00; CI: 0.36, 2.87).[194-198, 202, 203, 211, 215-217, 229, 315] Upon study entry, enrollees did not have a prostate cancer diagnosis, had no history of prostate nodules, or a PSA level > 4.0 ng/mL. Men who were taking medication known to affect androgen production and/or testosterone were likewise excluded. Across all 7 studies, 2,508 men (range of mean ages 55-74 years) with total testosterone levels <350 ng/dL (mean range: 232-303ng/dL) were treated with either transdermal or IM testosterone for a period of 12 weeks to 3 years. At the end of follow-up, 10 men who were on testosterone treatment (n=1,372) were diagnosed with prostate cancer, compared to 9 men in the placebo arm (n=1,136). Some of the cancers were detected during the treatment phase, while others were detected during post-study follow-up.[229] It was noted by some authors that it was difficult to implicate testosterone as the etiology since biopsies were taken at the end of study, and it was possible that the cancer was present throughout the trial[211] or age-related.[215] Prostate cancer incidence was the primary endpoint in only one of the seven studies,[211] while the balance of the trials were powered to measure physical strength, BMD, or sexual function, with prostate events recorded as adverse outcomes.

Another meta-analysis by Calof et al.[190] (2005) pooled data from 19 RCTs to determine the number of all-cause prostate events in men who were on exogenous testosterone treatment as compared to men who were on placebo. Studies were ineligible if they used supra-physiologic levels of testosterone or if participants were using androgens other than testosterone. A total of 651 men (mean age 62.9 years) received oral, transdermal, or IM testosterone, while 433 men received placebo for a period of 12 weeks to 36 months. The treatment and placebo arms did not differ at baseline in terms of age (62.9 years versus 64.4 years, respectively), total testosterone level (320 ng/dL versus 344 ng/dL, respectively), or PSA measurements (1.3 ng/mL in both arms). At the end of study the total number of prostate -related events was significantly greater in the testosterone arm than in the placebo arm (OR=1.79; CI: 1.07, 2.95). The authors conceded that it was not possible to determine if each individual prostate event occurred in unique individuals since the same person might have had more than one event leading to an overestimate in incidence. When individual prostate events were analyzed separately, there was not a statistically significant difference in incidence between the two groups in terms of prostate cancer (OR=1.09), PSA elevation to > 4ng/mL or PSA increase > 1.5 ng/mL during treatment (OR=1.19), any increase in International Prostate Symptom Score (OR=1.08), or acute urinary retention (OR=0.99).

18. Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy. (Expert Opinion)

It is the opinion of this Panel that until there is definitive evidence demonstrating that testosterone therapy is not safe for use in prostate cancer patients, the decision to commence testosterone therapy in men with a history of prostate cancer is a negotiated decision based on the perceived potential benefit of treatment.

Given the increasing incidence of both testosterone deficiency and prostate cancer with advancing age, it is common for the two conditions to co-exist in older men. Product labels for all testosterone formulations explicitly state that their use is contraindicated in men with a history of prostate cancer, which results from Huggins' precept that testosterone therapy feeds prostate cancer cell proliferation.

However, the saturation model introduced by Morgentaler is based on the concept that prostate cancer cells' response to the testosterone level to which they are exposed is not linear in nature. From a clinical standpoint, it dictates that there is a testosterone threshold beyond which prostate cells (benign or malignant) cease responding. *In-vitro* experiments have shown that prostate cancer cells fail to proliferate in the absence of testosterone; once testosterone is introduced, an initial proliferative response is observed

followed by a plateau after a certain testosterone concentration is reached. If the testosterone concentration is increased further, rather than further proliferation, the cells reduce their rate of proliferation.[343, 344] This phenomenon is known as the bipolar testosterone concept. It is probable that the saturation level varies from patient to patient and likely lies somewhere between 100-200 ng/dL.

Recent RCT data support Morgentaler's theory. Marks et al. studied 44 patients who were randomized to receive 150 mg of IM testosterone enanthate (n = 21) versus placebo (n = 19) for 6 months.[211] While on treatment, patients had blood drawn and prostate tissue biopsied to look at serum and prostatic tissue levels of testosterone. At the end of the study, serum testosterone levels rose in those men receiving testosterone therapy; however, no rise in testosterone levels were seen within the prostate tissue itself.

Post-Radical Prostatectomy Patients. Testosterone therapy can be considered in those men who have undergone radical prostatectomy (RP) with favorable pathology (e.g., negative margins, negative seminal vesicles, negative lymph nodes), and who have undetectable PSA postoperatively. Currently published studies have not demonstrated an increased risk of biochemical cancer recurrence in post-RP patients who are on testosterone therapy, nor does it define the optimal timing for commencement of testosterone therapy. The literature suggests that post-RP patients who had undetectable PSA levels and were subsequently put on testosterone therapy maintained undetectable PSA levels throughout treatment with no evidence of cancer recurrence.[345-347] Only one study by Pastuszak et al., (2013)[348] reported that study subjects experienced biochemical recurrence: 4/103 patients in the treatment group versus 8/49 in the reference group (p=0.02), all of whom were classified as having high-risk prostate cancer at study onset.

Radiation Therapy. There is also a dearth of data evaluating the safety of testosterone therapy in men treated with radiation therapy (RT). Available studies are retrospective in nature but have suggested that post-RT patients (with or without ADT exposure) placed on testosterone therapy do not experience recurrence of prostate cancer. Clinicians should be aware that a period of time should elapse after RT and before initiating testosterone therapy in order to allow the patient adequate time to regain functional endogenous testosterone production. While this period of waiting might preclude the need for testosterone therapy by allowing testosterone to return to normal levels organically, it is possible that men who underwent long courses of ADT may not regain physiological testosterone levels even one year after cessation of ADT.[349, 350]

The studies conducted in post-RT men who have been placed on testosterone therapy indicate that men experienced either a steady decline in PSA values to <0.1 ng/mL or had non-significant changes in PSA, with no patients exhibiting signs of prostate cancer progression or recurrence.[351-354] One study involving 36 men recorded a single patient as having a transient rise of PSA, but this was followed by a decline, while another patient in the same study did have end-of-study PSA >0.5 ng/mL. At the time of publication, this patient was five years post-implantation and had not undergone any biopsies.[351] A second retrospective study by Balbontin found that one patient out of the study population (N = 20) did experience a PSA bounce of 2 ng/mL above the nadir, but after a 6 month break from testosterone, PSA levels dropped and did not rise again even after testosterone was re-commenced.[352]

A study by Pastuszak et al. (2015)[355] found a significant increase in biochemical recurrence in high-risk patients who received testosterone therapy after RT or RT/ADT. All patients in the study (N=48) were stratified according to risk: low (Gleason Score ≤6), intermediate (Gleason Score =7), and high (Gleason Score ≥8). After 40.8 months of testosterone gel, IM injection, or SQ pellets, mean PSA remained unchanged in the low- and intermediate-risk strata (0.00 ng/mL and 0.09 ng/mL, respectively), but those in the high-risk group had significant increases (0.10 ng/mL at baseline versus 0.36 ng/mL at follow-up; p=0.018). Six patients experienced biochemical recurrence, all of whom had intermediate- or high-risk prostate cancer. Three of these men were brachytherapy patients alone, did not cease testosterone therapy, and their PSA values eventually decreased. Three others did stop testosterone in response to the PSA bounce, two of whom had negative prostate biopsies.

Active Surveillance. There are limited data in men on active surveillance who are candidates for testosterone therapy. There has been a concern that testosterone therapy might cause progression of previously existing, but undiagnosed, prostate cancer or that testosterone might cause high-grade prostatic intraepithelial neoplasias (PIN) to progress into frank carcinoma.

A paper by Rhoden and Morgentaler in 2003 looked at the effect of testosterone in patients who did and did not have PIN.[356] A total of 75 men (mean age 59.6 years) who were testosterone deficient (total

testosterone <300 ng/dL with ED and/or decreased libido) were followed for 12 months after initiation of testosterone therapy. Men were excluded if they had a history of prostate cancer, had undergone prostate surgery, or were taking finasteride or other drugs that altered PSA. Biopsies at baseline revealed that 55 patients were PIN- and 20 patients were PIN+. Mean PSA was 1.54 ng/mL, which did not differ significantly between the PIN+ and PIN- men at baseline (1.49 ng/mL; 1.53 ng/mL, respectively) or at the end of study (1.82 ng/mL; 1.78 ng/mL). After 12 months of testosterone therapy, 1/20 men in the PIN+ cohort and 0/55 men in the PIN- cohort were diagnosed with cancer, resulting in a cancer rate of 1.3%. The authors of the paper could not attribute the cancer diagnosis to testosterone treatment alone considering prostate cancer develops in as many as one quarter of PIN+ patients within three years.

Another retrospective study (Morgentaler 2011) followed 13 men (mean age 58.8 years) with untreated prostate cancer and testosterone deficiency (total testosterone <350 ng/dL and at least one symptom consistent with testosterone deficiency) who were diagnosed with either Gleason 6 or Gleason 7 cancer.[357] All patients received either transdermal testosterone, IM testosterone, or SQ testosterone pellets for a mean 3.1 years. PSA at initial biopsy was 5.5 ng/mL, which decreased to 3.6 ng/mL at 24 months ($p = 0.29$). An increase in serum PSA of 0.5 ng/mL or greater was found in 3 men while on testosterone therapy, and 4 experienced a decrease of the same magnitude on treatment. Prostate volume did not change in any patients on testosterone therapy. All patients had PSA and digital rectal exams every three months and biopsies annually. Of these, 14 biopsies (54%) revealed no cancer, and no patients required additional biopsy for clinical concerns.[357]

PSA Monitoring. Prostate cancer patients on testosterone therapy should have their PSA levels monitored on the same schedule as men without testosterone deficiency; however, clinicians may choose to increase the frequency of testing. PSA recurrence in men on testosterone therapy should be evaluated in the same fashion as untreated men. A discussion regarding the benefit of stopping testosterone therapy should include the possibility of a decline in PSA.

19. **Patients should be informed that there is no definitive evidence linking testosterone therapy to a higher incidence of venothrombolic events. (Moderate Recommendation; Evidence Level: Grade C)**

The concern about the possible association between testosterone therapy and venothrombolic events (VTE) led the FDA to require pharmaceutical companies to add a warning to their product labeling regarding post-marketing reports of VTE; however, this decision was based on anecdotal cases and not peer-reviewed literature.[358] Since the FDA warning in June 2014, four large observational studies[198, 359-361] have been conducted, none of which showed an association between testosterone therapy and an increased risk of VTE.

One RCT by Maggi et al. followed 715 testosterone deficient men for 12 weeks to evaluate the effects of a 2% transdermal testosterone agent on sex drive and energy. The men in the study had a mean baseline total testosterone of 200 ng/dL and at least 1 symptom associated with testosterone deficiency (low energy or decreased sex drive). At the conclusion of the study, no men who were on testosterone therapy had a major adverse cardiovascular event or VTE, while one patient in the placebo group did.[198] A five-year study by Baillargeon et al. reported that testosterone therapy did not increase the risk of VTE in patients who were on testosterone therapy, independent of the route of testosterone administration or exposure period.[359] A retrospective cohort study by Sharma et al. likewise did not detect a significant association between testosterone therapy and risk of VTE,[360] and neither did Li et al. who used a cohort and nested case-control analysis and found no significant association between testosterone therapy and incidence of overall VTE in men with testosterone deficiency.[361]

Conversely, a population-based retrospective case-control study utilizing a UK clinical database of 19,215 patients with confirmed VTE showed that there was increased risk of VTE in the first 6 months of testosterone therapy. The risk corresponded to an additional 10 cases per 10,000 person-years, which, while low in absolute terms, raised concern about using testosterone therapy in men who may be at increased risk for VTE prior to commencement of therapy.[362]

20. **Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). (Moderate Recommendation; Evidence Level: Grade B)**

Current evidence consistently shows that untreated low testosterone levels are associated with an increased

risk of MACE; however, studies that measure cardiovascular benefit or harm in men on testosterone therapy have returned inconsistent and controversial results. Until there is definitive evidence proving an association between testosterone therapy and subsequent MACE, the Panel recommends that clinicians counsel patients that the current scientific literature does not definitively demonstrate that testosterone therapy increases risk. Men who are on testosterone therapy should be advised to report the occurrence of any possible cardiovascular symptoms, such as chest pain, shortness of breath, dizziness, or transient loss of consciousness, during routine follow-up visits.

RCTs have failed to categorically define if testosterone therapy increases the incidence of MACE when compared to placebo. Some studies have suggested that testosterone therapy is associated with an increase in MACE[363-366] while others have suggested a decreased risk [207, 233, 259, 367, 368] and others a neutral effect.[190, 191, 202, 327, 369-373] The results and the methodology of these studies have been debated. Thresholds for low testosterone were not universal. There were inconsistently defined end points to categorize severe cardiac events, which included 'softer' endpoints (e.g., edema, tachycardia, hypertension) along with myocardial infarction and stroke.[194] The statistical analysis did not account for confounding factors; the duration of follow-up varied widely, from 12 weeks to 3 years; and many of the trials were not powered to detect cardiac events as primary endpoints, rather they were catalogued as adverse outcomes.

A meta-analysis of RCTs developed in support of this guideline indicate that there is no significant difference in MACE in men on testosterone therapy when compared to placebo. Across all studies, a total of 2,821 men (mean ages 52-74 years) were treated with IM or transdermal testosterone (n=1,555) or placebo (n=1,266) for a period of 16-52 weeks. The trials were not powered to measure MACE as a primary endpoint (outcome measures included efficacy or product, muscle strength, AMS scores, and sex drive); cardiac-related events were categorized as adverse outcomes. The pooled results showed that there was not a statistically significant difference in the incidence of myocardial infarction (OR=0.61; CI: 0.12, 1.68) [194-198, 208, 216-218, 226, 229, 328] in men using testosterone therapy compared to men on placebo; 6 RCTs showed there was not an increase in cardiovascular-related mortality (OR=0.54; CI: 0.17, 1.73)[194-196, 216-218, 226, 229, 328] among testosterone users compared to those on placebo; and 3 RCTs showed an equal likelihood of the incidence of cerebrovascular accident (OR=0.98; CI: 0.27, 2.64)[194-198, 229] between the placebo and treatment arms.

While seven of the trials in the above analysis showed decreased, but statistically insignificant, odds of having a cardiac event while on testosterone therapy, one trial did show an increased risk. The Basaria Testosterone in Older Men (TOM) trial published in 2014 was a randomized, double-blind, placebo-controlled study that showed that men who received transdermal testosterone (n=106) were significantly more likely to have a cardiac related event than those on placebo (n=103).[194] At the end of 6-months follow-up, there were a total of 23 cardiovascular events (in 9 men) in the testosterone therapy arm compared to 5 events in the placebo arm (p <0.001). Although the study was powered primarily to assess the effect of testosterone therapy on frailty, the TOM Trial was one of the first published studies to indicate that there may be increased cardiovascular risk associated with testosterone therapy. The definition for cardiovascular symptoms, either by self-report or medical chart review, was broadly defined, and some severe adverse events would not have met the classic definition for MACE, (e.g., edema, self-reported syncope, ectopy on electrocardiogram, tachycardia). Although study exclusion criteria included uncontrolled hypertension, unstable angina, myocardial infarction within the past three months, and congestive heart failure, there was a higher rate of hyperlipidemia and statin use at baseline in the testosterone therapy group as compared to the placebo group. The authors noted "the small number of overall events suggests the possibility that differences between the two groups may be due to chance alone."

Another meta-analysis of 26 RCTs by Corona et al. (2014)[372] found no causal association between testosterone therapy and MACE (defined as a composite of cardiovascular-related death, non-fatal acute myocardial infarction, and cerebrovascular accident) when compared to placebo (OR=1.01; CI: 0.57, 1.77). Across all studies, men had a mean baseline testosterone of 323 ng/dL, mean age of 59.9 years, and were followed for an average 34 weeks, during which time they were administered either a placebo or one of several testosterone modalities. There were 31 events in the treatment arm (n=1,895) and 20 events in the placebo group (n=1341). Specifically, the OR of acute myocardial infarction was 0.68 (p=0.34), acute coronary syndrome 0.92 (p=0.83), cerebrovascular accident 0.82 (p=0.76), and cardiovascular-related mortality 1.14 (p=0.75). The association between testosterone therapy and MACE remained insignificant

when adjusted for baseline testosterone level and trial duration >12 weeks.

Given the conflicting nature of the evidence, the Panel cannot definitively state that there is an association between testosterone therapy and subsequent MACE events nor can it be stated definitely that testosterone therapy is associated with reduced incidence of MACE. In 2014, the FDA added a warning to testosterone product labeling after reviewing five observational studies and two meta-analyses of RCTs that examined the effects of testosterone therapy on MACE. For further information on the testosterone therapy and the risk of MACE, please see Appendix D.

21. All men with testosterone deficiency should be counseled regarding lifestyle modifications as a treatment strategy. (Conditional Recommendation; Evidence Level: Grade B)

Men with testosterone deficiency should be counseled that lifestyle modifications, such as losing weight, or maintaining weight within the recommended range, along with increasing physical activity, has the potential to increase total testosterone levels and/or reduce signs and symptoms associated with testosterone deficiency.[374-377] High BMI coupled with low testosterone could put the patient at risk for a cardiovascular event, and patients who are overweight or obese should be counseled regarding weight loss programs concurrent with testosterone therapy. Clinicians should counsel patients that lifestyle modifications should be undertaken for the benefit of their overall health and that improvements in total testosterone levels might not be clinically meaningful.[376] The AACE suggests that significant improvements in testosterone levels do not occur until a patient loses 5-10% of his body weight.[69]

Small non-randomized trials support the concept that weight loss in men who are obese or morbidly obese is associated with an increase in testosterone levels. A 2016 study examined the mean total testosterone changes in 29 morbidly obese men (mean age: 31 years; mean BMI: 56.8) before and after gastric bypass surgery. At baseline, 22 patients had total testosterone <300 ng/dL, and 6 months post-surgery, total testosterone had increased significantly ($p \leq 0.001$) with 22 patients (75.9%) showing normalized total testosterone levels.[375]

Increases in testosterone for patients who lose weight might be cumulative over time. A study of 118 overweight and obese men with normal total testosterone levels (>350 ng/dL) placed subjects on either a low-fat/high-protein or low-fat/high-carbohydrate calorie restricted diet for 52 weeks. At the end of the study, total testosterone increased in both groups with neither group deriving more benefit than the other ($p \geq 0.244$). Although increases in total testosterone were noted in the first 12 weeks ($p=0.037$), the improvement was not significant until weeks 12-52 ($p=0.002$).[374]

It is possible that exercise programs coupled with diet may have a greater likelihood of success in achieving increases in total testosterone over calorie-restricted diets alone. Studies that randomized overweight or obese men to diet and exercise programs had significantly greater increases in total testosterone levels than men who underwent calorie reduction or exercise programs alone.[378, 379] It is also postulated that men who engage in quantitatively more exercise have the greatest increases in serum testosterone from baseline.[378]

Men with mild testosterone deficiency and whose weight is above the recommended range and/or who are physically inactive should be encouraged to consider low-risk lifestyle modifications followed by reassessment of testosterone levels, signs, and symptoms before deciding to start testosterone therapy. For adults in general, behavior-based interventions have been found to be safe and effective.

Treatment of Testosterone Deficiency

22. Clinicians should adjust testosterone therapy dosing to achieve a total testosterone level in the middle tertile of the normal reference range. (Conditional Recommendation; Evidence Level: Grade C)

The goal of testosterone therapy is the normalization of total testosterone levels combined with improvement in symptoms or signs. The Panel recommends that clinicians use the minimal dosing necessary to drive testosterone levels to the normal physiologic range of 450-600 ng/dL, which is the middle tertile of the normal range for most laboratories. The Panel recognizes that age-adjustments may be required to define this middle range; however, from a practical standpoint, 450-600 ng/dL represents a viable range for all age-groups. Achieving testosterone levels in this window should ameliorate any symptoms that are genuinely associated with testosterone deficiency.[168, 380]

The Panel recommends that patients on all modalities of testosterone have their symptoms/signs re-evaluated within three months after the commencement of

treatment to determine if dosing adjustments are necessary. While some patients may continue to experience symptom/sign relief after this time point, the majority of men have meaningful improvements within the first three months of therapy. In the event that patients do not experience symptomatic relief after reaching the specified target testosterone levels or remain testosterone deficient in the setting of symptom/sign improvement, testosterone therapy should be stopped. In the uncommon circumstance where men have prior available off-therapy testosterone laboratory data considered reliable (early morning testing, appropriate assay), clinicians may consider titrating testosterone therapy dosing to return patients to their 'baseline' total testosterone level.

The Panel recognizes that it might be difficult to achieve an on-treatment total testosterone level in such a narrow range in every patient, especially those using IM testosterone; however, the suggested range aims to limit the over-treatment of testosterone deficient men who have had physiologically lifelong total testosterone levels in the lower range of normal, while minimizing the under-treatment of men who have had physiologically lifelong total testosterone levels in the upper range of normal. For men with on-treatment testosterone levels that fall below the suggested target range but who have on-treatment amelioration of symptoms, up-titration may be considered in an effort to achieve symptom abolition. For men with on-treatment testosterone levels that fall below the suggested target range but who experience complete resolution of symptoms, there is no need to titrate dosing. For the patients with no or minimal symptoms associated with low testosterone levels, but rather the presence of signs (e.g., BMD loss), clinicians are encouraged to aim for on-treatment total testosterone levels in the 450-600 ng/dL target range and re-evaluate the patients' signs at an appropriate time point after reaching the therapeutic range.

While definitive age-specific reference ranges do not exist, some data suggest that patient age may play a role in setting therapeutic ranges, at least in the elderly population. A community dwelling study of 70-89 year-old healthy men (n=3690) in Perth, Australia established a reference range of 283-454 ng/dL (mean 361 ng/dL)[381] while other randomized trials of testosterone therapy in older men have achieved on-treatment mean total testosterone levels in the range of 430-600 ng/dL.[202, 226, 229] The Panel interprets the above data to support the mid-tertile range as a therapeutic target.

The target levels suggested here are physiological (eugonadal) not supraphysiological levels, and the Panel found no data to support the argument for dose escalation into the supraphysiological range in the pursuit of greater efficacy. One trial in healthy older men (age range 60-75 years) who were given graded doses of IM testosterone enanthate (25, 50, 125, 300 and 600 mg weekly) showed that men experience higher rates of serious adverse events when receiving the 300 mg and 600 mg weekly doses (producing nadir testosterone levels in the range of 1,800-3,300 ng/dL).[382] Case reports and case series have also linked use of high doses of anabolic steroids with a number of serious adverse events, including cardiovascular issues, coagulation abnormalities, mood disorders (e.g., withdrawal symptoms) and dependence issues.[383, 384]

23. Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive. (Strong Recommendation; Evidence Level: Grade A)

Exogenous testosterone therapy has been shown to interrupt normal spermatogenesis and can put patients in severely oligospermic or azoospermic states and should not be used in men trying to conceive. Normal sperm production depends on a functionally intact hypothalamic-pituitary-gonadal axis with normal secretion of pituitary LH and FSH to support intratesticular testosterone production and spermatogenesis. Exogenous testosterone suppresses the hypothalamic-pituitary-gonadal axis and intratesticular testosterone production, with dosages of testosterone enanthate 200 mg IM testosterone every week having been shown to decrease intratesticular testosterone levels by 94% within 3 weeks of initiation.[335] Clinicians may offer hCG (250 IU or 500 IU every other day) concurrent with exogenous testosterone, which in a single small study has been shown to maintain baseline levels of intratesticular testosterone.[335]

A systematic review of 33 RCT's by Grimes et al. evaluated the effectiveness of testosterone or testosterone plus progestin agents as a contraceptive agent in healthy men.[330] The final analysis suggested that the effects of testosterone alone on spermatogenesis varied widely. The general trend indicated that higher doses of testosterone were more likely to result in azoospermia than lower doses, however a dose-response effect was not consistently seen.

A larger study that examined the contraceptive efficacy of testosterone-induced azoospermia in men was

conducted by the WHO Task Force on Methods for the Regulation of Male Fertility.[385] A total of 271 healthy, fertile men across 7 countries were given 200 mg IM testosterone enanthate every week for 12 months. During the efficacy phase of the trial, adequate suppression of spermatogenesis occurred in 98% of study subjects (n=390) and 157 men became azoospermic during the 12-month follow-up period (mean time to azoospermia was 120 days).

24. Testosterone therapy should not be commenced for a period of three to six months in patients with a history of cardiovascular events. (Expert Opinion)

The currently available literature does not provide enough evidence to offer clear guidance on the use of testosterone therapy in men with existing, stable atherosclerotic CVD and/or a remote history of a myocardial infarction or a cerebrovascular accident. It is the opinion of the Panel that testosterone therapy, with close monitoring to ensure appropriate dosing and safety surveillance, may be considered in these patients after a three to six month waiting period. Clinicians should counsel patients on the association between low testosterone and the increased risk of cardiovascular events, as well as the ill-defined cardiovascular risks and benefits of testosterone therapy in the testosterone deficient patient.

This recommendation is supported by a recent review of studies that evaluate cardiovascular risk associated with testosterone therapy, most of which have excluded men who had a history of a cardiovascular event within the preceding three to six months.[194, 229, 386] In the recent Testosterone and TOM Trials,[194, 229] participants were excluded if they had a myocardial infarction or a cerebrovascular accident within the previous 3 months, had a history of unstable angina, New York Heart Association class III or IV congestive heart failure, a systolic blood pressure >160 mm Hg, or a diastolic blood pressure >100 mm Hg.[194, 229]

In the absence of long-term RCTs evaluating whether testosterone therapy results in cardiovascular benefit or harm, the decision to use testosterone therapy in such patients should be based on a shared decision-making approach between clinicians and patients.

25. Clinicians should not prescribe alkylated oral testosterone. (Moderate Recommendation; Evidence Level: Grade B)

Given the availability of other approved testosterone therapies, the use of 17-alpha-akylated androgens is not appropriate. Methyltestosterone is an oral androgen modified at the 17-alpha position resulting in decreased first pass hepatic clearance and is approved in the US for treatment of testosterone deficiency. It is rapidly metabolized in the liver; therefore, achieving consistently therapeutic testosterone levels is a challenge. Its use is also associated with liver toxicity, including abnormal liver function tests, cholestasis, and jaundice. One study of 60 patients undergoing long-term therapy of 50 mg methyltestosterone three times a day found that nearly one-third of patients, none of whom had a history of liver disease, returned abnormal liver function tests and/or liver scans.[387]

Testosterone undecanoate is an oral testosterone analogue that is absorbed via the intestinal lymphatics allowing it to avoid the first pass liver effect. It is approved in some countries for treatment of testosterone deficiency but is not currently approved in the US.

26. Clinicians should discuss the risk of transference with patients using testosterone gels/creams. (Strong Recommendation; Evidence Level: Grade A)

Topical testosterone preparations (e.g., gels, creams, liquids) have the potential to result in transference to others. Populations at increased risk of adverse effects from transference include women and children, however very limited data are available on the true risks of transference with topical agents. Several case reports have identified virilization and precocious puberty in children as well as hyperandrogenism in women following accidental exposure to topical testosterone.[388-391]

To address the issue, the FDA includes medication guides with topical testosterone preparations and recommends observing for signs and symptoms of early puberty in children as well as avoiding contact with the unwashed or uncovered areas where the drug has been applied.[392] In order to reduce risks, patients are advised to apply the medication only to suggested areas, wash hands after applying, cover the area with clothing after drying, wash the area prior to anticipated skin-to-skin contact, and wash regions of inadvertent contact in women and children.

More recently, a study evaluating the amount of residual testosterone identified on laundered clothing from men using an axilla-applied testosterone liquid reported the presence of 13% of a single axilla dose on 10x10 cm clothing samples.[393] After laundering the clothing with various other materials, as much as 5.8% of a standard dose of one axilla was transferred to

other garments. It is unclear if the transferred testosterone remained biologically active. These findings require further follow-up as they demonstrate that transference may hypothetically occur in the absence of skin-to-skin contact.

27. Clinicians may use aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators, or a combination thereof in men with testosterone deficiency desiring to maintain fertility. (Conditional Recommendation; Evidence Level: Grade C)

Low testosterone levels are highly prevalent among males presenting for an infertility workup and testosterone deficiency is commonly found in men who have non-obstructive azoospermia and oligospermia.[394] Half of all couples experiencing infertility will have a male factor involved and 30-70% of men undergoing a reproductive workup will have an endocrine abnormality of some type.[395, 396] Exogenous testosterone has inhibitory effects on the production of intratesticular testosterone, which is imperative to maintain normal spermatogenesis. For this reason, alternative therapies, including SERMs, AIs, and hCG, are commonly used to promote the endogenous production of testosterone. Each class of alternative therapy has a different mechanism of action: hCG acts as an LH agonist and stimulates Leydig cell production of testosterone, AIs block the conversion of testosterone to E2, and SERMs inhibit the negative feedback of E2 on LH production at the level of the hypothalamus and pituitary gland.

Table 6 provides pharmacologic information for SERMs, hCG, and AIs. While SERMs, hCG, and AIs are all categorized as "alternative therapies" to testosterone, they are actually a diverse group of agents. These agents share the common overall treatment effect of increasing intrinsic production of testosterone, but there are substantial differences in pharmacologic characteristics and mechanisms of action between them. Given these pharmacologic and mechanistic differences, combinations of these alternative therapies might, in some instances, be clinically appropriate.

Clinicians should understand that of these agents, only hCG has been approved by the FDA for use in males, specifically to treat males with hypogonadotropic hypogonadism. The overall quantity and quality of studies investigating the use of these alternative agents in males are limited. However, despite these limitations, several studies provide important insights into the impact of SERMs, AIs, and hCG on spermatogenesis.

Aromatase Inhibitors. Pavlovich et al. reported on the existence of a "treatable endocrinopathy" in a subset of infertile men characterized by low testosterone, elevated E2, and a low T:E ratio.[340] The authors hypothesized that treating this condition with AIs would result in improvement in both the T:E ratio and semen parameters. In two separate studies of infertile men with azoospermia or severe oligospermia who were treated with an AI, authors reported improvement in the both the T:E ratio and also semen parameters in oligospermic males.[337, 340] Reifsnyder et al. subsequently assessed the effect of AI therapy for azoospermic males with T:E ratios < 10:1 and serum testosterone levels <300 ng/dL and found no difference in sperm retrieval rates, pregnancy rates, or live birth rates among patients on AI therapy versus those not on therapy.[339] Ramasamy et al. more specifically studied a cohort of azoospermic males with KS who were treated with alternative therapies, including AIs, prior to microscopic testicular sperm extraction.[338] They reported better rates of successful sperm retrieval for men with higher baseline T:E ratios as well as those with higher preoperative T:E ratios and post-treatment testosterone >250 ng/dL after medical therapy.

Human Chorionic Gonadotropin. hCG is an LH analog that is usually prescribed to treat a deficiency in LH production. Most studies assessing hCG efficacy have been performed in males with congenital/ idiopathic hypogonadotropic hypogonadism.[397, 398] While the literature regarding hCG use in adult males with symptomatic testosterone deficiency is less robust, several important reports are worth discussing. Liu et al. conducted a double-blind, placebo controlled, randomized trial assessing response to hCG therapy in older men (mean age 67 years) with androgen deficiency.[399] The authors found a 150% increase in total testosterone level, which they concluded demonstrates that older males retain "testicular responsiveness" to gonadotropin therapy. As mentioned above, combination therapy with low dose hCG has been described as a means to maintain intratesticular testosterone levels[394] and preserve spermatogenesis[336] for men on exogenous testosterone. Finally, hCG therapy alone or in combination with SERMs has been shown to facilitate recovery of testosterone production and spermatogenesis in men with a prior history of exogenous testosterone use[333] or anabolic steroid abuse.[334] Return of sperm to the ejaculate in these men can be highly variable, taking up to two years after cessation of exogenous testosterone in some cases, with some men never experiencing return of sperm.[334]

Selective Estrogen Receptor Modulators. SERMs are oral agents that block E2 feedback resulting in increased LH secretion. Taylor et al. reported that clomiphene citrate has outstanding biochemical and clinical efficacy, with increases in serum testosterone similar to those for testosterone gel.[400] Additionally, these investigators found that clomiphene has a favorable side effect profile and is less expensive than testosterone gel. Two RCTs compared treatment of testosterone deficient males with SERMs versus testosterone versus placebo and found that sperm concentration was maintained (comparable to placebo) for males treated with the SERMs, but was significantly decreased for males on exogenous testosterone.[401, 402] Finally, Helo et al. conducted a prospective, double-blind, RCT comparing the SERM clomiphene citrate versus the AI anastrozole in infertile males with testosterone deficiency. The authors report that clomiphene resulted in significantly higher serum testosterone levels than anastrozole, but anastrozole resulted in significantly higher T:E ratios than clomiphene. Despite these effects, neither treatment led to significant changes in semen parameters.[403]

Finally, the clinician should adhere to several "key points" when prescribing these agents:

1. A serum LH level can help guide clinical decision-making after initiation of SERM therapy.
2. If after starting the SERM the testosterone level remains low and the LH level remains low or normal, then dose escalation of the SERM should be considered. This step might increase testosterone levels.
3. If after starting the SERM the testosterone level is low but the LH level is high, then the patient likely has testicular dysfunction. SERM dose escalation in this case is not likely to increase testosterone levels.
4. AIs should in general not be used for extended periods of time due to concerns regarding loss of BMD.[404] AIs can significantly suppress E2, which is essential in maintaining bone density.
5. With regular follow-up and careful titration of AI dosage, E2 can often be maintained in the therapeutic range, thus minimizing the risk of loss of bone density.
6. If AI therapy results in persistently elevated E2 levels, the AI should be discontinued due to lack of clinical efficacy.

While the therapeutic aim of each of these alternative therapies is to increase endogenous testosterone production, clinicians must keep in mind that the benefits of exogenous testosterone therapy in testosterone deficient men cannot be extrapolated to the benefits provided by these alternative therapies.

Table 6: Pharmacological Characteristics of Alternative Therapies

Selective Estrogen Receptor Modulators (SERMs)

Agent	Dosing	Pharmacokinetics	Mechanism of Action	Adverse Effects
Clomiphene citrate*	25- 50 mg orally every 1 -2 days	T Max = 5 hours T ½ = 5-7 days	Reduces negative feedback on pit gonadotropin release with a resultant increase in gonadotropins (LH, FSH)	Visual symptoms, flushing, headache, abdominal discomfort
Tamoxifen*	20 mg orally daily	T Max = 5 hours T ½ = 5-7 days	Inhibits hypothalamic and pituitary estrogen receptors, which blocks estrogen negative feedback on gonadotropin release. Thus, hypothalamic pituitary-gonadal gonadotropin release is increased.	Liver abnormalities, liver enzyme changes, ocular disturbances including cataracts, thromboembolic events including deep venous thrombosis and stroke

*Not FDA-approved for use in males

FSH: follicle-stimulating hormone, LH: luteinizing hormone, T Max: time to achieve max levels, T 1/2: half life

Aromatase Inhibitors (AIs)

Agent	Dosing	Pharmacokinetics	Mechanism of Action	Adverse Effects
Anastrozole*	0.05 - 1 mg every 1-3 days	T Max = 2-5 hours T ½ = 2 days	Inhibits conversion of testosterone to E2	Hot flashes, hypertension, nausea, back pain, bone pain, dyspnea, peripheral edema

*Not FDA-approved for use in males

[#] Disontinued in 2008. No longer available for medical

E2: estradiol, T Max: time to achieve max levels, T 1/2: half life

Human Chorionic Gonadotropin (hCG)

Agent	Dosing	Pharmacokinetics	Mechanism of Action	Adverse Effects
hCG[+]	500-4000 IU units SQ or IM 2-3 times per week	T Max 12 hours T ½ = 2 days	Virtually identical activity to LH. Stimulated Leydig cells to make testosterone.	Headache, irritability, depression, fatigue, edema, gynecomastia, injection site pain.

[+] FDA approved for use in males with hypogonadotropic hypogonadism and pediatric patients with cryptorchidism.

LH: luteinizing hormone, IM: intramuscular, SQ: subcutaneous, T Max: time to achieve max levels, T 1/2: half life

28. Commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible. (Conditional Recommendation; Evidence Level: Grade C)

In contrast to commercial pharmaceutical manufacturing, which is regulated by the FDA, compounded medications are regulated by state laws and, therefore, vary significantly from one region to another.[405] While testosterone gels and creams are the most commonly used forms of compounded testosterone therapies and are routinely less expensive than branded forms of testosterone, these preparations by individual pharmacies occur without direct FDA oversight and approval. Considerable variation in dosages and in ingredients results.

In 2001, the FDA performed an analysis of internet-purchased, compounded products following reports of contamination, poor compounding processes, and product toxicity.[406, 407] Among 29 product samples analyzed, which included testosterone among multiple medications, 31% demonstrated sub-potency ranging from 59-89% below target dose. Similarly, a survey conducted by the Missouri State Board of Pharmacy reported overall failure rates of 20-25% for all compounds tested, with specific samples containing 0-553% of the labeled potency.[408] A follow-up study by the FDA in 2006 confirmed failure rates of 33%, with potencies ranging from 68-268% of labeling claims.[409] Overall, the FDA concluded that problems with quality occurred throughout the country and that the issues were directly linked to the compounding practices themselves rather than due to variability in the active pharmaceutical ingredient.

With respect to testosterone specifically, Grober et al. conducted an analysis of compounded testosterone creams/gels from 10 pharmacies in Toronto, Canada.[410] Each pharmacy was given two prescriptions for 50 mg of testosterone, separated by 1 month to assess both intra-pharmacy and inter-pharmacy consistency. Overall, only 50% of Batch One and 30% of Batch Two samples achieved a potency within 20% of the prescribed dose. Two pharmacies provided samples with >20% of the prescribed dose, while one contained only minimal amounts of testosterone.

In addition to issues relating to the reliability of compounded products themselves, appropriate clinical studies on pharmacokinetics are lacking. As such, even if consistent testosterone levels could be achieved, providers issuing prescriptions for compounded testosterone need to consider performing additional monitoring and dose adjustments to ensure appropriate therapeutic levels.

Follow up of Men on Testosterone Therapy

29. Clinicians should measure an initial follow-up total testosterone level after an appropriate interval to ensure that target testosterone levels have been achieved. (Expert Opinion)

Patients who have been prescribed testosterone should have regular laboratory testing conducted to confirm that therapeutic levels of testosterone are maintained, especially given the suppression of LH by exogenous testosterone and the subsequent decrease in endogenous testosterone production by the testes. It is the opinion of this Panel that total testosterone should be tested after the commencement of therapy at a time point that allows a patient to be sufficiently established on a dosing regimen before determining if therapeutic levels have been achieved and if dosing alterations are required. For patients on daily medication, the Panel recommends that patients use medication the day of follow-up blood work.

Patients on topical gels, patches, and intranasal formulations should have their testosterone checked between two to four weeks after commencement of therapy. Although steady-state levels are generally reached within days following commencement, a longer interval takes into account the potential decreases in endogenous testosterone production when on exogenous testosterone.

Given the mechanisms of action of anastrozole, clomiphene citrate, and hCG, patients using these medications should wait a longer period before follow-up blood work is performed. The Panel recommends testing no sooner than four weeks after commencement.

Patients on short-acting IM or short-acting SQ pellets (testosterone cypionate or enanthate) should have their testosterone measured after several cycles such that testosterone level equilibration has been achieved. The Panel recommends that this be completed no earlier than three to four cycles. While no data exist on the optimal timing of the blood draw within a cycle, it has historically been recommended that blood draws be conducted mid-cycle. The main driving force behind such a strategy is convenience for patients and clinicians, although such timing has no ability to define peak and trough levels.

Patients who are on long-acting IM testosterone (testosterone undecanoate) should have blood work tested once steady state levels have been achieved. Testosterone undecanoate is typically re-administered at a time point 4 weeks after initial dosing and then every 10 weeks thereafter. As with short-acting IM testosterone injections, the general recommendation is mid-cycle testing, after equilibration, and halfway between the first two 10-week injections.

Patients who are on long-acting SQ pellets require two separate assessments of testosterone to determine the dose and frequency required. The first testosterone measurement should be obtained two to four weeks after initial implant to determine if the number of inserted pellets needs to be increased or decreased to achieve the appropriate therapeutic level. Patients should then be tested after 10-12 weeks.

31. **Testosterone levels should be measured every 6-12 months while on testosterone therapy. (Expert Opinion)**

Patients on testosterone therapy should have serum testosterone levels checked every 6-12 months to ensure maintenance of target levels. Given anecdotal concerns about clomiphene citrate-associated tachyphylaxis, it is recommended that patients using this therapeutic approach have total testosterone measured as outlined previously.

Please refer to Table 7 for a summary of follow-up testing for men being treated for testosterone deficiency. Testing intervals are the expert opinion of the Panel and are provided as a guide to aid clinicians in the follow-up of such patients.

32. **Clinicians should discuss the cessation of testosterone therapy three to six months after commencement of treatment in patients who experience normalization of total testosterone levels but fail to achieve symptom or sign improvement. (Clinical Principle)**

If patients achieve target testosterone levels, but do not feel that they have sufficient improvement in their symptoms, clinicians should question whether testosterone deficiency is the etiology of their symptoms. There is no utility in continuing testosterone therapy in men who achieve target testosterone levels without symptom improvement.

An exception can be made if patients do not have symptoms but have documented BMD loss. In this clinical scenario, an argument can be made to continue testosterone therapy. Similarly, in the event patients have unexplained anemia that improves on testosterone therapy, continuation can be considered even in the absence of other symptom improvement.

Table 7: Follow-up Laboratory Testing

Laboratory Test	Baseline	Testosterone Titration Phase	Stable Phase
Total Testosterone	Recommendation: Measure at the same lab using the same assay on two separate occasions in an early morning fashion	Recommendation: Measure two to four weeks after initiation of testosterone therapy (depending on type of therapy)	Recommendation: Measure every 6-12 months
Luteinizing Hormone	Recommendation: Measure with repeat total testosterone level if first level low	Recommendation: Measure four weeks after initiation of SERM therapy in men with persistently low testosterone levels	Recommendation: Measure in men on SERMs who cease responding (decrease in testosterone level after initial response—tachyphylaxis).
Follicle-Stimulating Hormone	Optional: Measure with repeat total testosterone level in men interested in fertility	Not Recommended	Not Recommended
Prolactin	Recommendation: Measure in men with testosterone deficiency who also have a low or low/normal LH level	Not Recommended	Recommendation: Measure every 6-12 months, only in patients being treated pharmacologically for hyperprolactinemia
Estradiol	Recommendation: Measure in testosterone deficient patients with baseline gynecomastia Optional: Measure in all patients with testosterone deficiency at baseline to assess pre-testosterone therapy level	Optional: Measure when checking total testosterone	Recommendation: Measure in patients developing breast symptoms or gynecomastia while on testosterone therapy and in all patients on AIs Optional: Measure in all patients on SERMs
Hemoglobin/ Hematocrit	Recommendation: Measure baseline levels to ensure pre-treatment level is <50%	Optional: Clinical judgment is recommended to determine need for hemoglobin/ hematocrit monitoring depending on baseline levels and the duration of time required to reach therapeutic target levels	Recommendation: Measure every 6-12 months or sooner depending on prior values to maintain hematocrit levels below 54%

AI: aromatase inhibitor, LH: luteinizing hormone, SERM: selective estrogen receptor modulator

Table 7: Follow-up Laboratory Testing

Laboratory Test	Baseline	Testosterone Titration Phase	Stable Phase
PSA	Recommendation: Measure in testosterone deficient patients over 40 years of age and in those testosterone deficient patients with a history of prostate cancer	Not Recommended	Recommendation: In men without a history of prostate cancer, testing should be conducted utilizing a shared decision-making approach, in accordance with the AUA Early Detection of Prostate Cancer Guideline Prostate cancer patients on testosterone therapy should have their PSA levels monitored on the same schedule as men without testosterone deficiency; however, clinicians may choose to increase the frequency of testing

AI: aromatase inhibitor, LH: luteinizing hormone, SERM: selective estrogen receptor modulator

FUTURE RESEARCH

There are several areas in the testosterone deficiency space, more specifically, epidemiology, diagnosis, treatment and adverse events, which warrant more detailed investigation.

Epidemiology

- Are there age-specific reference ranges for testosterone? This question should be answered for both total and free testosterone and should likely be focused on two assays, LCMS for total testosterone and equilibrium dialysis for free testosterone.
- What is the impact of changes in testosterone levels over the life-span of an individual patient? Specifically, in a man who has high-normal testosterone levels in his younger years, does a drop in testosterone as he ages (with resultant testosterone levels remaining in the normal range) put him at risk for symptoms and deleterious effects of low testosterone levels?
- Is there a threshold testosterone level that is linked to specific symptoms (e.g., fatigue, low sex drive, ED, depression, reduced physical function, cognitive effects) or signs (e.g., bone density loss, elevation of HbA1C, MACE)?
- Is there a genotype that predicts testosterone deficiency later in life?
- Are there biomarkers for the development of MACE in men with testosterone deficiency?
- Does exposure to chemotherapy put a man at increased risk for development of testosterone deficiency later in life?

Diagnosis of Testosterone Deficiency

- Further research is needed to understand the role of free testosterone level in the diagnosis of men with testosterone deficiency.
- What is the role of androgen receptor sensitivity (CAG repeat analysis) in the diagnosis of testosterone deficiency?
- There is a great need for the development of robust and reliable patient-reported outcome tools (e.g. questionnaires) in the screening and follow-up of response to therapy in men with testosterone deficiency.

Treatment of Testosterone Deficiency

Long-term analysis is needed on the impact of weight loss and exercise on testosterone levels and reversal of testosterone deficiency.

- There is great need for longer term studies looking at symptom and sign improvement.
- Trials are currently ongoing to develop orally administered exogenous testosterone agents. Approval of such agents would give men further (and likely palatable) therapeutic options.
- Further analysis of the role of subcutaneously administered testosterone. Trials are currently ongoing in this space.
- Greater study is needed on the roles of the different non-traditional testosterone therapies (e.g., SERMs, hCG, AIs).
- Long-term study is needed of the recovery of endogenous testosterone production after short, medium and long-term exogenous testosterone therapy.
- Study of long-term effects of testosterone therapy on MACE is needed.

Adverse Events of Testosterone Deficiency

- Greater study is needed on the prevalence of adverse events (e.g., polycythemia, VTE, gynecomastia, MACE).
- A more detailed analysis is required of the mechanisms of polycythemia development in men on testosterone therapy.
- Further exploration of the impact of long-term testosterone therapy in prostate cancer patients is a great need. In which sub-populations is testosterone therapy safe?
- There is a need for greater study of the bipolar testosterone concept.
- Longer-term studies are needed on spermatogenesis recovery strategies in men who have been on testosterone therapy.

REFERENCES

1. Malik RD, Lapin B, Wang CE et al: Are we testing appropriately for low testosterone?: characterization of tested men and compliance with current guidelines. J Sex Med 2015; **12:** 66.
2. Malik R, Wang C, Lapin B et al: Characteristics of men undergoing testosterone replacement therapy and adherence to follow-up recommendations in Metropolitan Multicenter Health Care System. Urology 2015; **85:** 1382.
3. Baillargeon J, Urban RJ, Kuo YF et al: Screening and monitoring in men prescribed testosterone therapy in the US, 2001-2010. Public Health Rep 2015; **130:** 143.
4. Millar AC, Lau AN, Tomlinson G et al: Predicting low testosterone in aging men: a systematic review. CMAJ 2016; **188:** E321.
5. Harman SM, Metter EJ, Tobin JD et al: Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001; **86:** 724.
6. Araujo AB, O'Donnell AB, Brambilla DJ et al: Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2004; **89:** 5920.
7. Mulligan T, Frick M, Zuraw Q et al: Prevalence of hypogonadism in males aged at least 45 years: the HIM study. International Journal of Clinical Practice 2006; **60:** 762.
8. Wu FC, Tajar A, Beynon JM et al: Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010; **363:** 123.
9. Dunn JF, Nisula BC and Rodbard D: Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 1981; **53:** 58.
10. Trost LW and Mulhall JP: Challenges in testosterone measurement, data interpretation, and methodological appraisal of interventional trials. J Sex Med 2016; **13:** 1029.
11. Paduch DA, Brannigan RE, Fuchs EF et al: The laboratory diagnosis of testosterone deficiency. Urology 2014; **83:** 980.
12. Wang C, Catlin DH, Demers LM et al: Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. J Clin Endocrinol Metab 2004; **89:** 534.
13. Vesper HW, Bhasin S, Wang C et al: Interlaboratory comparison study of serum total testosterone measurements performed by mass spectrometry methods. Steroids 2009; **74:** 498.
14. Pathologists CoA: Surveys and anatomic pathology education programs. Testosterone and estradiol accuracy abs, 2016.
15. Araujo AB, Esche GR, Kupelian V et al: Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab 2007; **92:** 4241.
16. Brand JS, van der Tweel I, Grobbee DE et al: Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol 2011; **40:** 189.
17. Wang C, Nieschlag E, Swerdloff R et al: ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. Int J Impot Res 2009; **21:** 1.
18. Plymate SR, Tenover JS and Bremner WJ: Circadian variation in testosterone, sex hormone-binding globulin, and calculated non-sex hormone-binding globulin bound testosterone in healthy young and elderly men. J Androl 1989; **10:** 366.
19. Bremner WJ, Vitiello MV and Prinz PN: Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983; **56:** 1278.
20. Crawford ED, Barqawi AB, O'Donnell C et al: The association of time of day and serum testosterone concentration in a large screening population. BJU Int 2007; **100:** 509.
21. Diver MJ, Imtiaz KE, Ahmad AM et al: Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. Clin Endocrinol 2003; **58:** 710.
22. Panizzon MS, Hauger R, Jacobson KC et al: Genetic and environmental influences of daily and intra-individual variation in testosterone levels in middle-aged men. Psychoneuroendocrinology 2013; **38:** 2163.
23. Brambilla DJ, Matsumoto AM, Araujo AB et al: The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. J Clin Endocrinol Metab 2009; **94:** 907.
24. Brambilla DJ, O'Donnell AB, Matsumoto AM et al: Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol 2007; **67:** 853.
25. Muehlenbein MP, Hirschtick JL, Bonner JZ et al: Toward quantifying the usage costs of human immunity: altered metabolic rates and hormone levels during acute immune activation in men. Am J Hum Biol 2010; **22:** 546.
26. Antonio L, Wu FC, O'Neill TW et al: Low free testosterone is associated with hypogonadal signs and symptoms in men with normal total testosterone. J Clin Endocrinol Metab 2016**:** jc20154106.
27. Kapoor D, Aldred H, Clark S et al: Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care 2007; **30:** 911.

28. Ogbera OA, Sonny C, Olufemi F et al: Hypogonadism and subnormal total testosterone levels in men with type 2 diabetes mellitus. J Coll Physicians Surg Pak 2011; **21:** 517.
29. Kang S, Park HJ and Park NC: Serum total testosterone level and identification of late-onset hypogonadism: a community-based study. Korean J Urol 2013; **54:** 619.
30. Almeida OP, Yeap BB, Hankey GJ et al: Low free testosterone concentration as a potentially treatable causeof depressive symptoms in older men. Arch Gen Psychiatry 2008; **65:** 283.
31. Ford AH, Yeap BB, Flicker L et al: Prospective longitudinal study of testosterone and incident depression in older men: the Health in Men study. Psychoneuroendocrinology 2016; **64:** 57.
32. Halabi S, Collins EG, Thorevska N et al: Relationship between depressive symptoms and hypogonadism in men with COPD. COPD 2011; **8:** 346.
33. Pastuszak AW, Badhiwala N, Lipshultz LI et al: Depression is correlated with the psychological and physical aspects of sexual dysfunction in men. Int J of Impot Res 2013; **25:** 194.
34. Sato Y, Tanda H, Kato S et al: Prevalence of major depressive disorder in self-referred patients in a late onset hypogonadism clinic. Int J of Impot Res 2007; **19:** 407.
35. Sunchatawirul K, Tantiwongse K, Chathaisong P et al: Hypogonadism among HIV-infected men in Thailand. Int J of STD AIDS 2012; **23:** 876.
36. Ponholzer A, Madersbacher S, Rauchenwald M et al: Serum androgen levels and their association to depression and alzheimer dementia in a cohort of 75-year-old men over 5 years: results of the VITA study. Int J of Impot Res 2009; **21:** 187.
37. Crum-Cianflone NF, Bavaro M, Hale B et al: Erectile dysfunction and hypogonadism among men with HIV. AIDS Patient Care STDS 2007; **21:** 9.
38. Shores MM, Moceri VM, Gruenewald DA et al: Low testosterone is associated with decreased function and increased mortality risk: a preliminary study of men in a geriatric rehabilitation unit. J Am Geriat Soc 2004; **52:** 2077.
39. Shores MM, Moceri VM, Sloan KL et al: Low testosterone levels predict incident depressive illness in older men: effects of age and medical morbidity. J Clin Psychiatry 2005; **66:** 7.
40. Pagano MJ and Stahl PJ: Variation in penile hemodynamics by anatomic location of cavernosal artery imaging in penile duplex doppler ultrasound. J Sex Med 2015; **12:** 1911.
41. Acar D, Cayan S, Bozlu M et al: Is routine hormonal measurement necessary in initial evaluation of men with erectile dysfunction? Arch Androl 2004; **50:** 247.
42. Ajo R, Segura A, Mira L et al: The relationship of salivary testosterone and male sexual dysfunction in opioid-associated androgen deficiency (OPIAD). Aging Male 2017**; 1**:1.
43. Chao JK, Hwang TI, Ma MC et al: A survey of obesity and erectile dysfunction of men conscripted into the military in Taiwan. J Sex Med 2011; **8:** 1156.
44. Chao JK, Kuo WH, Chiang HS et al: Association of metabolic syndrome, atherosclerosis risk factors, sex hormones in ED in aboriginal Taiwanese. Int J Impot Res 2012; **24:** 141.
45. Chao JK, Ma MC, Lin YC et al: Study on alcohol dependence and factors related to erectile dysfunction among aborigines in Taiwan. Am J Mens Health 2015; **9:** 247.
46. Chuang YC, Chung MS, Wang PW et al: Albuminuria is an independent risk factor of erectile dysfunction in men with type 2 diabetes. J Sex Med 2012; **9:** 1055.
47. Derosa G, Romano D, Tinelli C et al: Prevalence and associations of erectile dysfunction in a sample of Italian males with type 2 diabetes. Diabetes Res Clin Pract 2015; **108:** 329.
48. Dogru MT, Basar MM and Haciislamoglu A: The difference of heart rate recovery between males with and without erectile dysfunction. Ann Noninvasive Electrocardiol 2010; **15:** 223.
49. Guaraldi G, Beggi M, Zona S et al: Erectile dysfunction is not a mirror of endothelial dysfunction in HIV-infected patients. J Sex Med 2012; **9:** 1114.
50. Hall SA, Shackelton R, Rosen RC et al: Risk factors for incident erectile dysfunction among community-dwelling men. J Sex Med 2010; **7:** 712.
51. Holt SK, Lopushnyan N, Hotaling J et al: Prevalence of low testosterone and predisposing risk factors in men with type 1 diabetes mellitus: findings from the DCCT/EDIC. J Clin Endocrinol Metab 2014; **99:** E1655.
52. Hwang TI, Lo HC, Tsai TF et al: Association among hypogonadism, quality of life and erectile dysfunction in middle-aged and aged male in Taiwan. Int J Impot Res 2007; **19:** 69.
53. Jannini EA, Screponi E, Carosa E et al: Lack of sexual activity from erectile dysfunction is associated with a reversible reduction in serum testosterone. Int J Androl 1999; **22:** 385.
54. Jiang X, Luo Y, Zhao S et al: Clinical significance and expression of microrna in diabetic patients with erectile dysfunction. Exp Ther Med 2015; **10:** 213.
55. Kapoor D, Clarke S, Channer KS et al: Erectile dysfunction is associated with low bioactive testosterone levels and visceral adiposity in men with type 2 diabetes. Int J Androl 2007; **30:** 500.
56. Lee YC, Huang CH, Wang CJ et al: The associations among eNOS G894T gene polymorphism, erectile dysfunction and related risk factors. BJU Int 2007; **100:** 1116.
57. Lee YC, Liu CC, Huang CN et al: The potential impact of metabolic syndrome on erectile dysfunction in aging Taiwanese males. J Sex Med 2010; **7:** 3127.
58. Liao M, Huang X, Gao Y et al: Testosterone is associated with erectile dysfunction: a cross-sectional study in Chinese men. PLoS ONE 2012; **7:** e39234.

59. Low WY, Khoo EM, Tan HM et al: Depression, hormonal status and erectile dysfunction in the aging male: results from a community study in Malaysia. J Mens Health 2006; **3:** 263.
60. Satkunasivam R, Ordon M, Hu B et al: Hormone abnormalities are not related to erectile dysfunction and decreased libido found in many men with infertility. Fertil Steril 2014; **101:** 1594.
61. Schneider G, Nienhaus K, Gromoll J et al: Sex hormone levels, genetic androgen receptor polymorphism, and anxiety in >50-year-old males. J Sex Med 2011; **8:** 3452.
62. Sharifi F, Asghari M, Jaberi Y et al: Independent predictors of erectile dysfunction in type 2 diabetes mellitus: is it true what they say about risk factors? ISRN Endocrinol 2012; **2012:** 502353.
63. Shi MD, Chao JK, Ma MC et al: Factors associated with sex hormones and erectile dysfunction in male Taiwanese participants with obesity. J Sex Med 2014; **11:** 230.
64. Shi MD, Chao JK, Ma MC et al: The connection between type 2 diabetes and erectile dysfunction in Taiwanese aboriginal males. Int J Impot Res 2014; **26:** 235.
65. Soterio-Pires JH, Hirotsu C, Kim LJ et al: The interaction between erectile dysfunction complaints and depression in men: a cross-sectional study about sleep, hormones and quality of life. Int J Impot Res. 2017; **2:** 70.
66. Suija K, Kerkela M, Rajala U et al: The association between erectile dysfunction, depressive symptoms and testosterone levels among middle-aged men. Scand J Public Health 2014; **42:** 677.
67. Tsai CC, Liu CC, Huang SP et al: The impact of irritative lower urinary tract symptoms on erectile dysfunction in aging Taiwanese males. Aging Male 2010; **13:** 179.
68. Wu F, Chen T, Mao S et al: Levels of estradiol and testosterone are altered in Chinese men with sexual dysfunction. Andrology 2016; **4:** 932.
69. Garvey WT, Mechanick JI, Brett EM et al: American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 2016; **22 Suppl 3:** 1.
70. Corona G, Mannucci E, Fisher AD et al: Low levels of androgens in men with erectile dysfunction and obesity. J Sex Med 2008; **5:** 2454.
71. Corona G, Rastrelli G, Monami M et al: Body mass index regulates hypogonadism-associated CV risk: results from a cohort of subjects with erectile dysfunction. J Sex Med 2011; **8:** 2098.
72. Kaplan SA, Lee JY, O'Neill EA et al: Prevalence of low testosterone and its relationship to body mass index in older men with lower urinary tract symptoms associated with benign prostatic hyperplasia. Aging Male 2013; **16:** 169.
73. Vandenput L, Mellstrom D, Karlsson MK et al: Serum estradiol is associated with lean mass in elderly Swedish men. Eur J Endocrinol 2010; **162:** 737.
74. Pagano MJ, De Fazio A, Levy A et al: Age, body mass index, and frequency of sexual activity are independent predictors of testosterone deficiency in men with erectile dysfunction. Urology 2016; **90**: 112.
75. Li F, Yue H, Yamaguchi K et al: Effect of surgical repair on testosterone production in infertile men with varicocele: a meta-analysis. Int J Urol 2012; **19:** 149.
76. Niewoehner CB and Schorer AE: Gynaecomastia and breast cancer in men. BMJ 2008; **336:** 709.
77. Roy CN, Snyder PJ, Stephens-Shields AJ et al: Association of testosterone levels with anemia in older men: a controlled clinical trial. JAMA Intern Med 2017; **177:** 480.
78. Barbonetti A, Vassallo MR, Pacca F et al: Correlates of low testosterone in men with chronic spinal cord injury. Andrology 2014; **2:** 721.
79. Bello AK, Stenvinkel P, Lin M et al: Serum testosterone levels and clinical outcomes in male hemodialysis patients. Am J Kidney Dis 2014; **63:** 268.
80. Clark MJ, Schopp LH, Mazurek MO et al: Testosterone levels among men with spinal cord injury: relationship between time since injury and laboratory values. Am J Phys Med Rehabil 2008; **87:** 758.
81. Dhindsa S, Ghanim H, Batra M et al: Effect of testosterone on hepcidin, ferroportin, ferritin and iron binding capacity in patients with hypogonadotropic hypogonadism and type 2 diabetes. Clin Endocrinol 2016; **85:** 772.
82. Fukai S, Akishita M, Yamada S et al: Plasma sex hormone levels and mortality in disabled older men and women. Geriatr Gerontol Int. 2011; **11:** 196.
83. Grossmann M, Panagiotopolous S, Sharpe K et al: Low testosterone and anaemia in men with type 2 diabetes. Clin Endocrinol 2009; **70:** 547.
84. Gungor O, Kircelli F, Carrero JJ et al: Endogenous testosterone and mortality in male hemodialysis patients: is it the result of aging? Clin J Am Soc Nephrol 2010; **5:** 2018.
85. Hamilton EJ, Davis WA, Makepeace A et al: Prevalence and prognosis of a low serum testosterone in men with type 2 diabetes: the Fremantle Diabetes Study Phase II. Clin Endocrinol 2016; **85:** 444.
86. Dos Santos MR, Sayegh ALC, Groehs RVR et al: Testosterone deficiency increases hospital readmission and mortality rates in male patients with heart failure. Arquivos Brasileiros de Cardiologia 2015; **105:** 256.
87. Tajar A, Huhtaniemi IT, O'Neill TW et al: Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). J Clin Endocrinol Metab 2012; **97:** 1508.

88. Dabaja AA, Bryson CF, Schlegel PN et al: The effect of hypogonadism and testosterone-enhancing therapy on alkaline phosphatase and bone mineral density. BJU Int 2015; **115:** 480.
89. Kacker R, Conners W, Zade J et al: Bone mineral density and response to treatment in men younger than 50 years with testosterone deficiency and sexual dysfunction or infertility. J Urol 2014; **191:** 1072.
90. Amin S, Zhang Y, Sawin CT et al: Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham study. Ann Intern Med 2000; **133:** 951.
91. Moran J, Martin R, Pedrera-Canal M et al: Low testosterone levels are associated with poor peripheral bone mineral density and quantitative bone ultrasound at phalanges and calcaneus in healthy elderly men. Biol Res Nurs 2015; **17:** 169.
92. Abou-Seif MA and Youssef AA: Oxidative stress and male IGF-1, gonadotropin and related hormones in diabetic patients. Clin Chem Lab Med 2001; **39:** 618.
93. Achemlal L, Tellal S, Rkiouak F et al: Bone metabolism in male patients with type 2 diabetes. Clin Rheumatol 2005; **24:** 493.
94. Al Hayek AA, Khader YS, Jafal S et al: Prevalence of low testosterone levels in men with type 2 diabetes mellitus: a cross-sectional study. J Family Community Med 2013; **20:** 179.
95. Andersson B, Marin P, Lissner L et al: Testosterone concentrations in women and men with NIDDM. Diabetes Care 1994; **17:** 405.
96. Ando S, Rubens R and Rottiers R: Androgen plasma levels in male diabetics. J Endocrinol Invest 1984; **7:** 21.
97. Asare-Anane H, Ofori E, Agyemang Y et al: Obesity and testosterone levels in Ghanaian men with type 2 diabetes. Clin Diabetes 2014; **32:** 61.
98. Atlantis E, Fahey P, Martin S et al: Predictive value of serum testosterone for type 2 diabetes risk assessment in men. BMC Endocr Disord 2016; **16:** 26.
99. Barrett CE: Lower endogenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. Ann Intern Med 1992; **117:** 807.
100. Barrett CE, Khaw KT and Yen SS: Endogenous sex hormone levels in older adult men with diabetes mellitus. Am J Epidemiol 1990; **132:** 895.
101. Bellastella G, Maiorino MI, Olita L et al: Vitamin D deficiency in type 2 diabetic patients with hypogonadism. J Sex Med 2014; **11:** 536.
102. Chearskul S, Charoenlarp K, Thongtang V et al: Study of plasma hormones and lipids in healthy elderly thais compared to patients with chronic diseases: diabetes mellitus, essential hypertension and coronary heart disease. J Med Assoc Thai 2000; **83:** 266.
103. Chen RY, Wittert GA and Andrews GR: Relative androgen deficiency in relation to obesity and metabolic status in older men. Diabetes Obes Metab 2006; **8:** 429.
104. Chen RY and Ng KK: Self-referred older Asian males in a men's health clinic: the inter-relationships between androgens, metabolic parameters and quality of life measures. Aging Male 2010; **13:** 233.
105. Chen HL, Deng LL and Li JF: Prevalence of osteoporosis and its associated factors among older men with type 2 diabetes. Int J Endocrinol 2013; **2013**
106. Corona G, Mannucci E, Mansani R et al: Organic, relational and psychological factors in erectile dysfunction in men with diabetes mellitus. Eur Urol 2004; **46:** 222.
107. Corona G, Mannucci E, Petrone L et al: Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. Int J Impot Res 2006; **18:** 190.
108. Corrales JJ, Burgo RM, Garca-Berrocal B et al: Partial androgen deficiency in aging type 2 diabetic men and its relationship to glycemic control. Metabolism 2004; **53:** 666.
109. Defay R, Papoz L, Barny S et al: Hormonal status and NIDDM in the European and Melanesian populations of New Caledonia: a case-control study. The CALedonia DIAbetes mellitus (CALDIA) study group. Int J Obes Relat Metab Disord 1998; **22:** 927.
110. Dhindsa S, Miller MG, McWhirter CL et al: Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care 2010; **33:** 1186.
111. Elabbady A, Hashad MM, Kotb AF et al: Studying the effect of type 2 diabetes mellitus on prostate-related parameters: a prospective single institutional study. Prostate Int 2016; **4:** 156.
112. Haffner SM, Shaten J, Stern MP et al: Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT research group. Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996; **143:** 889.
113. Haffner SM, Moss SE, Klein BE et al: Sex hormones and DHEA-SO4 in relation to ischemic heart disease mortality in diabetic subjects. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care 1996; **19:** 1045.
114. Ho CH, Yu HJ, Wang CY et al: Prediabetes is associated with an increased risk of testosterone deficiency, independent of obesity and metabolic syndrome. PLoS ONE 2013; **8:** e74173.
115. Ibanez J, Gorostiaga EM, Alonso AM et al: Lower muscle strength gains in older men with type 2 diabetes after resistance training. J Diabetes Complications 2008; **22:** 112.
116. Jang Y, Lee JH, Cho EY et al: Differences in body fat distribution and antioxidant status in Korean men with cardiovascular disease with or without diabetes. Am J Clin Nutr 2001; **73:** 68.

117. Jin Q, Lou Y, Chen H et al: Lower free testosterone level is correlated with left ventricular diastolic dysfunction in asymptomatic middle-aged men with type 2 diabetes mellitus. Int J Clin Pract 2014; **68:** 1454.
118. Kim YS, Hong D, Lee DJ et al: Total testosterone may not decline with ageing in Korean men aged 40 years or older. Clin Endocrinol 2012; **77:** 296.
119. Lakshman KM, Bhasin S and Araujo AB: Sex hormone-binding globulin as an independent predictor of incident type 2 diabetes mellitus in men. J Gerontol A Biol Sci Med Sci 2010; **65:** 503.
120. Li J, Lai H, Chen S et al: Interaction of sex steroid hormones and obesity on insulin resistance and type 2 diabetes in men: the Third National Health and Nutrition Examination Survey. J Diabetes Complications 2016; **22:** 318.
121. Maiorino MI, Bellastella G, Petrizzo M et al: Circulating endothelial progenitor cells in type 1 diabetic patients with erectile dysfunction. Endocrine 2015; **49:** 415.
122. Martinez-Jabaloyas JM, Queipo-Zaragoza A, Pastor-Hernandez F et al: Testosterone levels in men with erectile dysfunction. BJU Int 2006; **97:** 1278.
123. Mattack N, Devi R, Kutum T et al: The evaluation of serum levels of testosterone in type 2 diabetic men and its relation with lipid profile. J Clin Diagn Res 2015; **9:** BC04.
124. Phillips GB: Evidence for hyperestrogenemia as the link between diabetes mellitus and myocardial infarction. Am J Med 1984; **76:** 1041.
125. Pitteloud N, Mootha VK, Dwyer AA et al: Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care 2005; **28:** 1636.
126. Rhoden EL, Ribeiro EP, Teloken C et al: Diabetes mellitus is associated with subnormal serum levels of free testosterone in men. BJU Int 2005; **96:** 867.
127. Salminen M, Vahlberg T, Raiha I et al: Sex hormones and the risk of type 2 diabetes mellitus: a 9-year follow up among elderly men in Finland. Geriatr Gerontol Int 2015; **15:** 559.
128. Selvin E, Feinleib M, Zhang L et al: Androgens and diabetes in men: results from the third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care 2007; **30:** 234.
129. Semple CG, Gray CE and Beastall GH: Androgen levels in men with diabetes mellitus. Diabet Med 1988; **5:** 122.
130. Shahwan MM, Spathis GS, Fry DE et al: Differences in pituitary and testicular function between diabetic patients on insulin and oral anti-diabetic agents. Diabetologia 1978; **15:** 13.
131. Small M, MacRury S, Beastall GH et al: Oestradiol levels in diabetic men with and without a previous myocardial infarction. QJ Med 1987; **64:** 617.
132. Stellato RK, Feldman HA, Hamdy O et al: Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts Male Aging Study. Diabetes Care 2000; **23:** 490.
133. Talukder SK, Afsana F and Khan SJ: Metabolic syndrome in men with sexual dysfunction. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2010; **4:** 143.
134. Tibblin G, Adlerberth A, Lindstedt G et al: The pituitary-gonadal axis and health in elderly men: a study of men born in 1913. Diabetes 1996; **45:** 1605.
135. van Dam EW, Dekker JM, Lentjes EG et al: Steroids in adult men with type 1 diabetes: a tendency to hypogonadism. Diabetes Care 2003; **26:** 1812.
136. Zhu H, Wang N, Han B et al: Low sex hormone-binding globulin levels associate with prediabetes in Chinese men independent of total testosterone. PLoS ONE 2016; **11:** e0162004.
137. Zietz B, Cuk A, Hugl S et al: Association of increased C-peptide serum levels and testosterone in type 2 diabetes. Eur J Intern Med 2000; **11:** 322.
138. Corona G, Monami M, Rastrelli G et al: Type 2 diabetes mellitus and testosterone: a meta-analysis study. Int J Androl 2011; **34:** 528.
139. Svartberg J, Jenssen T, Sundsfjord J et al: The associations of endogenous testosterone and sex hormone-binding globulin with glycosylated hemoglobin levels, in community dwelling men. The Tromso study. Diabetes Metab 2004; **30:** 29.
140. Aass N, Fossa SD, Theodorsen L et al: Prediction of long-term gonadal toxicity after standard treatment for testicular cancer. Eur J Caner 1991; **27:** 1087.
141. IJpma I, Renken RJ, Gietema JA et al: Taste and smell function in testicular cancer survivors treated with cisplatin-based chemotherapy in relation to dietary intake, food preference, and body composition. Appetite 2016; **105:** 392.
142. Nord C, Bjoro T, Ellingsen D et al: Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. Eur Urol 2003; **44:** 322.
143. Nuver J, Smit AJ, Wolffenbuttel BH et al: The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer. J Clin Oncol 2005; **23:** 3718.
144. Schmiegelow M, Lassen S, Poulsen HS et al: Gonadal status in male survivors following childhood brain tumors. J Clin Endocrinol Metab 2001; **86:** 2446.
145. Buchli C, Martling A, Abani MA et al: Risk of acute testicular failure after preoperative radiotherapy for rectal cancer: a prospective cohort study. Ann Surg. 2018; **267:** 326.

146. Bruheim K, Svartberg J, Carlsen E et al: Radiotherapy for rectal cancer is associated with reduced serum testosterone and increased FSH and LH. Int J Radiat Oncol Biol Phys 2008; **70:** 722.
147. Faria S, Cury F and Souhami L: Prospective phase I study on testicular castration induced by radiation treatment. Can J Urol 2015; **22:** 7635.
148. Gomes AR, Souteiro P, Silva CG et al: Prevalence of testosterone deficiency in HIV-infected men under antiretroviral therapy. BMC Infect Dis 2016; **16:** 628.
149. Faramarzia H, Marzban M, AminiLari M et al: Hypogonadism and associated factors in patients with HIV infection based on total and free testosterone. Shiraz E-Med J 2014; **15:** e19734.
150. Bhasin S, Storer TW, Asbel SN et al: Effects of testosterone replacement with a nongenital, transdermal system, androderm, in human immunodeficiency virus-infected men with low testosterone levels. J Clin Endocrinol Metab 1998; **83:** 3155.
151. Bhasin S, Storer TW, Javanbakht M et al: Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 2000; **283:** 763.
152. Bhasin S, Parker RA, Sattler F et al: Effects of testosterone supplementation on whole body and regional fat mass and distribution in human immunodeficiency virus-infected men with abdominal obesity. J Clin Endocrinol Metab 2007; **92:** 1049.
153. Blick G, Khera M, Bhattacharya RK et al: Testosterone replacement therapy outcomes among opioid users: the Testim registry in the United States (TRiUS). Pain Medicine 2012; **13:** 688.
154. Bliesener N, Albrecht S, Schwager A et al: Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. J Clin Endocrinol Metab 2005; **90:** 203.
155. Cepeda MS, Zhu V, Vorsanger G et al: Effect of opioids on testosterone levels: cross-sectional study using NHANES. Pain Med 2015; **16:** 2235.
156. Hosseini SY, Amini E, Safarinejad MR et al: Influence of opioid consumption on serum prostate-specific antigen levels in men without clinical evidence of prostate cancer. Urology 2012; **80:** 169.
157. Safarinejad MR, Asgari SA, Farshi A et al: Opium consumption is negatively associated with serum prostate-specific antigen (PSA), free PSA, and percentage of free PSA levels. J Addict Med 2013; **7:** 58.
158. Safarinejad MR, Asgari SA, Farshi A et al: The effects of opiate consumption on serum reproductive hormone levels, sperm parameters, seminal plasma antioxidant capacity and sperm DNA integrity. Reprod Toxicol 2013; **36:** 18.
159. Sussman EM, Chudnovsky A and Niederberger CS: Hormonal evaluation of the infertile male: has it evolved? Urol Clin North Am 2008; **35:** 147.
160. Fernandez A, Brada M, Zabuliene L et al: Radiation-induced hypopituitarism. Endocr Relat Cancer 2009; **16:** 733.
161. Kamischke A, Kemper DE, Castel MA et al: Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. Eur Respir J 1998; **11:** 41.
162. Martens HF, Sheets PK, Tenover JS et al: Decreased testosterone levels in men with rheumatoid arthritis: effect of low dose prednisone therapy. J Rheumatol 1994; **21:** 1427.
163. Mateo L, Nolla JM, Bonnin MR et al: Sex hormone status and bone mineral density in men with rheumatoid arthritis. J Rheumatol 1995; **22:** 1455.
164. Morley JE, Perry HM 3rd, Kevorkian RT et al: Comparison of screening questionnaires for the diagnosis of hypogonadism. Maturitas 2006; **53:** 424.
165. Martinez-Jabaloyas JM, Queipo-Zaragoza A, Rodriguez-Navarro R et al: Relationship between the Saint Louis University ADAM questionnaire and sexual hormonal levels in a male outpatient population over 50 years of age. Eur Urol 2007; **52:** 1760.
166. Smith KW, Feldman HA and McKinlay JB: Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. Clin Endocrinol 2000; **53:** 703.
167. Morley JE, Charlton E, Patrick P et al: Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 2000; **49:** 1239.
168. 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.
169. Basaria S: Male hypogonadism. Lancet 2014; **383:** 1250.
170. Mazzola CR, Katz DJ, Loghmanieh N et al: Predicting biochemical response to clomiphene citrate in men with hypogonadism. J Sex Med 2014; **11:** 2302.
171. Citron JT, Ettinger B, Rubinoff H et al: Prevalence of hypothalamic-pituitary imaging abnormalities in impotent men with secondary hypogonadism. J Urol 1996; **155:** 529.
172. Kars M, Souverein PC, Herings RM et al: Estimated age- and sex-specific incidence and prevalence of dopamine agonist-treated hyperprolactinemia. J Clin Endocrinol Metab 2009; **94:** 2729.
173. Molitch ME: Medication-induced hyperprolactinemia. Mayo Clin Proc 2005; **80:** 1050.

174. Brue T and Castinetti F: The risks of overlooking the diagnosis of secreting pituitary adenomas. Orphanet J Rare Dis 2016; **11:** 135.
175. Melmed S, Casanueva FF, Hoffman AR et al: Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011; **96:** 273.
176. Chahal J and Schlechte J: Hyperprolactinemia. Pituitary 2008; **11:** 141.
177. Mancini T, Casanueva FF and Giustina A: Hyperprolactinemia and prolactinomas. Endocrinol Metab Clin North Am 2008; **37:** 67.
178. Wong A, Eloy JA, Couldwell WT et al: Update on prolactinomas. Part 1: clinical manifestations and diagnostic challenges. J Clin Neurosci 2015; **22:** 1562.
179. Finkelstein JS, Lee H, Burnett-Bowie SA et al: Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013; **369:** 1011.
180. Wang C, Swerdloff RS, Iranmanesh A et al: Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab 2000; **85:** 2839.
181. Dobs AS, Meikle AW, Arver S et al: Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab 1999; **84:** 3469.
182. Paduch DA, Polzer PK, Ni X et al: Testosterone replacement in androgen-deficient men with ejaculatory dysfunction: a randomized controlled trial. J Clin Endocrinol Metab 2015; **100:** 2956.
183. Optimal evaluation of the infertile male. Edited by J. Jarow, Sigman, M, Kolettis, P, et al, 2011.
184. Petersen C and Soder O: The sertoli cell--a hormonal target and 'super' nurse for germ cells that determines testicular size. Horm Res 2006; **66:** 153.
185. Dierich A, Sairam MR, Monaco L et al: Impairing follicle-stimulating hormone (FSH) signaling in vivo: targeted disruption of the FSH receptor leads to aberrant gametogenesis and hormonal imbalance. Proc Natl Acad Sci USA 1998; **95:** 13612.
186. Tapanainen JS, Aittomaki K, Min J et al: Men homozygous for an inactivating mutation of the follicle-stimulating hormone (FSH) receptor gene present variable suppression of spermatogenesis and fertility. Nat Genet 1997; **15:** 205.
187. Coviello AD, Kaplan B, Lakshman KM et al: Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab 2008; **93:** 914.
188. Drinka PJ, Jochen AL, Cuisinier M et al: Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. J Am Geriatr Soc 1995; **43:** 899.
189. Tenover JS: Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab 1992; **75:** 1092.
190. 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 2005; **60:** 1451.
191. 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 2010; **95:** 2560.
192. Swerdloff RS and Wang C: Three-year follow-up of androgen treatment in hypogonadal men: preliminary report with testosterone gel. Aging Male 2003; **6:** 207.
193. Wang C, Cunningham G, Dobs A et al: Long-term testosterone gel (androgel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab 2004; **89:** 2085.
194. Basaria S, Coviello AD, Travison TG et al: Adverse events associated with testosterone administration. N Engl J Med 2010; **363:** 109.
195. Travison TG, Basaria S, Storer TW et al: Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. J Gerontol A Biol Sci Med Sci 2011; **66:** 1090.
196. Bachman E, Travison TG, Basaria S et al: Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. J Gerontol A Biol Sci Med Sci 2014; **69:** 725.
197. Brock G, Heiselman D, Maggi M et al: Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. J Urol 2016; **195:** 699.
198. Maggi M, Heiselman D, Knorr J et al: Impact of testosterone solution 2% on ejaculatory dysfunction in hypogonadal men. J Sex Med 2016; **13:** 1220.
199. Basaria S, Travison TG, Alford D et al: Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. Pain 2015; **156:** 280.
200. Ng Tang Fui M, Prendergast LA, Dupuis P et al: Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet: a randomised controlled trial. BMC Med 2016; **14:** 153.
201. Sih R, Morley JE, Kaiser FE et al: Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab 1997; **82:** 1661.
202. Amory JK, Watts NB, Easley KA et al: Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004; **89:** 503.

203. Page ST, Amory JK, Bowman FD et al: Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005; **90:** 1502.
204. Aversa A, Bruzziches R, Francomano D et al: Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. J Sex Med 2010; **7:** 3495.
205. Gianatti EJ, Dupuis P, Hoermann R et al: Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. J Clin Endocrinol Metab 2014; **99:** 3821.
206. Gianatti EJ, Dupuis P, Hoermann R et al: Effect of testosterone treatment on glucose metabolism in men with type 2 diabetes: a randomized controlled trial. Diabetes Care 2014; **37:** 2098.
207. 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 2011; **34:** 828.
208. Kalinchenko SY, Tishova YA, Mskhalaya GJ et al: Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol 2010; **73:** 602.
209. Konaka H, Sugimoto K, Orikasa H et al: Effects of long-term androgen replacement therapy on the physical and mental statuses of aging males with late-onset hypogonadism: a multicenter randomized controlled trial in japan (EARTH study). Asian J Androl 2016; **18:** 25.
210. Malkin CJ, Pugh PJ, Morris PD et al: Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. Heart 2004; **90:** 871.
211. Marks LS, Mazer NA, Mostaghel E et al: Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA 2006; **296:** 2351.
212. Mathur A, Malkin C, Saeed B et al: Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. Eur J Endocrinol 2009; **161:** 443.
213. Orengo CA, Fullerton L and Kunik ME: Safety and efficacy of testosterone gel 1% augmentation in depressed men with partial response to antidepressant therapy. J Geriatr Psychiatry Neurol 2005; **18:** 20.
214. Seftel AD, Mack RJ, Secrest AR et al: Restorative increases in serum testosterone levels are significantly correlated to improvements in sexual functioning. J Androl 2004; **25:** 963.
215. Steidle C, Schwartz S, Jacoby K et al: AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab 2003; **88:** 2673.
216. Srinivas-Shankar U, Roberts SA, Connolly MJ et al: Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2010; **95:** 639.
217. O'Connell MD, Roberts SA, Srinivas-Shankar U et al: Do the effects of testosterone on muscle strength, physical function, body composition, and quality of life persist six months after treatment in intermediate-frail and frail elderly men? J Clin Endocrinol Metab 2011; **96:** 454.
218. Tan WS, Low WY, Ng CJ et al: Efficacy and safety of long-acting intramuscular testosterone undecanoate in aging men: a randomised controlled study. BJU Int 2013; **111:** 1130.
219. Jones SD Jr, Dukovac T, Sangkum P et al: Erythrocytosis and polycythemia secondary to testosterone replacement therapy in the aging male. Sex Med Rev 2015; **3:** 101.
220. Wheeler KM, Smith RP, Kumar RA et al: A comparison of secondary polycythemia in hypogonadal men treated with clomiphene citrate versus testosterone replacement: a multi-institutional study. J Urol 2017; **197:** 1127.
221. Fennell C, Sartorius G, Ly LP et al: Randomized cross-over clinical trial of injectable vs. implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. Clin Endocrinol 2010; **73:** 102.
222. Carter HB, Albertsen PC, Barry MJ et al: Early detection of prostate cancer: AUA Guideline. J Urol 2013; **190:** 419.
223. Khera M, Bhattacharya RK, Blick G et al: Changes in prostate specific antigen in hypogonadal men after 12 months of testosterone replacement therapy: support for the prostate saturation theory. J Urol 2011; **186:** 1005.
224. Huang G, Travison T, Maggio M et al: Effects of testosterone replacement on metabolic and inflammatory markers in men with opioid-induced androgen deficiency. Clin Endocrinol 2016; **85:** 232.
225. Cherrier MM, Anderson K, Shofer J et al: Testosterone treatment of men with mild cognitive impairment and low testosterone levels. Am J Alzheimers Dis Other Demen 2015; **30:** 421.
226. Hildreth KL, Barry DW, Moreau KL et al: Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. J Clin Endocrinol Metab 2013; **98:** 1891.

227. Kaufman JM, Miller MG, Garwin JL et al: Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. J Sex Med 2011; **8:** 2079.
228. McNicholas TA, Dean JD, Mulder H et al: A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Intl 2003; **91:** 69.
229. Snyder PJ, Bhasin S, Cunningham GR et al: Effects of testosterone treatment in older men. N Engl J Med 2016; **374:** 611.
230. Svartberg J, Agledahl I, Figenschau Y et al: Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. Int J Impot Res 2008; **20:** 378.
231. Anderson JL, May HT, Lappe DL et al: Impact of testosterone replacement therapy on myocardial infarction, stroke, and death in men with low testosterone concentrations in an integrated health care system. Am J Cardiol 2016; **117:** 794.
232. Haring R, Volzke H, Steveling A et al: Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. Eur Heart J 2010; **31:** 1494.
233. Muraleedharan V, Marsh H, Kapoor D et al: Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013; **169:** 725.
234. Ponholzer A, Madersbacher S, Rauchenwald M et al: Vascular risk factors and their association to serum androgen levels in a population-based cohort of 75-year-old men over 5 years: results of the VITA study. World J Urol 2010; **28:** 209.
235. Hackett G, Heald AH, Sinclair A et al: Serum testosterone, testosterone replacement therapy and all-cause mortality in men with type 2 diabetes: retrospective consideration of the impact of PDE5 inhibitors and statins. Int J Clin Pract 2016; **70:** 244.
236. Holmegard HN, Nordestgaard BG, Jensen GB et al: Sex hormones and ischemic stroke: a prospective cohort study and meta-analyses. J Clin Endocrinol Metab 2016; **101:** 69.
237. Khurana KK, Navaneethan SD, Arrigain S et al: Serum testosterone levels and mortality in men with CKD stages 3-4. Am J Kidney Dis 2014; **64:** 367.
238. Chillaron JJ, Fernandez-Miro M, Albareda M et al: Age, insulin requirements, waist circumference, and triglycerides predict hypogonadotropic hypogonadism in patients with type 1 diabetes. J Sex Med 2015; **12:** 76.
239. Liu RT, Chung MS, Wang PW et al: The prevalence and predictors of androgen deficiency in Taiwanese men with type 2 diabetes. Urology 2013; **82:** 124.
240. Akishita M, Hashimoto M, Ohike Y et al: Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. Atherosclerosis 2010; **210:** 232.
241. Shen YC and Chuang YC: The prevalence and predictors of androgen deficiency in Taiwanese men with lower urinary tract symptoms. Urological Science 2016; **27:** 83.
242. Cheung KK, Lau ES, So WY et al: Low testosterone and clinical outcomes in Chinese men with type 2 diabetes mellitus - Hong Kong diabetes registry. Diabetes Res Clin Pract 2017; **123:** 97.
243. Araujo AB, Dixon JM, Suarez EA et al: Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011; **96:** 3007.
244. Beutel ME, Wiltink J, Hauck EW et al: Correlations between hormones, physical, and affective parameters in aging urologic outpatients. Eur Urol 2005; **47:** 749.
245. Blaya R, Thomaz LD, Guilhermano F et al: Total testosterone levels are correlated to metabolic syndrome components. Aging Male 2016; **2:** 85.
246. Corona G, Maseroli E, Rastrelli G et al: Characteristics of compensated hypogonadism in patients with sexual dysfunction. J Sex Med 2014; **11:** 1823.
247. Corrigan FE 3rd, Al Mheid I, Eapen DJ et al: Low testosterone in men predicts impaired arterial elasticity and microvascular function. Int J Cardiol 2015; **194:** 94.
248. Fleishman SB, Khan H, Homel P et al: Testosterone levels and quality of life in diverse male patients with cancers unrelated to androgens. J Clin Oncol 2010; **28:** 5054.
249. Garcia CE, Piqueras M, Huguet J et al: Hypertension, dyslipidemia and overweight are related to lower testosterone levels in a cohort of men undergoing prostate biopsy. Int J Impot Res 2012; **24:** 110.
250. Hall SA, Esche GR, Araujo AB et al: Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab 2008; **93:** 3870.
251. Liao CH, Chiang HS and Yu HJ: Serum testosterone levels significantly correlate with nocturia in men aged 40-79 years. Urology 2011; **78:** 631.
252. Malan NT, Hamer M, Lambert GW et al: Sex hormones associated with subclinical kidney damage and atherosclerosis in South African men: The SABPA study. J Hypertens 2012; **30:** 2387.
253. Malan NT, Stalder T, Schlaich MP et al: Chronic distress and acute vascular stress responses associated with ambulatory blood pressure in low-testosterone African men: the SABPA study. J Hum Hypertens 2014; **28:** 393.
254. Martínez-Jabaloyas JM: Testosterone deficiency in patients with erectile dysfunction: when should a higher cardiovascular risk be considered? J Sex Med 2014; **11:** 2083.
255. Novo S, Iacona R, Bonomo V et al: Erectile dysfunction is associated with low total serum testosterone levels and impaired flow-mediated vasodilation in intermediate risk men according to the Framingham risk score. Atherosclerosis 2015; **238:** 415.

256. Rabijewski M, Papierska L, Kozakowski J et al: The high prevalence of testosterone deficiency in population of Polish men over 65 years with erectile dysfunctions. Aging Male 2012; **15:** 258.
257. Rabijewski M, Papierska L and Piatkiewicz P: The prevalence of prediabetes in population of Polish men with late-onset hypogonadism. Aging Male 2014; **17:** 141.
258. Rubinstein A and Carpenter DM: Elucidating risk factors for androgen deficiency associated with daily opioid use. Am J Med 2014; **127:** 1195.
259. Sharma R, Oni OA, Gupta K et al: Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015; **36:** 2706.
260. Shores MM, Arnold AM, Biggs ML et al: Testosterone and dihydrotestosterone and incident ischaemic stroke in men in the cardiovascular health study. Clin Endocrinol 2014; **81:** 746.
261. Taira AV, Merrick GS, Galbreath RW et al: Factors impacting all-cause mortality in prostate cancer brachytherapy patients with or without androgen deprivation therapy. Brachytherapy 2010; **9:** 42.
262. Vlachopoulos C, Ioakeimidis N, Miner M et al: Testosterone deficiency: a determinant of aortic stiffness in men. Atherosclerosis 2014; **233:** 278.
263. Zheng R, Cao L, Cao W et al: Risk factors for hypogonadism in male patients with type 2 diabetes. J Diabetes Res 2016; **2016:** 5162167.
264. Shores MM, Matsumoto AM, Sloan KL et al: Low serum testosterone and mortality in male veterans. Arch Intern Med 2006; **166:** 1660.
265. Ganesh HK, Sarathi HA, George J et al: Prevalence of hypogonadism in patients with type 2 diabetes mellitus in an Asian Indian study group. Endocr Pract 2009; **15:** 513.
266. El Sakka AI: Impact of the association between elevated oestradiol and low testosterone levels on erectile dysfunction severity. Asian J Androl 2013; **15:** 492.
267. Shamim MO, Ali Khan FM and Arshad R: Association between serum total testosterone and body mass index in middle aged healthy men. Pak J Med Sci 2015; **31:** 355.
268. Cohen A, Lapin B, Wang CH et al: Variation in testosterone levels and health-related quality of life in men diagnosed with prostate cancer on active surveillance. Urology 2016; **94:** 180.
269. Bolam KA, Beck BR, Adlard KN et al: The relationship between BPAQ-derived physical activity and bone density of middle-aged and older men. Osteoporosis Int 2014; **25:** 2663.
270. Calderón B, Gómez-Martin JM, Vega-Piñero B et al: Prevalence of male secondary hypogonadism in moderate to severe obesity and its relationship with insulin resistance and excess body weight. Andrology 2016; **4:** 62.
271. Carrero J, Qureshi AR, Nakashima A et al: Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease. Nephrol Dial Transplant 2011; **26:** 184.
272. Carrero JJ, Qureshi AR, Parini P et al: Low serum testosterone increases mortality risk among male dialysis patients. J Am Soc Nephrol 2009; **20:** 613.
273. Dhindsa S, Upadhyay M, Viswanathan P et al: Relationship of prostate-specific antigen to age and testosterone in men with type 2 diabetes mellitus. Endocr Pract 2008; **14:** 1000.
274. Dhindsa S, Prabhakar S, Sethi M et al: Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004; **89:** 5462.
275. Farias JM, Tinetti M, Khoury M et al: Low testosterone concentration and atherosclerotic disease markers in male patients with type 2 diabetes. J Clin Endocrinol Metab 2014; **99:** 4698.
276. Ghazi S, Zohdy W, Elkhiat Y et al: Serum testosterone levels in diabetic men with and without erectile dysfunction. Andrologia 2012; **44:** 373.
277. Hackett GI, Cole NS, Deshpande AA et al: Biochemical hypogonadism in men with type 2 diabetes in primary care practice. British Journal of Diabetes and Vascular Disease 2009; **9:** 226.
278. Hernandez-Mijares A, Garcia-Malpartida K, Sola -Izquierdo E et al: Testosterone levels in males with type 2 diabetes and their relationship with cardiovascular risk factors and cardiovascular disease. J Sex Med 2010; **7:** 1954.
279. Kemp T and Rheeder P: The prevalence and association of low testosterone levels in a South African male, diabetic, urban population. Journal of Endocrinology, Metabolism and Diabetes of South Africa 2015; **20:** 41.
280. Kim JS, Kim BS, Jeon JY et al: Testosterone deficiency associated with poor glycemic control in Korean male diabetics. Endocrinol Metab 2014; **29:** 300.
281. Laaksonen DE, Niskanen L, Punnonen K et al: The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: a prospective cohort study. J Clin Endocrinol Metab 2005; **90:** 712.
282. Laghi F, Antonescu-Turcu A, Collins E et al: Hypogonadism in men with chronic obstructive pulmonary disease: prevalence and quality of life. Am J Respir Crit Care Med 2005; **171:** 728.
283. Phillips AC, Gale CR and Batty GD: Sex hormones and cause-specific mortality in the male veterans: the Vietnam experience study. QJM 2012; **105:** 241.
284. Schipf S, Haring R, Friedrich N et al: Low total testosterone is associated with increased risk of incident type 2 diabetes mellitus in men: results from the study of health in Pomerania. Aging Male 2011; **14:** 168.
285. Sonmez A, Haymana C, Bolu E et al: Metabolic syndrome and the effect of testosterone treatment in young men with congenital hypogonadotropic hypogonadism. Eur J Endocrinol 2011; **164:** 759.

286. Wang N, Han B, Li Q et al: Vitamin D is associated with testosterone and hypogonadism in Chinese men: results from a cross-sectional SPECT-china study. Reprod Biol Endocrinol 2015; **13:** 74
287. Zitzmann M, Brune M, Vieth V et al: Monitoring bone density in hypogonadal men by quantitative phalangeal ultrasound. Bone 2002; **31:** 422.
288. Qing XR, Wan CC, Shang XJ et al: Relative contributions of testosterone deficiency and metabolism syndrome at the risk of reduced quality of life: a cross-sectional study among Chinese mid-aged and elderly men. Andrologia. 2017; **49**: e12736.
289. Wehr E, Pilz S, Boehm BO et al: Low free testosterone is associated with heart failure mortality in older men referred for coronary angiography. Eur J Heart Fail 2011; **13:** 482.
290. Basaria S, Harman SM, Travison TG et al: Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial. JAMA 2015; **314:** 570.
291. Gianatti, EJ, Dupuis P, Hoermann R et al: Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. J Clin Endocrinol Metab 2014; **99:** 3821.
292. Morales A, Black A, Emerson L et al: Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. Aging Male 2009; **12:** 104.
293. Ng Tang Fui M, Hoermann R, Prendergast LA et al: Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial. Int J Obes 2017; **17**
294. Tan WS, Low WY, Ng CJ et al: Efficacy and safety of long-acting intramuscular testosterone undecanoate in aging men: a randomised controlled study. BJU Int 2013; **111:** 1130.
295. Chiang HS, Hwang TI, Hsui YS et al: Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. Int J Impot Res 2007; **19:** 411.
296. Corona G, Isidori AM, Buvat J et al: Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med 2014; **11:** 1577.
297. Saad F, Yassin A, Doros G et al: Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: observational data from two registry studies. Int J Obes 2016; **40:** 162.
298. 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 2007; **82:** 20.
299. Amory JK, Watts NB, Easley KA et al: Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004; **89:** 503.
300. Bachman E, Travison TG, Basaria S et al: Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/ hemoglobin set point. J Gerontol A Biol Sci Med Sci 2014; **69:** 725.
301. Steidle C, Schwartz S, Jacoby K et al: AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab 2003; **88:** 2673.
302. Sinclair M, Grossmann M, Hoermann R et al: Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: a randomised controlled trial. J Hepatol 2016; **65:** 906.
303. Ng Tang Fui M, Hoermann R, Prendergast LA et al: Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial. Int J Obes 2017; **41:** 420.
304. Basurto L, Zarate A, Gomez R et al: Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. Aging Male 2008; **11:** 140.
305. Brockenbrough AT, Dittrich MO, Page ST et al: Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. Am J Kidney Dis 2006; **47:** 251.
306. Dias JP, Shardell MD, Carlson OD et al: Testosterone vs. aromatase inhibitor in older men with low testosterone: effects on cardiometabolic parameters. Andrology 2017; **5:** 31.
307. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ et al: Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. JAMA Intern Med 2017; **177:** 471.
308. Wang YJ, Zhan JK, Huang W et al: Effects of low-dose testosterone undecanoate treatment on bone mineral density and bone turnover markers in elderly male osteoporosis with low serum testosterone. Int J Endocrinol 2013; **2013:** 570413.
309. Aversa A, Bruzziches R, Francomano D et al: Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study. Aging Male 2012; **15:** 96.
310. Bhasin S, Storer TW, Javanbakht M et al: Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 2000; **283:** 763.
311. 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) 2015; **37:** 9742.

312. Isidori AM, Giannetta E, Greco EA et al: Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol 2005; **63:** 280.
313. Guo C, Gu W, Liu M et al: Efficacy and safety of testosterone replacement therapy in men with hypogonadism: a meta-analysis study of placebo-controlled trials. Exp Ther Med 2016; **11:** 853.
314. Corona G, Giagulli VA, Maseroli E et al: Testosterone supplementation and body composition: results from a meta-analysis of observational studies. J Endocrinol Invest 2016; **9**: 967.
315. Vaughan C, Goldstein FC and Tenover JL: Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. J Androl 2007; **28:** 875.
316. Pope HG Jr, Cohane GH, Kanayama G et al: Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. Am J Psychiatry 2003; **160:** 105.
317. 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 2009; **29:** 216.
318. 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 2009; **70:** 1009.
319. Snyder PJ, Bhasin S, Cunningham GR et al: Effects of testosterone treatment in older men. N Engl J Med 2016; **374:** 611.
320. Resnick SM, Matsumoto AM, Stephens-Shields AJ et al: Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017; **317:** 717.
321. Heufelder AE, Saad F, Bunck MC et al: Fifty-two -week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. J Androl 2009; **30:** 726.
322. Kapoor D, Goodwin E, Channer KS et al: Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006; **154:** 899.
323. Grossmann M, Hoermann R, Wittert G et al: Effects of testosterone treatment on glucose metabolism and symptoms in men with type 2 diabetes and the metabolic syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. Clin Endocrinol 2015; **83:** 344.
324. 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 2014; **16:** 146.
325. Corona G, Giagulli VA, Maseroli E et al: Testosterone supplementation and body composition: results from a meta-analysis of observational studies. J Endocrinol Invest 2016; **39:** 967.
326. Corona G, Giagulli VA, Maseroli E et al: Therapy of endocrine disease: testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol 2016; **174:** R99.
327. 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 2007; **82:** 29.
328. Ho CC, Tong SF, Low WY et al: A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the aging male symptoms scale. BJU Int 2012; **110:** 260.
329. Tong SF, Ng CJ, Lee BC et al: Effect of long-acting testosterone undecanoate treatment on quality of life in men with testosterone deficiency syndrome: a double blind randomized controlled trial. Asian J Androl 2012; **14:** 604.
330. Grimes DA, Lopez LM, Gallo MF et al: Steroid hormones for contraception in men. Cochrane Database Syst Rev 2012; **3:** CD004316.
331. Liu PY, Swerdloff RS, Anawalt BD et al: Determinants of the rate and extent of spermatogenic suppression during hormonal male contraception: an integrated analysis. J Clin Endocrinol Metab 2008; **93:** 1774.
332. Samplaski MK, Loai Y, Wong K et al: Testosterone use in the male infertility population: prescribing patterns and effects on semen and hormonal parameters. Fertil Steril 2014; **101:** 64.
333. Kohn TP, Louis MR, Pickett SM et al: Age and duration of testosterone therapy predict time to return of sperm count after human chorionic gonadotropin therapy. Fertil Steril 2017; **107:** 351.
334. Wenker EP, Dupree JM, Langille GM et al: The use of hCG-based combination therapy for recovery of spermatogenesis after testosterone use. J Sex Med 2015; **12:** 1334.
335. Coviello AD, Matsumoto AM, Bremner WJ et al: Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. J Clin Endocrinol Metab 2005; **90:** 2595.
336. Hsieh TC, Pastuszak AW, Hwang K et al: Concomitant intramuscular human chorionic gonadotropin preserves spermatogenesis in men undergoing testosterone replacement therapy. J Urol 2013; **189:** 647.
337. Raman JD and Schlegel PN: Aromatase inhibitors for male infertility. J Urol 2002; **167:** 624.

338. Ramasamy R, Ricci JA, Palermo GD et al: Successful fertility treatment for Klinefelter's Syndrome. J Urol 2009; **182:** 1108.
339. Reifsnyder JE, Ramasamy R, Husseini J et al: Role of optimizing testosterone before microdissection testicular sperm extraction in men with nonobstructive azoospermia. J Urol 2012; **188:** 532.
340. Pavlovich CP, King P, Goldstein M et al: Evidence of a treatable endocrinopathy in infertile men. J Urol 2001; **165:** 837.
341. Huggins C and Hodges CV: Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin 1972; **22:** 232.
342. Morgentaler A: Testosterone therapy in men with prostate cancer: scientific and ethical considerations. J Urol 2013; **189:** S26.
343. Denmeade SR and Isaacs JT: Bipolar androgen therapy: the rationale for rapid cycling of supraphysiologic androgen/ablation in men with castration resistant prostate cancer. Prostate 2010; **70:** 1600.
344. Teply BA, Wang H, Luber B et al: Bipolar androgen therapy in men with metastatic castration-resistant prostate cancer after progression on enzalutamide: an open-label, phase 2, multicohort study. Lancet Oncol 2018; **19:** 76.
345. Kaufman JM and Graydon RJ: Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol 2004; **172:** 920.
346. Agarwal PK and Oefelein MG: Testosterone replacement therapy after primary treatment for prostate cancer. J Urol 2005; **173:** 533.
347. Khera M, Grober ED, Najari B et al: Testosterone replacement therapy following radical prostatectomy. J Sex Med 2009; **6:** 1165.
348. Pastuszak AW, Pearlman AM, Lai WS et al: Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. J Urol 2013; **2**: 639.
349. Dai B, Qu YY, Kong YY et al: Kinetics of testosterone recovery in clinically localized prostate cancer patients treated with radical prostatectomy and subsequent short-term adjuvant androgen deprivation therapy. Asian J Androl 2013; **15:** 466.
350. Yoon FH, Gardner SL, Danjoux C et al: Testosterone recovery after prolonged androgen suppression in patients with prostate cancer. J Urol 2008; **180:** 1438.
351. Sarosdy MF: Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. Cancer 2007; **109:** 536.
352. Balbontin FG, Moreno SA, Bley E et al: Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer. BJU Int 2014; **114:** 125.
353. Morales A, Black AM and Emerson LE: Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. BJU Int 2009; **103:** 62.
354. Pastuszak AW, Pearlman AM, Godoy G et al: Testosterone replacement therapy in the setting of prostate cancer treated with radiation. Int J Impot Res 2013; **25:** 24.
355. Pastuszak AW, Khanna A, Badhiwala N et al: Testosterone therapy after radiation therapy for low, intermediate and high risk prostate cancer. J Urol 2015; **194:** 1271.
356. Rhoden EL and Morgentaler A: Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. J Urol 2003; **170:** 2348.
357. Morgentaler A, Lipshultz LI, Bennett R et al: Testosterone therapy in men with untreated prostate cancer. J Urol 2011; **185:** 1256.
358. Freedman J, Glueck CJ, Prince M et al: Testosterone, thrombophilia, thrombosis. Transl Res 2015; **165:** 537.
359. Baillargeon J, Urban RJ, Morgentaler A et al: Risk of venous thromboembolism in men receiving testosterone therapy. Mayo Clin Proc 2015; **90:** 1038.
360. Sharma R, Oni OA, Chen G et al: Association between testosterone replacement therapy and the incidence of DVT and pulmonary embolism: a retrospective cohort study of the veterans administration database. Chest 2016; **150:** 563.
361. Li H, Benoit K, Wang W et al: Association between use of exogenous testosterone therapy and risk of venous thrombotic events among exogenous testosterone treated and untreated men with hypogonadism. J Urol 2016; **195:** 1065.
362. Martinez C, Suissa S, Rietbrock S et al: Testosterone treatment and risk of venous thromboembolism: population based case-control study. BMJ 2016; **355:** i5968.
363. 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 2013; **310:** 1829.
364. 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:** e85805.
365. Layton JB, Meier CR, Sharpless JL et al: Comparative safety of testosterone dosage forms. JAMA Intern Med 2015; **175:** 1187.
366. Xu L, Freeman G, Cowling BJ et al: Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 2013; **11:** 108.
367. Shores MM, Smith NL, Forsberg CW et al: Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012; **97:** 2050.

368. Cheetham TC, An J, Jacobsen SJ et al: Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency. JAMA Intern Med 2017; **177:** 491.
369. Nair KS, Rizza RA, O'Brien P et al: DHEA in elderly women and DHEA or testosterone in elderly men. N Engl J Med 2006; **355:** 1647.
370. Borst SE, Yarrow JF, Conover CF et al: Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. Am J Physiol Endocrinol Metab 2014; **306:** E433.
371. 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 1999; **84:** 2647.
372. Corona G, Maseroli E, Rastrelli G et al: Cardiovascular risk associated with testosterone -boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf 2014; **13:** 1327.
373. Baillargeon J, Urban RJ, Kuo YF et al: Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother 2014; **48:** 1138.
374. Moran LJ, Brinkworth GD, Martin S et al: Long-term effects of a randomised controlled trial comparing high protein or high carbohydrate weight loss diets on testosterone, SHBG, erectile and urinary function in overweight and obese men. PLoS One 2016; **11:** e0161297.
375. Boonchaya-Anant P, Laichuthai N, Suwannasrisuk P et al: Changes in testosterone levels and sex hormone-binding globulin levels in extremely obese men after bariatric surgery. Int J Endocrinol 2016; **2016:** 1416503.
376. Armamento-Villareal R, Aguirre LE, Qualls C et al: Effect of lifestyle intervention on the hormonal profile of frail, obese older men. J Nutr Health Aging 2016; **20:** 334.
377. Shiels MS, Rohrmann S, Menke A et al: Association of cigarette smoking, alcohol consumption, and physical activity with sex steroid hormone levels in US men. Cancer Causes Control 2009; **20:** 877.
378. Kumagai H, Zempo-Miyaki A, Yoshikawa T et al: Increased physical activity has a greater effect than reduced energy intake on lifestyle modification-induced increases in testosterone. J Clin Biochem Nutr 2016; **58:** 84.
379. Oshakbayev K, Dukenbayeva B, Togizbayeva G et al: Weight loss technology for people with treated type 2 diabetes: a randomized controlled trial. Nutr Metab 2017; **14:** 11.
380. Khera M, Broderick GA, Carson CC, 3rd et al: Adult-onset hypogonadism. Mayo Clin Proc 2016; **91:** 908.
381. Yeap BB, Alfonso H, Chubb SA et al: Reference ranges and determinants of testosterone, dihydrotestosterone, and estradiol levels measured using liquid chromatography-tandem mass spectrometry in a population-based cohort of older men. J Clin Endocrinol Metab 2012; **97:** 4030.
382. Lakshman KM, Kaplan B, Travison TG et al: The effects of injected testosterone dose and age on the conversion of testosterone to estradiol and dihydrotestosterone in young and older men. J Clin Endocrinol Metab 2010; **95:** 3955.
383. Corona G, Rastrelli G, Forti G et al: Update in testosterone therapy for men. J Sex Med 2011; **8:** 639.
384. Aaronson AJ, Morrissey RP, Nguyen CT et al: Update on the safety of testosterone therapy in cardiac disease. Expert Opin Drug Saf 2011; **10:** 697.
385. World Health Organization: Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. Fertil Steril 1996; **65:** 821.
386. Kloner RA, Carson III C, Dobs A et al: Testosterone and cardiovascular disease. J Am Coll Cardiol 2016; **67:** 545.
387. Murray-Lyon IM, Westaby D and Paradinas F: Hepatic complications of androgen therapy. Gastroenterology 1977; **73:** 1461.
388. de Ronde W: Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies. Hum Reprod 2009; **24:** 425.
389. Merhi ZO and Santoro N: Postmenopausal virilization after spousal use of topical androgens. Fertil Steril 2007; **87:** 976 e13.
390. Cavender RK and Fairall M: Precocious puberty secondary to topical testosterone transfer: a case report. J Sex Med 2011; **8:** 622.
391. Nelson D, Ho J, Pacaud D et al: Virilization in two pre-pubertal children exposed to topical androgen. J Pediatr Endocrinol Metab 2013; **26:** 981.
392. FDA: Medication guide
393. Satonin DK, Ni X, Mitchell MI et al: Amount of testosterone on laundered clothing after use of testosterone topical 2% solution by healthy male volunteers. J Sex Med 2016; **13:** 187.
394. Coviello AD, Bremner WJ, Matsumoto AM et al: Intratesticular testosterone concentrations comparable with serum levels are not sufficient to maintain normal sperm production in men receiving a hormonal contraceptive regimen. J Androl 2004; **25:** 931.
395. Jarow JP and Zirkin BR: The androgen microenvironment of the human testis and hormonal control of spermatogenesis. Ann N Y Acad Sci 2005; **1061:** 208.
396. Adamopoulos DA, Nicopoulou S, Kapolla N et al: The combination of testosterone undecanoate with tamoxifen citrate enhances the effects of each agent given independently on seminal parameters in men with idiopathic oligozoospermia. Fertil Steril 1997; **67:** 756.
397. Bistritzer T, Lunenfeld B, Passwell JH et al: Hormonal therapy and pubertal development in boys with selective hypogonadotropic hypogonadism. Fertil Steril 1989; **52:** 302.
398. Vicari E, Mongioi A, Calogero AE et al: Therapy with human chorionic gonadotrophin alone induces spermatogenesis in men with isolated hypogonadotrophic hypogonadism--long-term follow-up. Int J Androl 1992; **15**: 320.

399. Liu PY, Wishart SM and Handelsman DJ: A double-blind, placebo-controlled, randomized clinical trial of recombinant human chorionic gonadotropin on muscle strength and physical function and activity in older men with partial age-related androgen deficiency. J Clin Endocrinol Metab 2002; **87:** 3125.
400. Taylor F and Levine L: Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. J Sex Med 2010; **7:** 269.
401. Kim ED, McCullough A and Kaminetsky J: Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement. BJU Int 2016; **117:** 677.
402. Wiehle RD, Fontenot GK, Wike J et al: Enclomiphene citrate stimulates testosterone production while preventing oligospermia: a randomized phase II clinical trial comparing topical testosterone. Fertil Steril 2014; **102:** 720.
403. Helo S, Ellen J, Mechlin C et al: A randomized prospective double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone in hypogonadal infertile men. J Sex Med 2015; **12:** 1761.
404. Burnett-Bowie SA, McKay EA, Lee H et al: Effects of aromatase inhibition on bone mineral density and bone turnover in older men with low testosterone levels. J Clin Endocrinol Metab 2009; **94:** 4785.
405. Administration USFDA: Compounding Quality Act, Title I of the Drug Quality and Security Act, 2013.
406. Administration USFDA: Consumer update: The special risks of pharmacy compounding, 2007.
407. Administration USFDA: Report: Limited FDA survey of compounded drug products, 2003.
408. Pharmacy MSBo: Compounded drug testing report fiscal year 2006.
409. Administration USFDA: 2006 limited FDA survey of compounded drug products, 2006.
410. Grober ED, Garbens A, Bozovic A et al: Accuracy of testosterone concentrations in compounded testosterone products. J Sex Med 2015; **12:** 1381.
411. Isidori AM, Giannetta E, Gianfrilli D et al: Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol 2005; **63:** 381.
412. Miller J, Britto M, Fitzpatrick S et al: Pharmacokinetics and relative bioavailability of absorbed testosterone after administration of a 1.62% testosterone gel to different application sites in men with hypogonadism. Endocr Pract 2011; **17:** 574.
413. Roskos KV, Maibach HI and Guy RH: The effect of aging on percutaneous absorption in man. J Pharmacokinet Biopharm 1989; **17:** 617.
414. Feldmann RJ and Maibach HI: Percutaneous penetration of steroids in man. J Invest Dermatol 1969; **52:** 89.
415. Bucks DA, Maibach HI and Guy RH: Percutaneous absorption of steroids: effect of repeated application. J Pharm Sci 1985; **74:** 1337.
416. Bucks DA, McMaster JR, Maibach HI et al: Bioavailability of topically administered steroids: a "mass balance" technique. J Invest Dermatol 1988; **91:** 29.
417. Mazer N, Bell D, Wu J et al: Comparison of the steady-state pharmacokinetics, metabolism, and variability of a transdermal testosterone patch versus a transdermal testosterone gel in hypogonadal men. J Sex Med 2005; **2:** 213.
418. Wang C, Berman N, Longstreth JA et al: Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a general clinical research center study. J Clin Endocrinol Metab 2000; **85:** 964.
419. Morgentaler A, McGettigan J, Xiang Q et al: Pharmacokinetics and drying time of testosterone 2% gel in men with hypogonadism: a multicenter, open-label, single-arm trial. Int J Impot Res 2015; **27:** 41.
420. Grober ED, Khera M, Soni SD et al: Efficacy of changing testosterone gel preparations (Androgel or Testim) among suboptimally responsive hypogonadal men. Int J Impot Res 2008; **20:** 213.
421. Wang C, Ilani N, Arver S et al: Efficacy and safety of the 2% formulation of testosterone topical solution applied to the axillae in androgen-deficient men. Clin Endocrinol 2011; **75:** 836.
422. Dobs AS, McGettigan J, Norwood P et al: A novel testosterone 2% gel for the treatment of hypogonadal males. J Androl 2012; **33:** 601.
423. Kaufman JM, Miller MG, Fitzpatrick S et al: One-year efficacy and safety study of a 1.62% testosterone gel in hypogonadal men: results of a 182-day open-label extension of a 6-month double-blind study. J Sex Med 2012; **9:** 1149.
424. Meikle AW, Mazer NA, Moellmer JF et al: Enhanced transdermal delivery of testosterone across nonscrotal skin produces physiological concentrations of testosterone and its metabolites in hypogonadal men. J Clin Endocrinol Metab 1992; **74:** 623.
425. Sandberg AA and Slaunwhite WR, Jr: Metabolism of 4-c14-testosterone in human subjects. I. Distribution in bile, blood, feces and urine. J Clin Invest 1956; **35:** 1331.
426. Hellman L and Rosenfeld RS: Metabolism of testosterone-1,2-3h in man. Distribution of the major 17-ketosteroid metabolites in plasma: relation to thyroid states. J Clin Endocrinol Metab 1974; **38:** 424.
427. Arver S, Dobs AS, Meikle AW et al: Improvement of sexual function in testosterone deficient men treated for 1 year with a permeation enhanced testosterone transdermal system. J Urol 1996; **155:** 1604.
428. Mazer N, Bell D, Wu J et al: Comparison of the steady-state pharmacokinetics, metabolism, and variability of a transdermal testosterone patch versus a transdermal testosterone gel in hypogonadal men. J Sex Med 2005; **2:** 213.

429. Raynaud JP, Legros JJ, Rollet J et al: Efficacy and safety of a new testosterone-in-adhesive matrix patch applied every 2 days for 1 year to hypogonadal men. J Steroid Biochem Mol Biol 2008; **109:** 168.
430. Yu Z, Gupta SK, Hwang SS et al: Testosterone pharmacokinetics after application of an investigational transdermal system in hypogonadal men. J Clin Pharmacol 1997; **37:** 1139.
431. FDA: Androderm drug label information.
432. Dinsmore WW and Wyllie MG: The long-term efficacy and safety of a testosterone mucoadhesive buccal tablet in testosterone-deficient men. BJU Int 2012; **110:** 162.
433. Ross RJ, Jabbar A, Jones TH et al: Pharmacokinetics and tolerability of a bioadhesive buccal testosterone tablet in hypogonadal men. Eur J Endocrinol 2004; **150:** 57.
434. Wang C, Swerdloff R, Kipnes M et al: New testosterone buccal system (Striant) delivers physiological testosterone levels: pharmacokinetics study in hypogonadal men. J Clin Endocrinol Metab 2004; **89:** 3821.
435. Dobs AS, Matsumoto AM, Wang C et al: Short-term pharmacokinetic comparison of a novel testosterone buccal system and a testosterone gel in testosterone deficient men. Curr Med Res Opin 2004; **20:** 729.
436. Rogol AD, Tkachenko N and Bryson N: Natesto a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men. Andrology 2016; **4:** 46.
437. Kaminetsky J, Jaffe JS and Swerdloff RS: Pharmacokinetic profile of subcutaneous testosterone enanthate delivered via a novel, prefilled single-use autoinjector: a phase II study. Sex Med 2015; **3:** 269.
438. Morgentaler A, Dobs AS, Kaufman JM et al: Long acting testosterone undecanoate therapy in men with hypogonadism: results of a pharmacokinetic clinical study. J Urol 2008; **180:** 2307.
439. Wang C, Harnett M, Dobs AS et al: Pharmacokinetics and safety of long-acting testosterone undecanoate injections in hypogonadal men: an 84-week phase III clinical trial. J Androl 2010; **31:** 457.
440. Schubert M, Minnemann T, Hubler D et al: Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. J Clin Endocrinol Metab 2004; **89:** 5429.
441. Fennell C, Sartorius G, Ly LP et al: Randomized cross-over clinical trial of injectable vs. implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. Clin Endocrinol (Oxf) 2010; **73:** 102.
442. Jockenhovel F, Minnemann T, Schubert M et al: Comparison of long-acting testosterone undecanoate formulation versus testosterone enanthate on sexual function and mood in hypogonadal men. Eur J Endocrinol 2009; **160:** 815.
443. Middleton T, Turner L, Fennell C et al: Complications of injectable testosterone undecanoate in routine clinical practice. Eur J Endocrinol 2015; **172:** 511.
444. Ong GS, Somerville CP, Jones TW et al: Anaphylaxis triggered by benzyl benzoate in a preparation of depot testosterone undecanoate. Case Rep Med 2012; **2012:** 384054.
445. Mackey MA, Conway AJ and Handelsman DJ: Tolerability of intramuscular injections of testosterone ester in oil vehicle. Hum Reprod 1995; **10:** 862.
446. Kaminetsky JC, Moclair B, Hemani M et al: A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for the treatment of male hypogonadism. J Sex Med 2011; **8:** 1186.
447. McCullough AR, Khera M, Goldstein I et al: A multi-institutional observational study of testosterone levels after testosterone pellet (Testopel®) insertion. J Sex Med 2012; **9:** 594.
448. Pastuszak AW, Mittakanti H, Liu JS et al: Pharmacokinetic evaluation and dosing of subcutaneous testosterone pellets. J Androl 2012; **33:** 927.
449. Conners W, Flinn K and Morgentaler A: Outcomes with the "V" implantation technique vs. standard technique for testosterone pellet therapy. J Sex Med 2011; **8:** 3465.

Appendix A: Testosterone Literature Methodology Review

As with all AUA guideline documents, recommendations are based where possible on data extracted from the evidence report, which was generated by methodologists from Mayo Clinic. The development of the evidence report was particularly challenging in the testosterone space due to the heterogeneity in the literature resulting in difficulties comparing data across studies. As the reader delves into this guideline, and more importantly reads the literature, it should be borne in mind that studies have varied significantly in areas, such as patient age, failure to control for concomitant comorbidities associated with low testosterone levels, use of total versus free testosterone, and the testosterone cut-offs used to define low levels. This is further complicated by laboratory methodology issues, such as time of day for the blood draws analyzed, number of levels checked, and assays used.

Thousands of articles on testosterone deficiency and testosterone therapy have been published over the past several decades. To accurately interpret the published testosterone literature, it is important to critically evaluate various aspects of study design, including the population evaluated, study inclusion/exclusion criteria, duration of follow-up, primary endpoints, adverse event reporting, statistical reporting, and clinical relevance of findings.

Study Design. Study design is one of the most important aspects of any investigation because it defines the reliability of outcomes and the extent to which they may be extrapolated to other groups. Meta-analyses of RCTs and cohort studies provide the highest levels of evidence and reliability, followed by individual RCTs, prospective cohorts, retrospective cohorts, and observational studies.

When reviewing results from meta-analyses, it is important to recognize that the overall reliability is dependent on the quality of the weakest study included in the analysis. For example, outcomes of meta-analyses using RCTs alone are generally more robust than those that also include cohort studies. Meta-analyses that are limited to only including RCTs may be restricted to a small number of studies and relevant studies may be excluded that could provide sufficient power to make alternative conclusions. This is particularly relevant for the current guideline as it provides context to situations where the pooled odds ratios and mean differences may contradict or fail to support published meta-analyses.

Study Population. Individual study factors, such as the heterogeneity and demographics of the study population, the comorbidities of the study population and how they are controlled in the analysis, and confidence intervals also impact overall study quality. Study populations in individual trials included in any meta-analysis have a significant impact on the reliability of outcomes. Differences in age, geography, date of initial testing (testosterone immunoassay testing was more commonly used before 2005), comorbid conditions, and baseline and therapeutic testosterone levels across studies introduce heterogeneity in the pooled population. Readers should recognize that guideline statements have been generalized in an attempt to provide a clinically useful document with the understanding that certain populations and clinical scenarios will fall outside of the initial criteria upon which the studies were based. Actual patient scenarios will require individual adaptation with variability in expected outcomes. It also highlights that treating clinicians should have specific endpoints for treatment in mind, with regular monitoring of these outcomes to assure that ongoing therapy is warranted and effective.

Criteria for Testosterone Deficiency and Study Duration. The current guideline only included studies in the meta-analysis that used morning total testosterone <350 ng/dL as an inclusion criterion. Despite this standardization, there remains significant variability among studies. The mean testosterone in the patient population across all the studies was 249 ng/dL but this does not take into account that there were some patients who entered with lower baseline testosterone levels and may have been more likely to demonstrate greater improvements in symptoms compared to those who entered with testosterone levels closer to eugonadal levels, while still meeting the inclusion criteria.[411]

Study duration is also a significant factor. Testosterone therapy likely yields rapid improvements in some symptoms, while others require a longer time course to show improvement.[297] RCTs are commonly of short duration (<1 year), which leads to study results that might have a bias towards lack of benefit in certain symptoms/signs while failing to identify therapeutic benefit, which can require additional time to manifest.

Primary Endpoints, Adverse Events, and Statistical Measures. One important aspect of study design is the specific endpoints and objective

measures used to identify outcomes. Studies are often specifically powered and designed to address a key efficacy endpoint, such as a particular symptom improvement, and not to address secondary symptom improvement or adverse events. Although one objective of meta-analyses is to increase study power to identify significant results, this often results in an amalgamation of studies that may have different primary and secondary endpoints, thereby reducing the reliability of the outcomes.

Beyond statistical significance, clinical relevance is another key factor. In analyzing the literature, it is imperative to determine whether or not statistically significant results are clinically meaningful. For example, a particular study might show that testosterone therapy is correlated with a statistically significant improvement in the IIEF scores in a given population; however, the clinician may not feel that this has any clinical meaning for the patient in terms of his QoL or sexual function.

Appendix B: Therapeutic Agents for Treatment of Testosterone Deficiency

Transdermal Agents – Gels and Solutions

Pharmacokinetics and Pharmacodynamics. The unique pharmacokinetic profiles of transdermal testosterone preparations relate to several factors, including the delivery system (alcohols or other penetration enhancers), concentration, surface area applied, and location of application.[228, 412] Transdermal drug solubility has been variably estimated, with most studies reporting systemic absorption rates ranging from 13-20%.[413-415] Repeated application to the same site (after washing) does not reduce uptake, and the use of an occlusive dressing has been shown to increase absorption by approximately 2.5 fold.[415, 416]

Topical gels and liquids generally demonstrate less variability in absorption uptake when compared to other therapies.[417] After application, steady state levels are achieved within 24-72 hours, with testosterone levels returning to baseline within 4 days of discontinuation.[418, 419]

Dosing Strategies. Liquids and gels should be applied to clean, dry skin, and the treatment site should not be washed until the time of next application to optimize delivery. If insufficient testosterone levels are achieved with one topical agent, including with dose adjustments, substitution with another topical agent is a viable treatment strategy.[420]

Efficacy. Topical liquid and gel formulations are able to achieve testosterone levels in the normal range in 74-87% of men and are relatively similar among the various preparations.[421-423] Given the variable absorption profiles among patients, dose adjustments may be required to achieve appropriate therapeutic delivery. There is no consistent data at this time that demonstrate that one agent achieves higher serum levels than others.

Adverse Effects. Adverse effects specific to topical preparations include application site reactions (3-16% erythema or rash), and risk of transference. Patients should be particularly cautioned against contact with women and children after application of the gel to limit the possibility of inadvertent transmission. Transference may be mitigated by washing hands, covering the application site with clothing, and washing the region prior to anticipated direct contact with others.

Transdermal Agents – Patches

Pharmacokinetics and Pharmacodynamics. Testosterone patches consist of a mixture of testosterone, penetration agents, and a gelatinous matrix separated from the skin by a microporous membrane. Initial studies of testosterone patches demonstrated increases in total testosterone from a baseline 167 ng/dL to a peak of 1,154 ng/dL at 5.7 hours, with a decrease to 490 ng/dL over the next 12 hours.[424] Following removal, the observed testosterone half-life was 116 minutes.[425, 426] A multicenter, open label study confirmed mirroring of the circadian rhythm when the patch is applied in the evening with a morning peak of 740 ng/dL and a night-time trough of 213 ng/dL.[427]

When applied to the abdomen, the patch exhibits slightly lower minimum testosterone values (over 24 hours) compared to other methods of delivery and some gels, with bioequivalence noted for average and maximum testosterone values.[428] Two RCTs compared patches to IM testosterone administration and demonstrated improved maintenance of testosterone values within normal physiologic levels and closer representation of the natural circadian rhythm.[181, 429] However, it is noteworthy that pharmacokinetic comparisons of any one modality to another are dependent on the dosing and schedule of administration. In the case of topical patches, the testosterone levels achieved directly relate to the amount of surface area exposed to drug.[430]

Dosing Strategies. Patches are currently available in 2 and 4 mg formulations, with a 4mg starting dose recommended and titration to 6 mg permitted.

Efficacy. Patches are able to achieve testosterone levels within normal physiologic ranges (2 patches every 24-48 hours) in 77-100% of individuals with >85% achieving values >300 ng/dL.[181, 429]

Adverse Effects. The most common adverse effect with patches is application site reactions, which have been historically reported in up to 60% of patients.[181] Other adverse effects include pruritus, application site vesicles, and back pain.[431] Compared to topical gels and solutions, the rate of transference is likely minimal.

Buccal Agents

One of the oral alternatives for testosterone therapy is the 30 mg sustained-release muco-adhesive buccal pellet applied to the upper gums above the incisor teeth twice daily.[432]

Pharmacokinetics. Absorption through the oral mucosa avoids liver deactivation that is experienced by other formulations. Testosterone is released from the tablet in a manner similar to the normal daily rhythm of endogenous testosterone, with serum levels rising rapidly after buccal absorption and peak levels reached by the second 12-hour daily dose. It restores the circulating testosterone level to the physiological range. Removal of the system results in a rapid drop in testosterone levels.[433]

Dosing. The progressive hydration tablet with a matrix containing 30 mg of testosterone is placed in position on the gum above the right or left canine and is held in position for approximately 30 seconds. It adheres to the buccal surface as it slowly hydrates, becoming soft and gelatinous. It is administered twice daily, 12 hours apart.[432]

***Efficacy*.** In a 12-week study in 82 men, 72.6% of patients achieved a total testosterone concentration within the physiological range at steady state.[434] Men treated with the agent were compared to a group of patients given 5 mg of a testosterone gel formulation, and no differences in mean testosterone serum levels were observed between the two groups.[435] The study showed 92% of buccal versus 83% of gel patients achieved testosterone levels in the physiologic range.

Adverse Effects. In clinical trials up to two years long, the most common side effects were gum-related disorders: gum or mouth irritation (9.2%), gum tenderness (3.1%), gum pain (3.1%), and gum edema (2%).[432] Another limitation of this therapy includes displacement of the buccal device during exertion activities.

Intranasal Gel

An intranasal testosterone gel applied topically into the nose was approved by the FDA in 2014.

Pharmacokinetics. Following application, testosterone is absorbed through the nasal mucosa to achieve maximum concentrations in about 40 minutes, with a serum half-life of 10-100 minutes.

Dosing. The product is provided in a metered pump that supplies 5.5 mg of testosterone per actuation. The recommended dose is two pumps (one to each nostril) applied three times daily.

Efficacy. In a 90-day open label trial of 306 testosterone deficient men using two actuations (11mg) of the drug applied three times daily, results were reported for 73 men at day 90. Sixty-nine of 73 men (90%) had an average testosterone concentration within the specified normal range for the study (300-1,050 ng/dL). The mean testosterone concentration was 421 ng/dL.[436]

Adverse Effects. In the clinical trial leading to FDA approval, side effects related to nasal delivery included nasopharyngitis, rhinorrhea, and epistaxis occurring in 7-10% of men.[436]

Injectable Agents (Short-Acting)

Injectable testosterone is available in several forms, including short acting and long-acting preparations. Although IM injections are the traditional route for injectable agents, the SQ route has also been described with short-acting agents.[437]

Pharmacokinetics and Pharmacodynamics. The pharmacokinetics of short-acting testosterone therapy depends on the dose, interval, and method of delivery (SQ versus IM). In a study directly comparing the pharmacokinetics of 2 doses of SQ testosterone enanthate injected weekly (50 or 100 mg) and 1 concentration of IM testosterone enanthate injected once (200 mg), the IM testosterone achieved the highest peak testosterone (mean 2,261 ng/dL) followed by SQ 100 mg (1,345 ng/dL) and SQ 50 mg (622 ng/dL).[437] The time-to-peak level was slightly faster with IM testosterone (33 hours) compared to SQ 100 mg (36 hours) and SQ 50 mg (45 hours). The half-life for IM testosterone was also shorter at 173 hours versus 240 hours for SQ testosterone. Mean testosterone values over a 7-day time period were 1,659, 896, and 422 ng/dL for IM testosterone SQ 100, and SQ 50, respectively.

Dosing Strategies. The optimal dosing strategy has not been defined for short-acting IM testosterone preparations. In general, smaller dosages at more frequent intervals are preferred over high, less frequent administrations to limit the duration of time spent outside (above or below) the normal reference range. As an example, a starting dose of 100 mg weekly is preferred to 200 mg every 2 weeks or 300-400 mg monthly. The best time to obtain monitoring blood tests for IM testosterone has not been definitively established. Given the half-life of approximately seven days, it is reasonable to obtain testosterone levels four

weeks after starting therapy. Historically, testosterone levels have been measured mid-cycle (day three to four); however, such a measurement protocol misses the ability to define peak and trough levels. While mid-cycle testing is convenient for patients, there may be value in assessing peak level (18-36 hours after injection) as the adverse events (e.g., polycythemia, hyperestrogenism) are likely at least partially related to the peak level. Likewise, there might be value in defining the trough level (measured prior to injection on day one) to ensure patients remains therapeutic throughout the entire cycle. Furthermore, the concept of testosterone 'crash' is well recognized by clinicians, with large differences between peak and trough levels potentially leading patients to become symptomatic towards the end of the cycle despite having therapeutic trough testosterone levels.

Efficacy. In contrast to topical agents where a percentage of men have difficulty achieving therapeutic levels within standard dosing ranges, injectable testosterone preparations are able to achieve therapeutic levels in almost any clinical scenario. However, compared to other agents, short-acting injections can result in longer times in the supra-therapeutic and sub-therapeutic ranges, which may impact overall efficacy and rates of adverse events. This may be overcome by altering injection dose and frequency.

Adverse Effects. Adverse effects that are more common with short acting injectable agents include local site reactions (7-33%) and abnormally elevated Hb/Hct (19-44%; mean 1.6 mg/dL in the current meta-analysis of RCTs).[181, 182, 191, 194, 195, 201, 203-214, 216-218, 220, 299-301, 310]

Injectable Agents (Long-Acting)

Testosterone undecanoate is the only currently available long-acting injection therapy available as a 750 mg (3 mL) preparation and must be administered in the office under supervision.

Pharmacokinetics and Pharmacodynamics. The pharmacokinetic profile of long-acting IM testosterone therapy has been detailed in several studies.[438-440] Morgentaler et al. reported outcomes of the currently available preparation (750 mg in 3 mL oil) administered at weeks 0, 4, and every 10 weeks thereafter.[438] Peak concentrations were achieved at a mean 7 days after injection (range 4-42 days). Results after the third injection demonstrated median peak and trough T levels of 813 ng/dL and 317 ng/dL, respectively, with overall median values of 476 ng/dL during the 10-week period. These data are notable as they demonstrate far less variability between peak and trough levels compared to shorter-acting preparations.[441, 442]

No RCTs have compared the current formulation of IM testosterone undecanoate available in the United States to other therapies. One study reported comparative pharmacokinetics between IM testosterone enanthate (250 mg every 3 weeks) and IM testosterone undenaconate (1,000 mg every 9 weeks, a dosage that is only available outside the United States).[440] Results demonstrated that IM testosterone enanthate achieved trough levels of 239 ng/dL compared to 470 ng/dL with IM testosterone undecanoate at the end of the 10-week cycle.

Dosing Strategies. The manufacturer-recommended dosing of IM testosterone undecanoate is 750 mg administered at weeks 0, 4, and every 10 weeks thereafter. The dosing at 0 and 4 weeks represents the loading period followed by regular dosing is every 10 weeks. Further individualization may be considered based on trough testosterone levels at the end of a 10-week injection cycle. For trough total testosterone values <300 ng/dL, the interval may be decreased by 1 week (9 weeks) until values >300 ng/dL are achieved at the end of an injection period. For trough total testosterone values >600 ng/dL, the interval may be prolonged by 1 week (11 weeks) until total testosterone levels <600 ng/dL are noted at the end of an injection period.

Efficacy. Administration of 750 mg of IM testosterone undecanoate at weeks 0, 4, and every 10 weeks thereafter maintained total testosterone levels between 300-1,000 ng/dL for 94% of men.[438] No men experienced maximal values <300 ng/dL, and only 5% had mean concentrations <300 ng/dL during the 10 weeks. Mean peak levels were 890 ng/dL, with 92% of men remaining below 1,500 ng/dL.

Adverse Effects. The most common adverse effects associated with IM testosterone undecanoate 750 mg administered every 10 weeks include injection site pain, acne, and fatigue (all ≤5%).[438, 439] Coughing related to the oil-based preparation has been reported secondary to pulmonary microemboli (POME) and reactions to the benzyl benzoate component.[438, 443, 444] Due to these risks, the FDA has issued a boxed warning and requires that providers be risk evaluation and mitigation strategy certified to administer the therapy. Patients should be monitored for 30 minutes in a healthcare setting after injection to monitor for POME or anaphylactic-type symptoms.

Although the absolute risks of POME and anaphylaxis require ongoing study, data from 342 patients undergoing 3,022 injections (1,000 mg in 4 mL) over a period of 3.5 years demonstrated that POME occurred after 1.9% of injections (12% of patients experienced at least one POME), with coughing episodes lasting 1-10 minutes in duration.[443] All episodes were managed conservatively in the clinic, with no supplemental oxygen required. No episodes of anaphylaxis occurred. Findings are similar to the previously cited pharmacokinetic study (750 mg in 3 mL) in which one patient in 130 (<1%) experienced coughing lasting 10 minutes.[438] It is notable that similar findings have also been observed with other oil-based testosterone preparations that are currently most often self-administered at home (typically with lower volumes of injection).[445]

Long-acting IM testosterone injection may also result in higher rates of polycythemia when compared to topical therapies, which is consistent with other short-acting IM testosterone therapies. In the current meta-analysis of RCTs, long-acting IM testosterone resulted in a mean increase in Hb levels of 1.4 mg/dL compared to 1.6 mg/dL with short-acting IM testosterone, 0.9 mg/dL with transdermal preparations, and 0.7 mg/dL with topical patches.[182, 194, 195, 201, 203-214, 216-218, 299-301, 310]

Subcutaneous pellets

SQ testosterone pellets were initially developed and FDA approved in 1972 and were reformulated in the USA in 2008.

Pharmacokinetics and Pharmacodynamics. The unique pharmacokinetic profile of testosterone pellets is due to their crystalline structure, which dissolves slowly in SQ spaces. Individual pellets consist of 75 mg of testosterone and may be combined to deliver variable doses of testosterone therapy.

Initial pharmacokinetic data were provided by Kaminetsky et al.[446] who selected the number of pellets inserted based on testosterone levels and BMI: six pellets for baseline total testosterone level <315 ng/dL and BMI <18.5, eight pellets for BMI 18.5-24.9, 10 pellets for BMI 25-30, and 12 pellets for BMI >30. Men with total testosterone level <225 ng/dL received 10 pellets for BMI <25 and 12 pellets for BMI ≥25. Of the 30 patients enrolled, none met criteria for 6 pellets, and a median of 10 pellets were implanted. Peak total testosterone levels were achieved 1 week after implantation (845 ng/dL) and were conserved until at least week 4 (838 ng/dL), with LH suppressed by week 4. The percentage of men with total testosterone values >315 ng/dL declined from 100% at 4 weeks to 86%, 75%, and 14% by 12, 20, and 24 weeks, respectively.

Mean peak total testosterone levels are dose-dependent, with a mean of 746, 866, and 913 ng/dL noted with 8, 10, and 12 pellets administered (not BMI adjusted).[446] The duration of effect is similar, however, and is relatively independent of dosing. These findings are supported by a multi-institutional study that reported that with variable dosing and clinical protocols, most men required re-implantation after four months, with all men returning to sub therapeutic levels by six months.[447]

Based on these initial data, Kaminetsky and colleagues performed a follow-up re-dosing study with 2 fewer pellets administered if peak testosterone levels were >1,000 ng/dL and 2 additional pellets given for testosterone levels <500 ng/dL. With new dosing, mean testosterone levels declined to 275 ng/dL by week 16, with only 32% having levels >315 ng/dL at that time point.

Dosing Strategies. Currently, the FDA recommends placement of two to six pellets every three to six months, which has been the recommendation since the approval of pellets in 1972. These recommendations, however, are not based on current testosterone pellet formulations and contrast with pharmacokinetic data available. Definitive dosing protocols have not been described.[446,447, 448]

Testosterone levels should be obtained at one to four weeks after insertion.[446] These 'peak' levels facilitate adjustment of future pellet number: peak level >1,000 ng/dL, reduce by 2 pellets at next insertion; <500 ng/dL, increase by 2 pellets. Subsequent testosterone levels should be assessed around three months after implantation and re-checked every two to four weeks thereafter if persistently therapeutic levels are found. Although no consensus exists, it is reasonable to perform re-implantation when total testosterone levels are <400 ng/dL. Due to variations within

the same individual, it is recommended to obtain end-of-cycle testosterone measurements prior to implantation to ensure that levels are sub-therapeutic.[446]

Efficacy. Data from a large, multi-institutional series using varied protocols (inserted pellet number ranged from 6 to >10 pellets), demonstrated therapeutic levels in 100% of men at 4 weeks and maintained levels >300 ng/dL at 4 months. It is notable that the majority of providers elected to utilize ≥10 pellets (63%), with 27% of cases including 8-9 pellets, and only 10% of

cases using 6-7 pellets. No providers utilized five or fewer pellets, which contrasts with the FDA recommended dosing.[221]

Adverse Effects. Mild level adverse events specific to SQ pellet insertion includes polycythemia (48-50%), ecchymosis (32-36%), tenderness (20-32%), pain (28-29%), and swelling (16-18%), all of which resolve by 4 months post-insertion.[446] Moderate level adverse events were less common (e.g., pain 3%, erythema 3%, ecchymoses 7%) and improved within 1 week. Pellet extrusions are also possible and may be reduced by the use of a V technique whereby 2 channels are created for pellet insertion, thus keeping the most superficial pellet >1cm away from the skin.[449] Results of the modified technique resulted in reduced extrusion (7.5% down to 0.8%), infection (5% down to 1.2%), pain (5% down to 1.2%), but an increase in hematoma occurrence (0% up to 1.2%). Of note, hematoma rates were not impacted by the use of anti-coagulants (1.7%), although many practitioners are cautious about pellet use in this population. In one retrospective comparative series, the rate of polycthemia (Hct >52%) with pellets was also higher (13%) than topical gels (5%) but lower than IM testosterone agents (19%) ($p=0.03$).[220]

Appendix C: Adjunctive Testing

Test	Indication	Clinician Response
Serum Luteinizing Hormone	LH is an appropriate first-line test in conjunction with a repeat testosterone level to determine the etiology of the testosterone deficiency. A low or low/normal LH level points to a secondary, or central hypothalamic-pituitary defect, (hypogonadotropic hypogonadism); while an elevated LH indicates a primary testicular defect (hypergonadotropic hypogonadism). The location of the defect may be an important factor in deciding upon further evaluation of such a patient.	Men with low testosterone and low to low/normal LH, should have a prolactin level measured. Men with low to low/normal LH levels are candidates for the use of SERMs in the management of their testosterone deficiency. Men with very high LH levels (without an obvious cause, such as chemotherapy) are at increased risk for KS, which can be diagnosed using a karyotype.
Serum Follicle-stimulating Hormone	Men who are interested in preserving their fertility warrant a baseline FSH prior to the commencement of SERMs, hCG, or AI. The presence of an elevated FSH level suggests abnormal spermatogenesis.	Men with elevated FSH levels should have a semen analysis. Men with very high FSH levels (without an obvious cause, such as chemotherapy) are at increased risk for KS, which can be diagnosed using a karytotype.
Serum HbA1C	While data supporting the link between testosterone deficiency and diabetes is mixed, in the middle-aged or older testosterone deficient man with obesity, metabolic syndrome, or chronic exposure to corticosteroids, measuring a HbA1C level should be considered.	An abnormal HbA1C level should prompt referral (primary care clinician, internist, endocrinologist) for further evaluation and management.
Serum Prolactin	Men with low testosterone level accompanied by a low/ low-normal LH level warrant measurement of serum prolactin to investigate for hyperprolactinemia. If prolactin is mildly elevated (≤1.5 times the upper limit of normal) a repeat prolactin should be drawn to rule out a spurious elevation.	If the prolactin level is mildly elevated, a repeat prolactin level should be measured to rule out a spurious elevation. For persistently elevated prolactin levels referral to an endocrinologist should be considered.
Serum Estradiol	Serum E2 levels should be measured in a patient with baseline gynecomastia or breast symptoms. For those men who develop gynecomastia or breast symptoms while on testosterone therapy, measuring a E2 level is optional.	If E2 is persistently elevated (>40 pg/mL) at baseline, referral to an endocrinologist should be made. For gynecomastia/breast symptoms that develop while on testosterone therapy, a period of monitoring should be considered, as breast symptoms sometimes abate. If gynecomastia/breast symptoms persist on testosterone therapy and the E2 level is elevated, reduction may be accomplished through dose adjustment of the testosterone therapy if the on-treatment testosterone levels are in the upper range of normal. If the on-treatment testosterone levels are low/normal, E2 level reduction can be accomplished by the use of AIs.

AI: aromatase inhibitor, E2: estradiol, FSH: follicle-stimulating hormone, hCG: human chorionic gonadotropin, Hg: hemoglobin, Hct: hematocrit, KS: Klinefelter syndrome, LH: luteinizing hormone, SERM: selective estrogen receptor modulator, SHBG: sex hormone-binding globulin

Appendix C: Adjunctive Testing		
Test	**Indication**	**Clinician Response**
Pituitary MRI	Men with sustained elevated prolactin levels, very low total testosterone levels (<150 ng/dL) and unexplained failure to produce LH/FSH warrant a pituitary MRI to identify sellar (pituitary adenoma, prolactinoma, infiltrative diseases of the pituitary) or parasellar processes.	The clinician may decide to refer such patients to an endocrinologist prior to ordering an MRI or may order the MRI first and refer only for abnormalities. For clinicians experienced in managing prolactinomas, bromocriptine or cabergoline may be prescribed without endocrinology input.
Bone Densitometry	Men with testosterone deficiency are at increased risk of bone density loss. Consideration of a baseline dual energy X-ray absorptionometry (DEXA) scan is warranted, particularly in middle-aged or older men with severe testosterone deficiency or in men with a history low trauma bone fracture.	Results are used to assess baseline bone health and if abnormal to follow changes over time whether the patient opts for testosterone therapy or not. Patients with osteoporosis should be referred to an endocrinologist.
Karyotype	A karyotype should be considered in men with unexplained hypergonadotropic hypogonadism. The most common chromosomal abnormality identified is 47,XXY, also known as KS, although other chromosomal abnormalities can also be found.	For those clinicians inexperienced in managing KS, referral to a more experienced clinician is advisable.
Hemoglobin/ Hematocrit	Prior to initiation of testosterone therapy, all patients should undergo baseline assessment of Hb/Hct.	If baseline Hct >50%, the clinician should with-hold testosterone therapy until the etiology of the high Hct is explained (polycthemia vera, living at altitude, obstructive sleep apnea, tobacco use). While on testosterone therapy, a Hct ≥54% warrants intervention. In men with high on-treatment testosterone levels, dose adjustment should be attempted as first-line management. In men with low-normal on-treatment testosterone levels, measuring a SHBG level and a free testosterone level using a reliable assay such as equilibrium dialysis is suggested. If SHBG levels are low/free testosterone levels are high, dose adjustment of the testosterone therapy should be considered. Men with on-treatment low/normal total and free testosterone levels should be referred to a hematologist for further evaluation.
AI: aromatase inhibitor, E2: estradiol, FSH: follicle-stimulating hormone, hCG: human chorionic gonadotropin, Hg: hemoglobin, Hct: hematocrit, KS: Klinefelter syndrome, LH: luteinizing hormone, SERM: selective estrogen receptor modulator, SHBG: sex hormone-binding globulin		

Appendix D: Testosterone Therapy and the Risk of Major Adverse Cardiac Events

Given the conflicting nature of the evidence, the Panel cannot definitively state that there is an association between testosterone therapy and subsequent MACE events nor can it be stated definitely that testosterone therapy is associated with reduced incidence of MACE. However, the FDA added a warning to testosterone product labeling after reviewing five observational studies and two meta-analyses of RCTs that examined the effects of testosterone therapy on MACE.

Two of the trials and one meta-analysis pointed to an increased risk of cardiovascular events,[363, 364, 366] two revealed no cardiovascular risk,[233, 367] and one was neutral with respect to risk.[373] The Corona meta-analysis,[372] which showed that there was no increased risk of cardiovascular events, was not officially reviewed but was taken into consideration in the final analysis. Although the committee reviewing the evidence concluded that there was not enough data to definitively state that testosterone therapy posed a significant cardiovascular risk, the FDA nonetheless required testosterone product manufacturers to add information to the labeling about a possible increased risk of myocardial infarction and cerebrovascular accidents in patients using testosterone therapy.

Two of the retrospective studies included in the FDA review pointed to an increased risk of cardiovascular events in men on testosterone therapy. Vigen et al. (2013)[363] conducted a retrospective analysis of patients who received a prescription for testosterone therapy after coronary angiography. The end-points included all -cause mortality as well as cardiovascular events. Patients were excluded if they had previously been on testosterone therapy, had a total testosterone >300 ng/dL, had a baseline Hct >50%, a PSA ≥4 ng/mL, or had commenced testosterone therapy after a myocardial infarction. Over a mean duration of 27.5 months, 1,223 men received testosterone therapy, and 7,486 were placed on placebo. In the testosterone therapy group, the raw data revealed a 2% myocardial infarction rate and a 3% cerebrovascular accident rate compared to 6% and 6%, respectively, in those patients not receiving testosterone. Complex statistical analysis using a methodology known a stabilized inverse propensity treatment weighting was utilized to adjust for 50 potentially confounding variables. Following inverse propensity treatment weighting, the cumulative percentage of patients who met the primary outcome 3 years post-angiography was 25.7% on treatment and 19.9% in the placebo group. This resulted in a calculated OR for developing a cardiovascular event in the testosterone therapy group of 1.29 (CI: 1.04 - 1.58; p=0.02), after adjusting for the presence of CVD. Two errata were published because of significant data errors in the original dataset. It is also unclear if everyone receiving a testosterone prescription actually used the medication, considering that 17.6% of patients in the treatment group filled only a single prescription. There was also inadequate documentation of on-treatment testosterone levels with 40% of men having no documented laboratory testing performed after the prescribing of testosterone therapy.

Finkle et al. (2014)[364] conducted a retrospective analysis of the Truven healthcare database (n=55,593) and compared non-fatal myocardial infarction events in men who were on testosterone therapy to those on PDE5 inhibitors. The authors compared the relative risk ratio (RRR) of developing a myocardial infarction within 90 days of receiving a testosterone or PDE5 inhibitor prescription compared to the year prior when patients were not using any medication. For men without a history of CVD, the RRR for having a myocardial infarction in those aged <65 years was 0.91 (CI: 0.60, 1.37) and for men ≥ 65 years of age 2.41 (CI: 1.12, 5.17). For men with a history of CVD, the RRR were more striking: <65 years of age 2.07 (CI: 1.05, 4.11) and ≥65 years 1.91 (CI: 0.66, 5.5). This analysis was limited in that it used an insurance claims database, had an abbreviated follow-up, and compared testosterone therapy to a class of medications (PDE5 inhibitors) known to be endothelial stabilizers and potentially cardioprotectants.

The Xu meta-analysis of 27 randomized placebo-controlled trials pointed to an increase in cardiovascular risk in men using testosterone therapy, although the results were statistically insignificant.[366] A total of 2,994 men were randomized to either testosterone (n=1,773) or placebo (n=1,261) for 12 weeks to 3 years. There was a total of 115 cardiac events in men on treatment and 65 in the placebo arm (OR=1.54; CI 1.09, 2.18). Included in these events were 33 deaths, 22 of which were in men who were on testosterone therapy, and 11 in the placebo groups. A stratification of trials according to funding showed that those supported by pharmaceutical companies (n=13) showed decreased odds of having a cardiovascular event in testosterone patients (OR=0.89; CI: 0.50, 1.60), while those not funded by industry showed that the risk of a cardiovascular related event on testosterone therapy was greater (OR=2.06; CI: 1.34, 3.17). Despite the homogenous nature of the trials included, it was noted

that there was a risk of publication bias since it is possible that trials favoring testosterone therapy might remain unpublished. Other limitations included the possible subjective nature in reporting some adverse events.

Conversely, the Shores, [367] Muraleedharan,[233] and Baillargeon[373] studies determined that there was no increased risk of MACE in men who were on testosterone therapy. The Shores study was an observational study of 1,031 men (mean age 62.1 years) with total testosterone level <250 ng/dL (mean 181 ng/dL). Over a mean period of 41 months, 398 were reported to be on testosterone therapy, while 631 were not. Mortality in testosterone treated men was 10.3% (mortality rate of 3.4 deaths/1,000 person-years) compared with 20.7% (5.7 deaths/1,000 person -years) in men who were not on treatment ($p<0.0001$). After adjustment for confounding factors, testosterone therapy remained associated with a decreased risk of death (HR: 0.61; CI 0.42, 0.88).

The Muraleedharan study looked at men with type 2 diabetes and stratified the population (n=581; mean age 59 years) into those who had normal testosterone levels (>300 ng/dL, n=343) and low testosterone levels (<300 ng/dL, n=238). Of the men with low testosterone, 64 received treatment via gel or IM injections for 42 months and were followed for nearly 6 years. At the 6-month time point, there were 34 deaths from CVD (17 in each group) and an overall death rate of 17.2% and 9% in the in the low and normal testosterone groups, respectively. When comparing the likelihood of survival, there was a significant decrease in survival in the low testosterone group compared to those with normal testosterone (adjusted HR=2.02; CI: 1.2, 3.4; $p<0.01$). Furthermore, a comparison of patients on treatment compared to those who were not showed that the HR for decreased survival was 2.3 (CI: 1.3, 3.9; $p<0.01$). The increases in mortality were found to be independent of age, BMI, pre-existing CVD, current smoking status, and statin therapy. The authors conceded that those patients treated had more severe testosterone deficiency, which may have resulted in treatment bias.

Finally, the Baillargeon study showed that testosterone therapy was not associated with an increased risk of myocardial infarction (HR=0.84; CI: 0.69 -1.02). The authors conducted a retrospective analysis of 6,355 Medicare beneficiaries who had at least 1 testosterone injection (mean number of injections over the entire study period 8.2) and matched them to 19,065 men who were testosterone therapy naïve for the preceding 12 months. Although confounders were accounted for in the analysis, concurrent medications that may have reduced the risk for myocardial infarction or other testosterone therapies used outside of the study protocol were not controlled for or assessed.

Since the FDA warning in 2015, other studies have failed to demonstrate a risk of cardiovascular events in patients on testosterone therapy. The T-Trials (2017)[229] randomized 790 men (mean age 72 years) to either testosterone gel (n=395) or placebo (n=395) for 1 year to measure the effect of testosterone on physical and sexual function and patient vitality. Over half of the men were obese (BMI >30), and 70% had documented hypertension at baseline. At the end of the year-long treatment period, two men from the treatment arm had a definite myocardial infarction, and none were recorded in the placebo arm. During the subsequent year of follow-up, eight men from the placebo group and one man who had been on treatment were adjudicated to have had a definite myocardial infarction. Although the study was not powered to detect cardiovascular events as a primary endpoint, the authors did not detect increased risk in the testosterone group.

ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ADAM	Androgen Deficiency in the Aging Male
ADT	Androgen deprivation therapy
AI	Aromatase inhibitor
AMS	Aging Male Survey
ASCVD	Atherosclerotic cardiovascular disease
AUA	American Urological Association
BMD	Bone mineral density
BMI	Body mass index
CDC	Centers for Disease Control
CV	Coefficient of variation
CVD	Cardiovascular disease
DEXA	Dual-energy X-ray absorptiometry
E2	Estradiol
ED	Erectile dysfunction
EMAS	European Male Aging Study
FSH	Follicle-stimulating hormone
Hb	Hemoglobin
Hct	Hematocrit
hCG	Human chorionic gonadotropin
HDL	High-density lipoproteins
IIEF	International Index of Erectile Function
IM	Intramuscular
KS	Klinefelter syndrome
LCMS	Liquid chromatography/mass spectrometry
LTBF	Low-trauma bone fracture
LH	Luteinizing hormone
MACE	Major adverse cardiac event
MMAS	Massachusetts Male Aging Study
PIN	Prostatic intraepithelial neoplasia
POME	Pulmonary microemboli
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RP	Radical prostatectomy
RRR	Relative risk ratio
RT	Radiation therapy
SERM	Selective estrogen receptor modulator
SHBG	Sex hormone-binding globulin
SQ	Subcutaneous
T:E	Testosterone:estradiol ratio
TMSC	Total motile sperm count
TOM	Testosterone in Older Men
VTE	Venothrombolic event

Evaluation and Management of Testosterone Deficiency Panel, Consultants, and Staff

John P. Mulhall, MD (Chair)
Memorial Sloan Kettering Cancer Center
New York, NY

Ronald W. Lewis, M.D. (Vice Chair)
Augusta University
Augusta, GA

Robert Brannigan MD
Northwestern University
Evanston, IL

Kelly A. Chiles, MD, MSc
George Washington University
Washington DC

Emily Graham Kurtz, MD
MPOWER MD Concierge Wellness
Cardiovascular and Internal Medicine
Nashville, TN

Deborah J. Lightner
The Mayo Clinic
Rochester, MN

Martin M. Miner, M.D.
The Miriam Hospital
Providence, RI

Landon Trost, M.D.
The Mayo Clinic
Rochester, MN

Christian J. Nelson, Ph.D.
Memorial Sloan Kettering Cancer Center

Elizabeth A. Platz, ScD, MPH
Hopkins Bloomberg School of Public Health
Baltimore, MD

Lakshmi Ramanathan, PhD
Memorial Sloan Kettering Cancer Center
New York, NY

J. Bruce Redmon, M.D.
University of Minnesota
Minneapolis, MN 55455

Consultants
Hassan Murad, M.D., MPH
Mouaz Alsawas, M.D.

Staff
Heddy Hubbard, Ph.D., MPH, RN, FAAN
Abid Khan, MHS, MPP
Erin Kirkby, MS
Nenellia Khachatourian Bronson, MA
Leila L. Rahimi, MHS
Brooke Bixler, MPH
Shalini Selvarajah, MD, MPH

CONFLICT OF INTERESTS DISCLOSURES

All panel members completed COI disclosures. Disclosures listed include both topic– and non-topic-related relationships.

Consultant/Advisor: John P. Mulhall, Pfizer, Lilly

Leadership Position: Robert E. Brannigan, The American Society for Reproductive Medicine; **John P. Mulhall,** Association of Peyronie's Disease Advocates

Scientific Study or Trial: Kelly A. Chiles, Pfizer; **Christian J. Nelson**, National Institutes of Health

Other: Robert E. Brannigan, National Institutes of Health

PEER REVIEWERS

We are grateful to the persons listed below who contributed to the Guideline by providing comments during the peer review process. Their reviews do not necessarily imply endorsement of the Guideline.

Bradley Anawalt, MD
Peter C. Albertsen, MD
Nelson Bennett, MD
Arthur L. Burnett, MD
Peter Clark, MD
Pat Fulgham, MD
Peter Gann, MD
David Ginsberg, MD
Wayne J. Hellstrom, MD
Blake Hamilton, MD
Jim Hotaling, MD
Lawrence Jenkins, MD
Edward Kim, MD
Melissa Kaufmann, MD
Jed Kaminetsky, MD
Tobias Kohler, MD
Barry Kogan, MD
Louis Kavoussi, MD
Mohit Khera, MD
Stacy Loeb, MD
Larry Lipshultz, MD
Andrew McCullough, MD
Abraham Morgentaler, MD
Akanksha Mehta, MD
Jesse N. Mills, MD
Mark E. Molitch, MD
Kevin T. McVary, MD
Ajay Nangia, MD
Alexander W. Pastuszak, MD
Hossein Sadeghi-Nejad, MD
Alan Shindel, MD
Thomas F. Stringer, MD
Ira Sharlip, MD
Jaspreet S. Sandhu, MD
Peter N. Schlegel, MD
Mark Sigman, MD
Richard Sadovsky, MD
Roger E. Schultz, MD
Peter Stahl, MD
J. Brantley Thrasher, MD
Richard Watson, MD
Nenette K. Wenger, MD
J. Stuart Wolf, MD
Hubert Vesper, MD

DISCLAIMER

This document was written by the Evaluation and Management of Testosterone Deficiency Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2016. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology, cardiology, family medicine, and psychology with specific expertise on this disorder. The mission of the Panel was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of muscle-invasive bladder cancer.

Funding of the Panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the Panel provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (‘off label‘) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.