Diagnosis, Treatment, and Follow-up of Men with Androgen Deficiency

Physician Performance Measurement Set

Approved
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Background

These clinical performance measures were developed by the Endocrine Society (ES) using the Physician Consortium for Performance Improvement (PCPI™) model for performance measure development. Designed for individual quality improvement efforts, the measures may also be used in data registries, continuing medical education programs, and in board certification programs. The measures include:

Measure #1: Testosterone measurement
Measure #2: Baseline gonadotropin measurement
Measure #3: Follow-up hematocrit or hemoglobin
Measure #4: Follow-up testosterone measurement

The performance measures are based upon the *Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline (revised)* (J Clin Endocrinol Metab June 2010. 95(6):2536-2559). These measures were determined to be the most clinically relevant based on the medical evidence and they could be used to evaluate care being provided by the individual physician.

This measure set was prepared by a work group of experts in androgen deficiency and performance measures. The measures were provided to the American Urological Association (AUA) and Society's membership for comment, and were reviewed by the Endocrine Society's Performance Measures Subcommittee (PMSC), Clinical Affairs Core Committee (CACC), and ultimately approved by the Society's Council. At each stage of review, the task force received written comments and incorporated needed changes. Task Force members had final responsibility for and control for the development of the measure set.

The Endocrine Society used this measure set to develop *The Diagnosis, Treatment, and Follow-up of Men with Androgen Deficiency Practice Improvement Module (PIM)*. The PIM is a web based tool designed to meet the needs of endocrinologists to improve performance in effectively diagnosing and managing male patients with androgen deficiency, including engaging these patients in positive and meaningful self-management activities with the goal of improving health care outcomes. This activity is approved by the American Board of Internal Medicine's (ABIM) Approved Quality Improvement (AQI) Pathway for 20 points toward the Self-Evaluation of Practice Performance (Part 4) requirement of Maintenance of Certification (MOC).

Please note: the Society has included information in the measure specifications related to the American Medical Association's Current Procedural Terminology, which is a registered trademark of the AMA (CPT® Copyright 2004 - 2013 American Medical Association) with permission.

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Topic Relevance

In population-based surveys of middle aged and older men, symptoms of low libido, erectile dysfunction, hot flushes, fatigue, loss of vigor, irritability, depressed mood, impaired concentration, reduced physical performance, or sleep disturbance, were associated with low testosterone levels. In these surveys, the prevalence of symptomatic androgen deficiency was approximately 6% of the population of middle –aged to older men and increased with age, waist circumference and poor self-reported health status. Hypogonadism is therefore common in American men, yet only 5% of candidates receive treatment.[i]

According to US Census Bureau projections, the number of Americans ages 65 or older will rise from approximately 35 million (12.4% of all Americans) in 2000 to nearly 55 million (16.3% of total) by 2020 and nearly 87 million (20.7%) in 2050.[ii] In addition to a two-fold increase in the number of elderly patients, octogenarians will comprise the fastest-growing population segment according to age.[iii]

This gap in care can profoundly affect the health of our aging men. Even in younger men with symptoms, infertility may be a consequence of androgen deficiency. Male infertility contributes to 50% of all infertility cases. However, both low testosterone and supraphysiologic androgen administration can lead to infertility. The impaired sperm production that supraphysiological testosterone administration causes is often reversible, but in some series has been shown to take anywhere from 3 months to years.

Inappropriate testosterone use is also a major concern of these times. In the sports arena, so far, 45 NFL players have had a ban or suspension placed on them. Among Major League Baseball players, 7 % have tested positive for steroids. This inappropriate use has trickled down to the US population. According to ProjectEAT, a five-year, longitudinal study, overall, 1.5% of adolescents reported using steroids.[iv] In a 2002 study by Texas A&M University, it was estimated that up to 42,000 Texas students were abusing steroids.

It is important that testosterone be used to replace hormonal deficiency, and not be used inappropriately in pharmacological doses for enhancement of physical performance or muscular size. The testosterone process measures listed here will assist us to prescribe testosterone to only those individuals in whom it is medically indicated.

Because the diagnosis and management of androgen deficiency in men poses several challenges (symptoms and signs are nonspecific and modified by age, comorbid illness, severity and duration of androgen deficiency, variation in androgen sensitivity, and previous testosterone therapy; evidence of proper care is weak; long-term health consequences of low testosterone levels are unknown for older men and men with chronic illness; the impact of untreated androgen deficiency on mortality is unclear; the benefits and adverse effects of long-term testosterone therapy on patients are not known), these performance measures were determined to be of critical importance to standardize care as outlined in the clinical guidelines.

These performance measures were developed to be the most clinically relevant based on the medical evidence and represent key clinical steps in the optimal care and management of patients with androgen deficiency. There is the possiblity of significant negative impact if practitioners fail to perform the correct initial diagnosis steps or follow-up appropriately. By addressing this potential gap in quality care, practitioners will improve their abilities to initially diagnosis androgen deficiency in men and to manage their patients' care appropriately.

ES Disclosure Process

The Society's Diagnosis, Treatment, and Follow-up of Men with Androgen Deficiency Performance Measures were developed by a Society work group, under guidance of the Society's Performance Measures Sub-Committee (PMSC) and the Clinical Affairs Core Committee (CACC). All persons in control of content, including all members of the various Society committees, subcommittees and faculty workgroups, as well as staff, disclose all relevant financial relationships of the individual or spouse/partner that have occurred within the last 12 months with any commercial interest(s) whose products or services are related to the content. Financial relationships are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (e.g., stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Any conflicts of interest are resolved prior to the individual's control of content, using the peer-review process as the primary mechanism to resolve conflicts.

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Measure Specifications

Measure #1: Testosterone Measurement

Measure Description

Percentage of male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy, who have a l testosterone measurement performed within six months prior to initiating testosterone therapy

Measure Detail

Numerator Statement	*Patients who have a testosterone measurement performed within six months prior to initiating testosterone therapy.*
Denominator Statement	All male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy
Denominator Exceptions	Documentation of medical reason(s) for not performing a testosterone measurement within six months prior to initiating testosterone therapy (e.g. bilateral orchiectomy, congenital absence of testes, Kallmann syndrome, documented longstanding hypogonadotropic hypogonadism, and history of hypophysectomy with longstanding hypogonadism)
Supporting Guideline	Testosterone Therapy in Men with Androgen Deficiency Syndromes (The Endocrine Society – 2010)[5] The Endocrine Society suggests the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. The Endocrine Society recommends confirmation of the diagnosis by repeating measurement of total testosterone.[5 6]

Measure Importance

Relationship to desired outcome

Administration of testosterone in men with low testosterone levels can remediate some symptoms of hypogonadism. The potential benefits of testosterone therapy in these men include improvement of sexual function, increases in libido, reduction in fatigue, improvement in bone mineral density, increases in lean body mass and decrease of anemia. [7] Testosterone administration is only appropriate in men with testosterone deficiency, and it should not be used in patients without this condition. Therefore, the measurement of serum testosterone, to properly diagnose androgen deficiency, is extremely important. The requirement of clinicians to measure testosterone prior to therapy will reduce the number of patients who are prescribed testosterone inappropriately.

Opportunity for Improvement

Numerous studies have documented the prevalence of hypogonadism, especially in the aging male. [8] This is often unrecognized and untreated.[9] [10] In addition, the inappropriate use of testosterone in athletes and others who are eugonadal, to enhance athletic performance and affect appearance should be discouraged. The requirement of documentation of low testosterone levels measured by a reliable assay prior to consideration of testosterone use should help reduce its inappropriate use by the medical community.

A morning testosterone measurement is preferred but either total or free or bioavailable testosterone drawn at other times of the day may be considered adequate for the purposes of documentation that a clinician measured testosterone levels to identify testosterone deficiency prior to treatment.[11] It is true, however, that low testosterone values measured at times other than the morning can sometimes be misleading. Free or bioavalable testosterone concentrations should be measured when total testosterone concentrations are close to the lower limit of the normal range and when altered SHBG levels

	are suspected, e.g. in older men and men with obesity, diabetes mellitus, chronic illness, or thyroid disease. [12] [13]Laboratory reports of free or bioavailable testosterone, in general,, include reported measurements of total testosterone. The requirement for measurement of total testosterone should in no way indicate that measuring free or bioavailable testosterone for specific individuals is inappropriate or unwarranted.
Exception Justification	A testosterone level prior to initiating testosterone therapy is not necessary for some medical conditions (e.g. bilateral orchiectomy, congenital absence of testes, Kallmann syndrome, documented longstanding hypogonadotropic hypogonadism, status-post hypophysectomy with longstanding hypogonadism)
Harmonization with Existing Measures	Harmonization with existing measures is not applicable to this measure.

Measure Designation

Measure purpose	Quality Improvement Accountability
Type of measure	Process Measure
Care setting	Ambulatory Care
Data source	Electronic Health Record System Paper Medical Record Flow Sheet Administrative Claims Data* *Adequate data source only if new codes are developed specific to the intent of this measure and in certain circumstances, documentation of prescriptions filled for testosterone preparations can be used

Technical Specifications: Administrative Data

Denominator (Eligible Population)	All male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy CPT® E/M Service Code: • 99201-99205, 99212-99215, 99241-99245 AND ICD-9 Code for: Testicular Hypo function 257.0, 257.2 Impotence-organic 607.84 Pituitary Adenoma 227.3 Panhypopituitarism 253.2 Iatrogenic hypopituitarism 253.7 Empty sella syndrome 253.8 AND Report the CPT Category II code: • XXXXF: *Receiving testosterone therapy* in development for this numerator
Numerator	*Patients who have a testosterone measurement performed within six months prior to initiating testosterone therapy.* Report the CPT Category II code:

	• XXXXF: *testosterone measurement performed within six months prior to initiating testosterone therapy* in development for this numerator
Denominator Exceptions	Documentation of medical reason(s) for not performing a testosterone within six months prior to initiating testosterone therapy • Append modifier to CPT Category II code: XXXXF-1P

Measure #2: Baseline Gonadotropin (LH or FSH) Measurement

Measure Description

Percentage of male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy, who have a baseline gonadotropin (LH or FSH) measurement performed within six months prior to initiating testosterone therapy

Measure Detail

Numerator Statement	*Patients who have a baseline gonadotropin (LH or FSH) measurement performed within six months prior to initiating testosterone therapy.*
Denominator Statement	All male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy.
Denominator Exceptions	Documentation of medical reason(s) for not performing a baseline gonadotropin (LH or FSH) measurement within six months prior to initiating testosterone therapy (e.g. karyotype diagnosis of Klinefelter's syndrome, prior history of total hypophysectomy, history of bilateral orchiectomy or anatomically confirmed congenital absence of testes.)
Supporting Guideline	Testosterone Therapy in Men with Androgen Deficiency Syndromes (The Endocrine Society – 2010 [5] The Endocrine Society recommends measurement of serum LH and FSH levels to distinguish between primary (testicular) and secondary (pituitary) hypogonadism. Men with primary hypogonadism have low testosterone levels in association with elevated LH and FSH levels, whereas men with secondary hypogonadism have low testosterone levels associated with low or inappropriately normal LH levels.

Measure Importance

Relationship to desired outcome	In male patients with testicular failure, it is important to rule out secondary causes, such as pituitary insufficiency.[14] [15] Measurement of gonadotropins is necessary for this.[16] In men deemed to have secondary hypogonadism, initial diagnostic evaluation is needed to exclude pituitary adenoma, hyperprolactinemia, hemochromatosis and other infiltrative diseases, medications (e.g. opiates or glucocorticoids, and genetic disorders associated with gonadotropin deficiency. In men taking chronic opiates, secondary hypogonadism is common, but the etiology should be confirmed with the measurement of serum LH, with or without FSH. Secretion of LH and FSH by the pituitary is pulsatile which can result in some variability in serum levels. LH levels respond to and correlate more directly with androgen levels; however, FSH levels may be a more sensitive measure of testicular failure. Although measurement of both gonadotropins is encouraged by the Endocrine Society, measurement of either LH or FSH will be deemed sufficient for meeting this provider accountability measure.
Opportunity for Improvement	Occasionally, patients are started on testosterone therapy without the diagnosis of secondary hypogonadism. If this is done, important remediable clinical conditions, like pituitary and hypothalamic tumors and other lesions, as well as panhypopituitarism, might not be identified.
Exception Justification	Measurement of gonadotropin levels before initiating testosterone therapy is not necessary for some medical conditions (e.g. karyotype diagnosis of Klinefelter's syndrome, prior history of total hypophysectomy, history of bilateral orchiectomy or anatomically confirmed congenital absence of testes).

Harmonization with Existing Measures	Harmonization with existing measures is not applicable to this measure.

Measure Designation

Measure purpose	Quality Improvement Accountability
Type of measure	Process Measure
Care setting	Ambulatory Care
Data source	Electronic Health Record System Paper Medical Record Flow Sheet Administrative Claims Data* *Adequate data source only if new codes are developed specific to the intent of this measure and in certain circumstances, documentation of prescriptions filled for testosterone preparations can be used

Technical Specifications: Administrative Data

Denominator (Eligible Population)	All male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy CPT® E/M Service Code: • 99201-99205, 99212-99215, 99241-99245 AND ICD-9 Code for: Testicular hypo function 257.0, 257.2 Impotence-organic 607.84 Pituitary Adenoma 227.3 Panhypopituitarism 253.2 Iatrogenic hypopituitarism 253.7 Empty sella syndrome 253.8 AND Report the CPT Category II code: • XXXXF: *Receiving testosterone therapy* in development for this numerator
Numerator	*Patients with baseline gonadotropin (LH or FSH) measurement performed within six months prior to initiating testosterone therapy.* Report the CPT Category II code: • XXXXF: Baseline *gonadotropin measurement performed within six months prior to initiating testosterone therapy* in development for this numerator
Denominator Exceptions	Documentation of medical reason(s) for not performing a baseline gonadotropin (LH or FSH) measurement within six months prior to initiating testosterone therapy • Append modifier to CPT Category II code: XXXXF-1P

Measure #3: Hematocrit or Hemoglobin Test

Measure Description

Percentage of male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy, who have a hematocrit or hemoglobin test performed within two to six months after initiation of testosterone therapy

Measure Detail

Numerator Statement	*Patients who have a hematocrit or hemoglobin test performed within two to six months after initiation of testosterone therapy.*
Denominator Statement	All male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy
Denominator Exceptions	Documentation of patient reason(s) for not performing a hematocrit or hemoglobin test within two to six months after initiation of testosterone therapy (e.g. patient refusal)
Supporting Guideline	Testosterone Therapy in Men with Androgen Deficiency Syndromes (The Endocrine Society – 2010) [5] The Endocrine Society recommends determining hematocrit at baseline, at 3 months and then annually. If hematocrit is greater than 54%, stop therapy until hematocrit decreases to a safe level, evaluate the patient for hypoxia and sleep apnea, and reinitiate therapy at a reduced dose.

Measure Importance

Relationship to desired outcome	Testosterone –treated men were nearly four times more likely than placebo treated men to experience hematocrit greater than 50% and the risk for a clinically significant increase in hematocrit increases with age.[17 18] Men with a pre-treatment hematocrit of greater than 50% are also at increased risk of erythrocytosis.[19] Monitoring of hematocrit in men on testosterone replacement can identify individuals who develop erythrocytosis and prevent its medical consequences. Although the guidelines specify hematocrit measurement, documentation of hemoglobin measurement as a surrogate for identification of erythrocytosis is deemed adequate to meet the requirements of this accountability measure. NOTE: Ideally, hematocrit or hemoglobin test should be completed within 2-3 months after initiation of testosterone therapy.
Opportunity for Improvement	The adverse effects of erythrocytosis, which is significantly increased with testosterone treatment, can be addressed with monitoring of hematocrit at appropriate intervals after initiation of therapy. Steps can be taken to reverse erythrocytosis and avoid its serious consequences.
Exception Justification	
Harmonization with Existing Measures	Harmonization with existing measures is not applicable to this measure.

Measure Designation

Measure purpose	Quality Improvement Accountability
Type of measure	Process Measure
Care setting	Ambulatory Care
Data source	Electronic Health Record System Paper Medical Record Flow Sheet Administrative Claims Data* *Adequate data source only if new codes are developed specific to the intent of this measure and in certain circumstances, documentation of prescriptions filled for testosterone preparations can be used.

Technical Specifications: Administrative Data

Denominator (Eligible Population)	All male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy CPT® E/M Service Code: • 99201-99205, 99212-99215, 99241-99245 AND ICD-9 Code for: Testicular hypo function 257.0, 257.2 Impotence-organic 607.84 Pituitary Adenoma 227.3 Panhypopituitarism 253.2 Iatrogenic hypopituitarism 253.7 Empty sella syndrome 253.8 AND Report the CPT Category II code: • XXXXF: *Receiving testosterone therapy* in development for this numerator
Numerator	*Patients who have a hematocrit or hemoglobin test performed within two to six months after initiation of testosterone therapy.* Report the CPT Category II code: • XXXXF: *Hematocrit or hemoglobin test performed within two to six months after initiation of testosterone therapy* in development for this numerator
Denominator Exceptions	Documentation of patient reason(s) for not performing a hematocrit or hemoglobin test • Append modifier to CPT Category II code: XXXXF-2P

Measure #4: Follow-up Testosterone Measurement

Measure Description

Percentage of male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy, who have a follow-up testosterone performed within six months after initiation of testosterone therapy

Measure Detail

Numerator Statement	*Patients who have a follow-up testosterone measurement performed within six months after initiation of testosterone therapy.*
Denominator Statement	All male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy.
Denominator Exceptions	Documentation of patient reason(s) for not performing follow-up testosterone measurement within six months after initiation of testosterone therapy (e.g. patient refusal)
Supporting Guideline	Testosterone Therapy in Men with Androgen Deficiency Syndromes (The Endocrine Society – 2010) [5] The Endocrine Society suggests monitoring testosterone levels 3 to 6 months after initiation of testosterone therapy.

Measure Importance

Relationship to desired outcome

For effective treatment, therapy should restore serum testosterone to the mid-normal range. This cannot be accomplished without monitoring of serum testosterone. Monitoring testosterone can identify those patients who are under-replaced or are taking excessive doses of testosterone.

The optimal strategies for interval monitoring after therapy vary with the mode of therapy, whether it be transdermal gel, transdermal patch, buccal tablet, or intramuscular injection.[20 21 22 23] When injections are used, documentation of the time after injection at which the level is measured is strongly encouraged to allow appropriate interpretation of the resulting values. Similarly, when testosterone patch is used, the documentation of the hours after the patch is placed can be helpful for interpretation of results. The optimal time of measurement of testosterone in relationship to the mode of testosterone administration is recommended in Table 8 of the Endocrine Society Guideline.[5] To account for these variabilities, a measurement of serum testosterone within 6 months after initiation of therapy is deemed acceptable to meet the accountability measure.

Opportunity for Improvement

Undertreatment and overtreatment of men with hypogonadism on testosterone therapy occur commonly. Measurement of testosterone and dose adjustment can remediate these situations. [17, 19]

A total testosterone level is preferred but a free or bioavailable testosterone is also considered adequate. As indicated above, the relationship between administration of testosterone and optimal time of measurement of serum testosterone varies with the mode of administration. The pharmacokinetic profiles of the various preparations are listed in The Endocrine Society Guidelines, 2010. [5]

Free or bioavalable testosterone concentrations should be measured when total testosterone concentrations are close to the lower limit of the normal range and when altered SHBG levels are suspected, e.g. in older men and men with obesity, diabetes mellitus, chronic illness, or thyroid disease. [21] Laboratory reports of free or bioavailable testosterone, in general, include reported measurements of total testosterone. The requirement for measurement of total testosterone should in no way indicate that measuring free or bioavailable testosterone for specific individuals is inappropriate or unwarranted.

Exception Justification	
Harmonization with Existing Measures	Harmonization with existing measures is not applicable to this measure.

Measure Designation

Measure purpose	Quality Improvement Accountability
Type of measure	Process Measure
Care setting	Ambulatory Care
Data source	Electronic Health Record Paper Medical Record Flow Sheet Administrative Claims Data* *Adequate data source only if new codes are developed specific to the intent of this measure and in certain circumstances, documentation of prescriptions filled for testosterone preparations can be used.

Technical Specifications: Administrative Data

Denominator (Eligible Population)	All male patients aged 18 years and older with androgen deficiency who are receiving testosterone therapy. CPT® E/M Service Code: • 99201-99205, 99212-99215, 99241-99245 AND ICD-9 Code for: Testicular hypo function 257.0, 257.2 Impotence-organic 607.84 Pituitary Adenoma 227.3 Panhypopituitarism 253.2 Iatrogenic hypopituitarism 253.7 Empty sella syndrome 253.8 AND Report the CPT Category II code: • XXXXF: *Receiving testosterone therapy* in development for this numerator
Numerator	*Patients who have a follow-up testosterone measurement performed within six months of beginning testosterone therapy.* Report the CPT Category II code: • XXXXF: *Follow-up testosterone measurement performed within six months after initiating testosterone therapy* in development for this numerator
Denominator Exceptions	Documentation of patient reason(s) for not performing a follow-up testosterone • Append modifier to CPT Category II code: XXXXF-2P

References

[1] Food and Drug Administration. http://www.fda.gov/fdac/departs/196_upd.htm.

[2] US Census Bureau. US interim projections by age, sex, race, and Hispanic origin. 2004. Available at: http://www.census.gov/ipc/www/usinterimproj/. Accessed January 25, 2005.

[3] Batchelor WB, Jollis JG, Friesinger GC. The challenge of health care delivery to the elderly patient with cardiovascular disease: demographic, epidemiologic, fiscal, and health policy implications. Cardiol Clin 1999; 17: 1-15.

[4] Longitudinal findings from ProjectEAT. Pediatrics. 2007;119:476-486

[5] Bhasin S, Cunningham GR, Hayes, FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. 2010 Testosterone therapy in men with androgen deficiency syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 95:2536-2559

[6] Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB 2007. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol (Oxf) 67:853-862

[7] Seftel AD, Mack RJ, Secrest AR, Smith TM 2004. Restorative Increases in serum testosterone levels are significantly correlated to improvements in sexual functioning J Androl 25:963-972

[8] Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB 2002. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 87:589-598

[9] Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR 2001. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 86:724-731

[10] Gray A, Feldman HA, McKinlay JB, Longcope C 1991. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J. Clin. Endocrinol Metab 73:1016-1025

[11] Kelleher S, Conway AJ, Handelsman DJ 2004. Blood testosterone threshold for androgen deficiency symptoms. J. Clin. Endocrinol Metab 89:3813-3817

[12] Wang C, Catlin DH, Demers LM, Starcevic B, Swerdloff RS 2004. Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry J. Clin. Endocrinol Metab 89:534-543

[13] Vermeulen A, Verdonck L, Kaufman JM 1999. A critical evaluation of simple methods for the estimation of free testosterone in serum. J. Clin. Endocrinol Metab 84:3666-3672

[14] Ascoli P, Cavagnini F. 2006. Hypopituiatrism. Pituitary 9:335-42

[15] McClure, RD. 1988 Endocrine evaluation and therapy of erectile dysfunction. Urol Clin North Am 15:53-64

[16] Lenzi A, Balercia G, Bellastella A, Colao A, Fabbri A, Foresta C, Galdiero M, Gandini L, Krausz C, Lombard G, Lombardo F, Maggi, M, Radicioni A, Selice R, Sinisi AA, Forti G. 2009 Epidemiology, diagnosis, and treatment of male hypogonadotropic hypogonadism. 32:934

[17] Bhasin S, Woodhouse L et al 2001. Testosterone dose response relationships in healthy young men. Am J Physiol Endocrinol Metab 281: E1172-E1181.

[18] Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S 2005. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Bil Sci Med Sci 60:1451-1457

[19] Coviello AD, Kaplan B, Lakshmann KM, Chen T, Singh AB, Bhasin S. 2008. Effects of graded doses of testosterone on erythropoesis in healthy older men. J Clin Endocrinol Metab 93:914-919

[20] McNicholas TA, Dean JD, Mulder H et al. 2003. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int 91:69-74.

[21] Wang C, Swedloff RS, Iranmanesh A et al. 2000 Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clinic Endocrinol Metab 85:2839-2853

[22] Bhasin S, Zhang A, Coviello A, Jasuja R, Ulloor J, Sing R, Vesper H, Vasan RS. 2008. The impact of assay quality and reference ranges on clinical decision making in the diagnosis of androgen disorders. Steroids 73:1311-1317

[23] Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. 2007. Utility, limitations and pitfalls in measuring testosterone: An Endocrine Society Position Statement. J. Clin. Endocrinol Metab 92:405-413

[24] Bhasin S, Singh AB, Mac RP, Cart B, Lee MI, Cunningham GR 2003 Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plane. J Androl 24:299-311

[25] Fowler JE, Whitmore WF 1981 The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol 126:372-376

[26] Rhoden EL, Morgentaler A 2004 Risks of Testosterone Therapy and Recommendations for Monitoring. N Engl J Med 2004;350:482-92.

[27] Endogenous Hormones Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P and Key TJ: Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008; 100: 170.

[28] American Urological Association Prostate Specific Antigen Best Practice Statement: 2009 Update. http://www.auanet.org/content/media/psa09.pdf?CFID=2198102&CFTOKEN=78261699&jsessionid=84302f0e8bbc8d2d0d505741e16774f69482

[29] Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer JAMA. 1997 277:1456-60.

[30] Carter HB 1997 PSA variability versus velocity. Urology 49:305

[31] Riehmann M, Rhodes PR, Cook TD, Grose GS, Bruskewitz RC 1993 Analysis of variation in prostate-specific antigen values. Urology 42:390-397