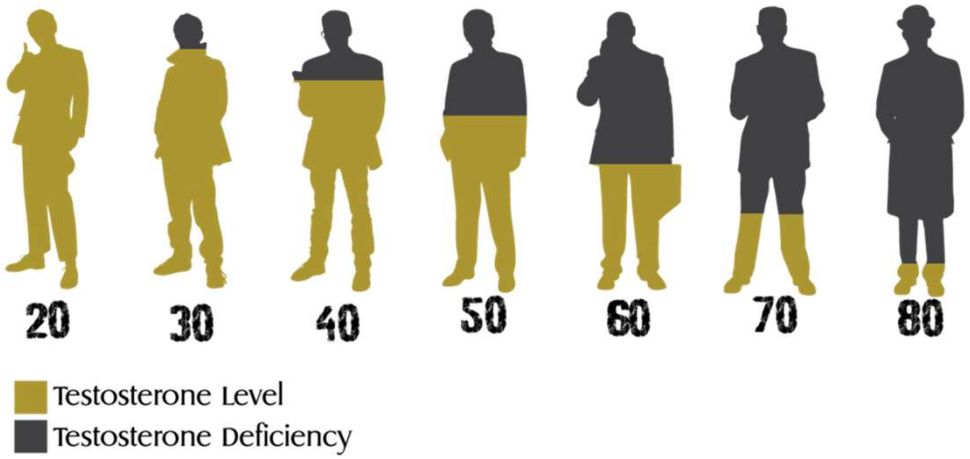
THERAPY OPTIONS FOR MEN WITH TESTOSTERONE DEFICIENCY (TD)

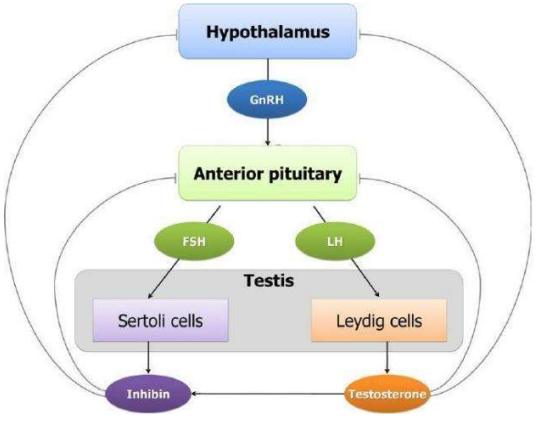
NAVIGATING THE AVAILABLE DATA & A REVIEW OF GUIDELINES

Cynthia R. Stuart, DO
cstuart@doctorstuart.net

TESTOSTERONE DEFICIENCY

- TD is a well-established, significant medical condition that negatively affects
  - General health
  - Quality of life
  - Male sexuality
  - Reproduction





HYPOTHALAMIC PITUITARY AXIS (HPA)

CLASSIFICATION OF HYPOGONADISM AND CAUSES OF PRIMARY AND SECONDARY HYPOGONADISM

PRIMARY

- Abnormality of the hypothalamic-pituitary axis at the testicular level.
- Low testosterone level, impairment of spermatogenesis and elevated FSH & LH.

SECONDARY

- Central defects of the hypothalamus or pituitary.
- Low testosterone level, impairment of spermatogenesis and low or normal FSH & LH.

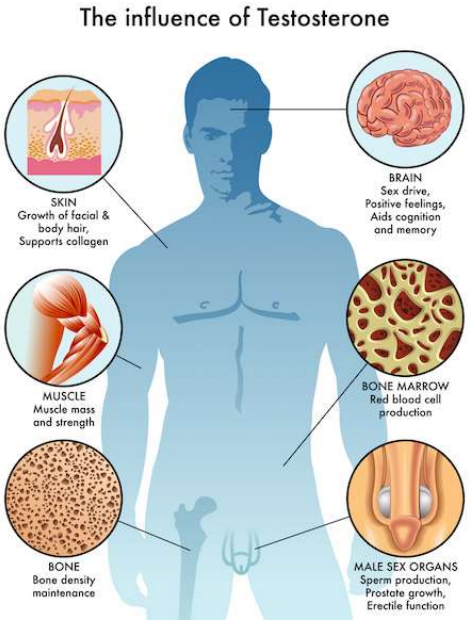
COMBINED PRIMARY & SECONDAY

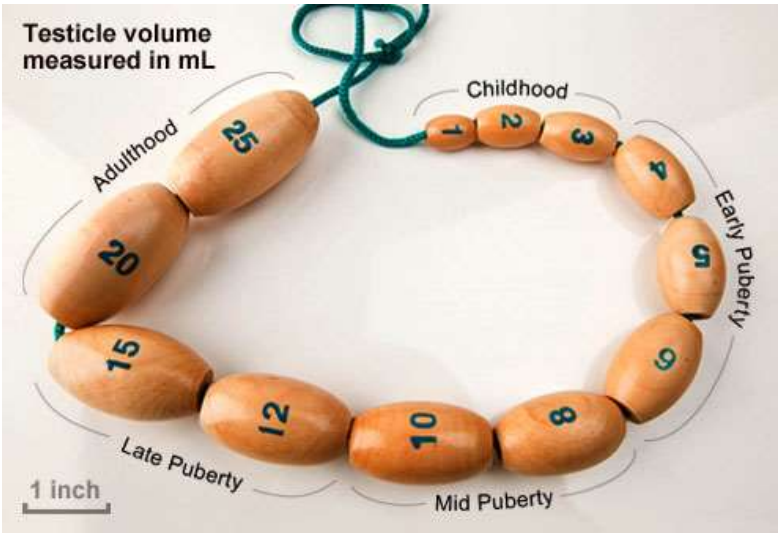
- Testicular failure results in impaired spermatogenesis and variable gonadotropin levels.
- Causes include hemochromatosis, sickle cell disease, thalassemia, glucocorticoid treatment and alcoholism.

TESTOSTERONE DEFICIENCY?

SIGNS & SYMPTOMS

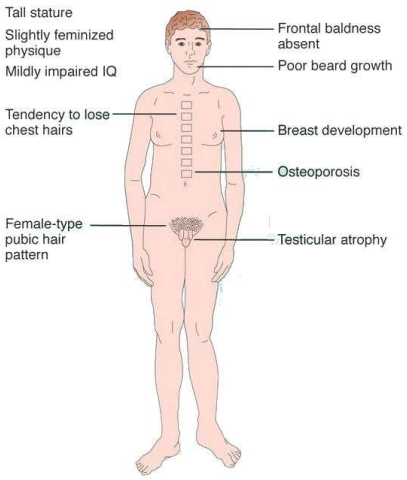
- Increased weight & body fat
- Decreased muscle mass & strength
- Sleep disturbances
- Mood swings/Irritability/Withdrawn
- Anxiety
- Loss of competitive edge
- Low libido
- Erectile Dysfunction
- Loss of spontaneous erections
- Low energy/fatigue
- Hot flushes/sweats
- Loss of body hair
- Breast enlargement
- Loss of testicular volume
- Poor blood sugar control
- Low velocity fractures & Decreased BMD
- Loss of height

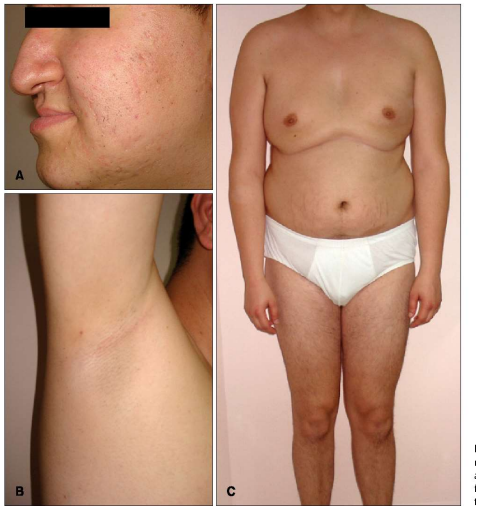




TESTICULAR VOLUME

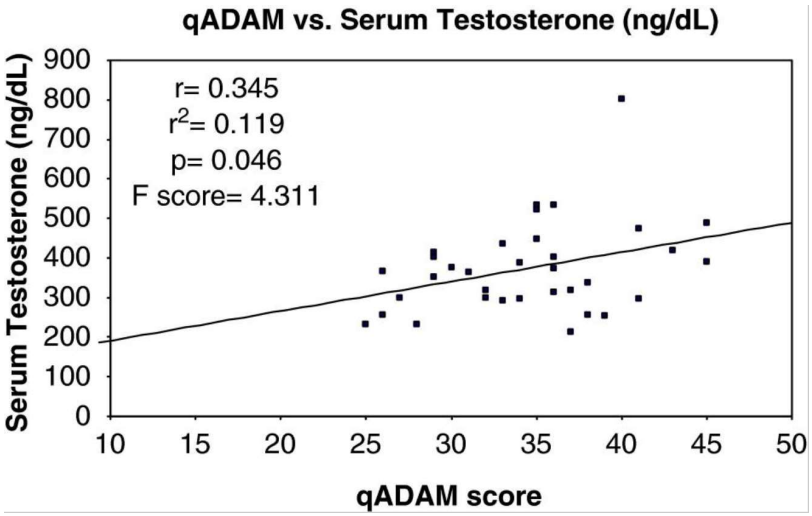
FINDINGS IN KLINEFELTER'S SYNDROME





ADAM QUESTIONNAIRE

		YES	NO
1	Do you have a decrease in libido (sex drive)?		
2	Do you have a lack energy?		
3	Do you have a decrease in strength and/or endurance?		
4	Have you lost height?		
5	Have you noticed a decreased "enjoyment of life"?		
6	Are you sad and/or grumpy?		
7	Are your erections less strong?		
8	Have you noticed a recent deterioration in your ability to play sports?		
9	Are you falling asleep after dinner?		
10	Has there been a recent deterioration in your work performance?		



THE qADAM QUESTIONNAIRE CORRELATES PREDICTABLY WITH SERUM TESTOSTERONE, INDICATING THAT IT HAS POTENTIAL AS A SCREENING AS WELL AS A DIAGNOSTIC TOOL.

THE qADAM CORRELATED WITH OTHER INSTRUMENTS OF SEXUAL & HORMONAL FUNCTION, SUCH AS THE EPIC AND THE SHIM QUESTIONNAIRES.

THE QUANTITATIVE ADAM QUESTIONNAIRE: A NEW TOOL IN QUANTIFYING THE SEVERITY OF HYPOGONADISM: INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, JANUARY 2010
O MOHAMED, R E FREUNDLICH, H K DAKIK, E D GROBER, B NAJARI, L I LIPSHULTZ, AND M KHERA.

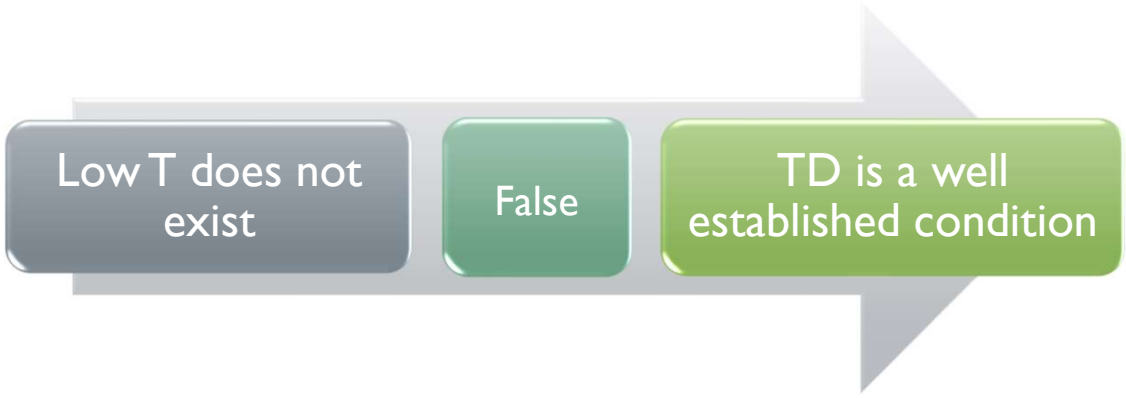
QUANTITATIVE ADAM QUESTIONNAIRE (qADAM)

	Terrible (1)	Poor (2)	Average (3)	Good (4)	Excellent (5)
How would you rate your libido (sex drive)?					
How would you rate your energy level?					
How would you rate your strength/endurance?					
How would you rate your enjoyment of life?					
How would you rate your happiness level?					
How strong are your erections? 1=extremely weak, 5= extremely strong					
How would you rate your work performance over the past 4 weeks?					
How often do you fall asleep after dinner? 1 (never), 2 (1-2/wk), 3 (3-4/wk), 4 (5-6/wk), 5 (every night)					
How would you rate your sports ability over the past 4 weeks?					
How much height have you lost? 1 (2"or more), 2 (1.5-1.9"), 3 (1-1.4"), 4 (05.-0.9"), 5 (none-0.4")					

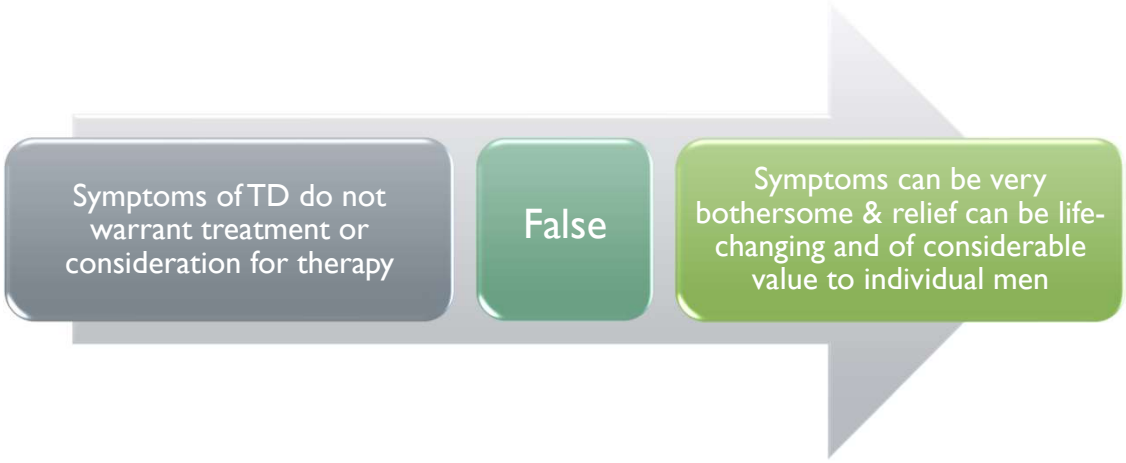
INTERNATIONAL PROSTATE SYMPTOM SCORE (I-PSS)

	Not at all 0	Less than 1 in 5 1	Less than ½ the time 2	About ½ the time 3	More than ½ the time 4	Almost always 5	Your Score
How often have you had the sensation of not emptying your bladder?							
How often have you had to urinate less than every two hours?							
How often have you found you stopped and started again several times when you urinated?							
How often have you found it difficult to postpone urination?							
How often have you had a weak urinary stream?							
How often have you had to strain to start urination?							
	None	1 time	2 times	3 times	4 times	5 times	
How many times did you typically get up at night to urinate?							
	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?							

HORMONOPHOBIA

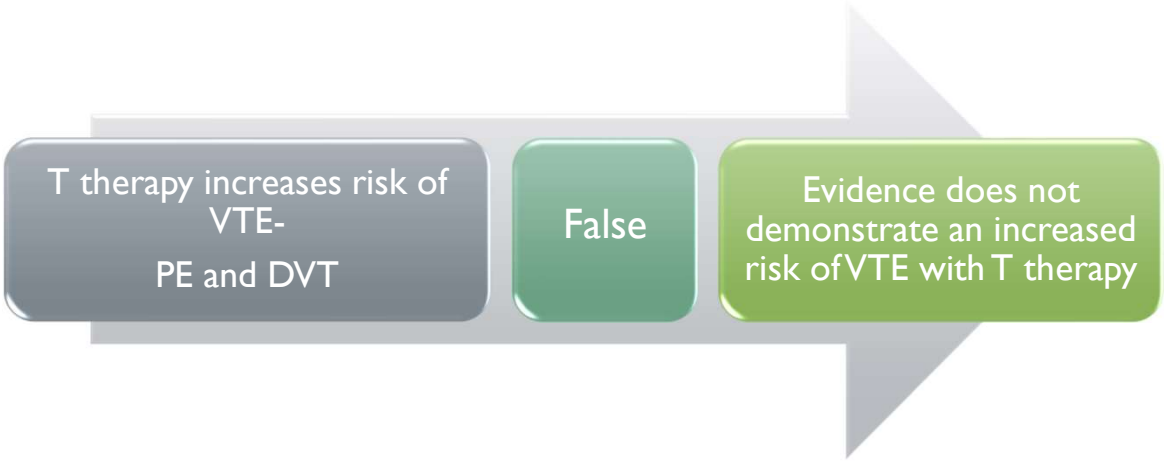


HORMONOPHOBIA

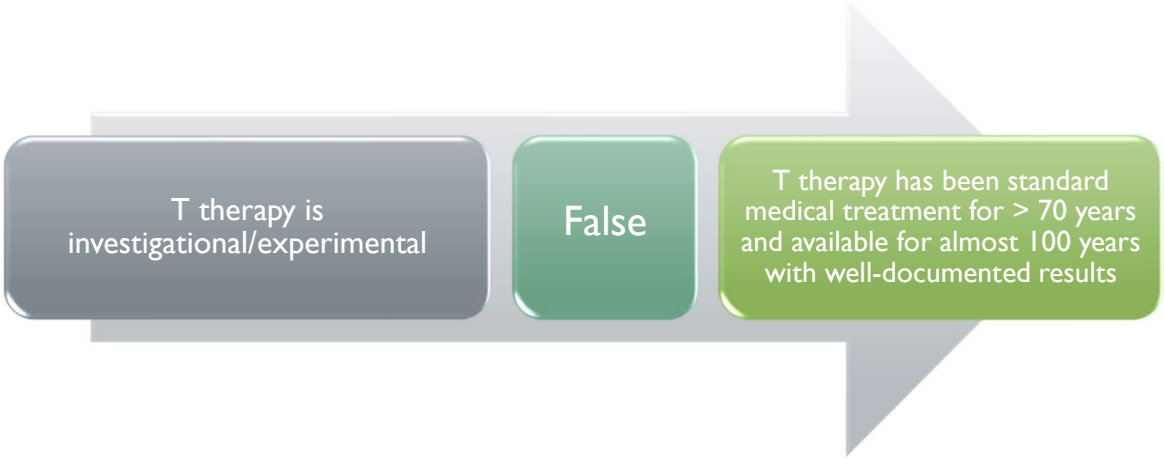


HORMONOPHOBIA

HORMONOPHOBIA



HORMONOPHOBIA



HORMONOPHOBIA

Declines in testosterone represent normal aging and do not merit treatment

False

Age alone has little impact on T levels. No justification to single out TD as not deserving of treatment in comparison to all other age-related medical conditions (HTN, CVD, OA, etc.)

BENEFITS OF TESTOSTERONE THERAPY

WHAT YOU CARE ABOUT

- Improved BS control
- Improved BP control
- Decreased risk of dementia
- Improved CV health
- Maintenance of or Improved BMP
- Improved anemia

WHAT YOUR PATIENTS CARE ABOUT

- Increased vitality
- Increased energy
- Increased mental clarity
- Improved libido
- Improved sexual function
- Improved sleep
- Improved body composition
- Decreased joint and muscle pain
- Faster exercise recovery

WHY CONSIDER REPLACING TESTOSTERONE?

- Relief of symptoms
- Improved quality of life, relationships, self-esteem, mood, and mental & physical performance
- Decrease body fat and improve blood sugar control through regulation of insulin, fat metabolism & glucose
- Cardiovascular disease
  - Low T levels correlate w/increased risk of atherosclerosis
  - T therapy correlates w/a decrease in the thickness of the carotid intima
  - In men with known heart disease, T therapy improved cardiac function
  - No evidence that treatment with testosterone increases cardiovascular disease risk
- Improved anemia
- Low testosterone level is associated with an increased risk of prostate cancer
- Low testosterone level is associated with an increased risk of all cause mortality

FUNDAMENTAL CONCEPTS REGARDING TESTOSTERONE DEFICIENCY AND TREATMENT: INTERNATIONAL EXPERT CONSENSUS RESOLUTIONS

- TD is a well-established, significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life.
- Symptoms and signs of TD occur as a result of low levels of testosterone and may benefit from treatment regardless of whether this is an identified underlying etiology.
- TD is a global public health concern.
- Testosterone therapy for men with TD is effective, rational and evidence-based.
- There is no T concentration threshold that reliably distinguishes those who will respond to treatment from those who will not.
- There is no scientific basis for any age-specific recommendations against the use of T therapy in adult men.
- The evidence does not support increased risks of cardiovascular events with T therapy.
- The evidence does not support increased risk of prostate cancer with T therapy.
- The evidence supports a major research initiative to explore possible benefits of T therapy for cardiometabolic disease, including diabetes.

TESTOSTERONE THERAPY IN MEN WITH HYPOGONADISM: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE

- Recommend against routine screening in asymptomatic men.
- Diagnose men with symptoms & signs of TD and unequivocally and consistently low serum T < 300 ng/dL and/or low free T concentrations.
- Recommend distinguishing between primary (testicular) & secondary (pituitary-hypothalamic) causes by measuring LH & FSH levels.
- Recommend further evaluation of hypothalamic, pituitary, and/or testicular dysfunction as needed.
- Recommend T therapy to induce and maintain secondary sex characteristics and correct symptoms of TD.
- Recommend against offering T therapy in all men > 65 years old with TD. If has bothersome symptoms or clinical signs, treat as you would any other patient.
- Recommend against T therapy for the sole purpose of improving glycemic control.
- Recommend considering short-term T therapy in HIV-infected men with TD & weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and encourage lean muscle mass gain.
- Recommend evaluating the patient's response after initiation of therapy to assess whether the patient has responded to treatment, is experiencing any adverse side effects & is complying with treatment as prescribed.
- Recommend counseling men 40-69 years old who are at increased risk of PCa (AA men & men with first degree relative with PCa) encourage monitoring. Shared decision making.
- Recommend counseling men 55 to 69 years old who are at average risk of PCa and who have a life expectancy > 10 years, regarding options for PCa screening. If patient choses to screen, do so before starting T therapy, then at 3 & 6 months, then annually.

TESTOSTERONE THERAPY IN MEN WITH HYPOGONADISM: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE

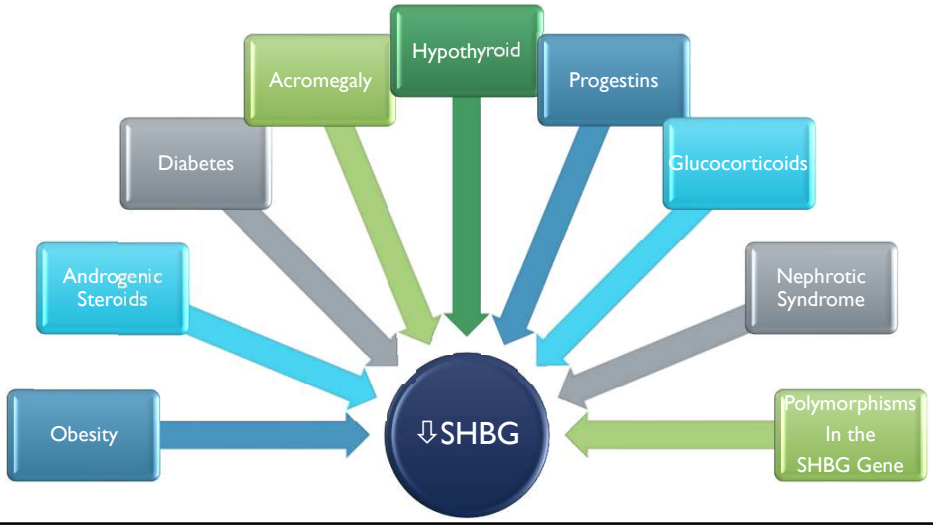
Recommend AGAINST Testosterone Therapy	Urology Consult for Men on Testosterone Therapy	Prostate Cancer Screening for men on Testosterone Therapy
Men planning fertility soon **Men** with breast or PCa **Palpable** prostate nodule **If PSA** level > 4 ng/mL, **If PSA** > 3ng/mL w/high risk of PCa w/o urology evaluation **Elevated** hematocrit **Untreated** severe OSA **Severe** unevaluated LUTS **Uncontrolled** Heart Failure **AMI** or CVA in the past 6 months **Thrombophilia**	**PSA** increases 1.4 ng/mL above baseline **PSA** rises above 4.0 ng/mL **Prostatic** abnormality detected on DRE	Following the initial 12 months of therapy, shared decision making based on: • Age • Life expectancy • Personal risk factors • Race

FIRST THINGS FIRST

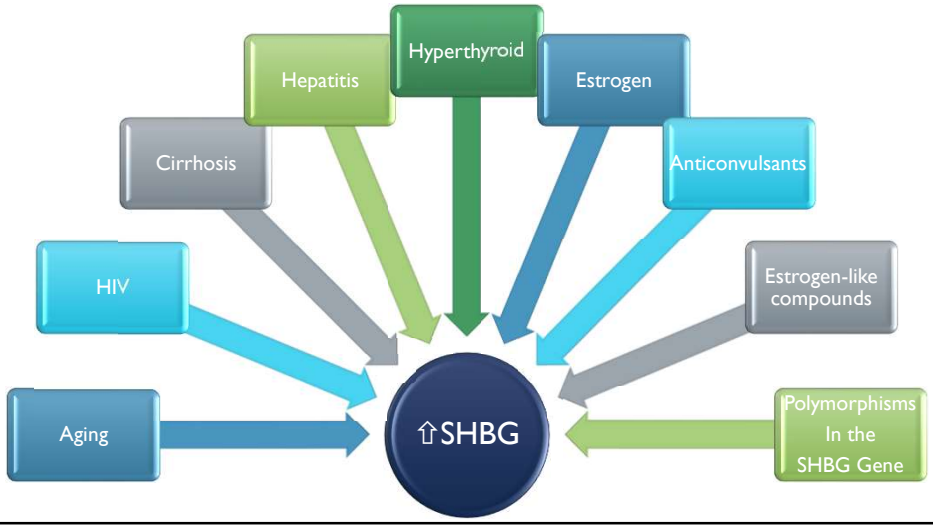
SCREENING FOR TESTOSTERONE DEFICIENCY

Choose a lab that only uses approved assays that are consistent with the **CDC Hormone Standardization Program for Testosterone** • Test range around 265 – 915 ng/dL	Testing should be performed in the morning (preferably before 10 am) after at least 6 hours of fasting • Food intake and glucose suppress testosterone production	Order a Free T on men who have • a condition that alters SHBG levels • an initial total testosterone at or near normal range (200-400 ng/dL)	Free T is determined either directly from equilibrium dialysis assays or by calculations that use TT, SHBG & albumin concentrations • Do not use labs who use direct analog-based free T immunoassays, as they are inaccurate

CONDITIONS WHEN MEASUREMENTS OF FREE TESTOSTERONE SHOULD BE ORDERED



CONDITIONS WHEN MEASUREMENTS OF FREE TESTOSTERONE SHOULD BE ORDERED



CLASSIFICATION OF HYPOGONADISM AND CAUSES OF PRIMARY HYPOGONADISM

Organic

- Klinefelter's Syndrome
- Cryptorchidism
- Myotonic dystrophy
- Anorchia
- Some cancers
- Chemotherapy
- Testicular irradiation/damage
- Orchiectomy
- Orchitis
- Testicular trauma, including torsion (can cause late presentation)
- Advanced age

CLASSIFICATION OF HYPOGONADISM AND CAUSES OF PRIMARY HYPOGONADISM

Functional

- Medications (androgen synthesis inhibitors)
- End-stage renal disease

CLASSIFICATION OF HYPOGONADISM AND CAUSES OF SECONDARY HYPOGONADISM

Organic

- Hypothalamic-pituitary tumor/radiation or surgery
- Iron overload syndromes (Hemochromatosis)
- Infiltrative/destructive disease of Hypothalamus/Pituitary
- Idiopathic hypogonadotropic hypogonadism

CLASSIFICATION OF HYPOGONADISM AND CAUSES OF SECONDARY HYPOGONADISM

Functional

- Hyperprolactinemia
- Opioids, methadone, long-acting analgesics, anabolic steroid use, glucocorticoids
- Alcohol and marijuana abuse
- Systemic illness (current illness i.e., DM & past infections, i.e., measles)
- Nutritional deficiency/excessive exercise/rapid weight loss
- Severe obesity (⇧ estrogen ⇩ testosterone)
- Obstructive sleep apnea
- Organ failure (liver, heart, and lung)
- Comorbid illnesses associated with aging (combined primary & secondary)

THINGS TO CONSIDER

Avoid testing men for TD who have recently had or are recovering from a severe illness.

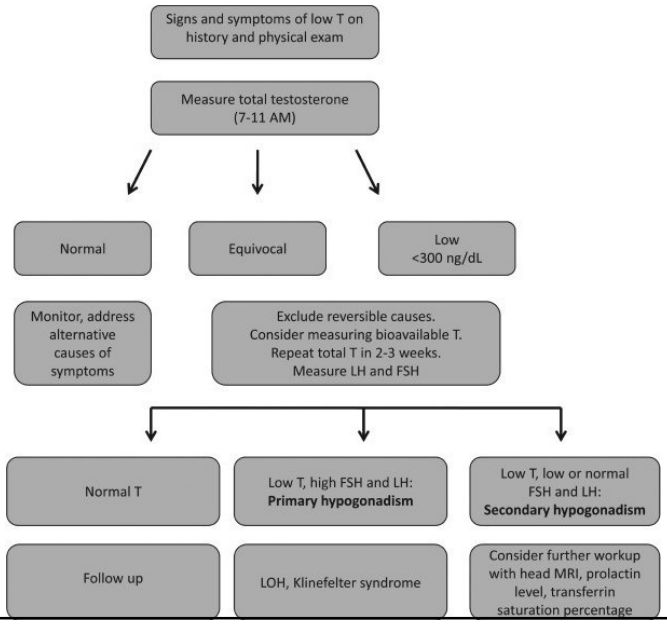
Avoid testing for TD in men who are using short-term course of medications that suppress T levels.

Long-term use of medications that suppress testosterone concentrations may be balanced with T therapy

Avoid treating men who are planning fertility in the near future

Absolute Contraindications to Testosterone Therapy

Metastatic prostate or breast cancer	A HCT of 55% or greater	Sensitivity to T therapy



GUIDELINES AT A GLANCE

* Testicular exam, noting size & consistency.
Note distribution & amount of body hair.
Assess the prostate w/DRE & PSA.
Penile size is not affected by post-pubertal TD.

CLINICAL PEARLS

FSH, LH, and prolactin are measured to determine Primary vs Secondary Causes

- If FSH & LH levels are elevated, this suggests a primary testicular cause. FSH > LH
- If FSH & LH levels are low or normal, a hypothalamic or pituitary cause should be considered
- Elevated prolactin level suggests that further investigation of the pituitary gland is warranted

Anabolic steroid abuse (AAS) withdrawal syndrome.

- Attempt to salvage endogenous testosterone production
- Most men will recover within 6 -12 month without intervention, but hCG or clomiphene can be used if fertility is desired or symptoms are severe

If DVT occurs, a complete evaluation for underlying clotting disorder should be ordered.

- NO evidence of ↑ risk of VTE with T therapy

CLINICAL PEARLS & TROUBLESHOOTING

CVD	Baseline BP checks, repeat Q3-6 months, then annually.
High Estrogen	Due to aromatization of testosterone into estrogen. Can cause irritability/mood swings, weight gain & gynecomastia. Diindolemethane (DIM) 300 mg daily (broccoli & other cruciferous vegetables) or anastrozole 1 mg per week.
Erythrocytosis	Baseline HCT, repeat at 3 & 6 months, then annually. Hold T therapy if ≥ 55%. Recheck until HCT normal, then restart T therapy at a lower dose.

CLINICAL PEARLS & TROUBLESHOOTING

Fluid Retention	H & P. Stop T therapy if HF is uncontrolled. Diuretic, compression and elevation to address peripheral edema from fluid shift.
BPH	Patient questionnaire & history. Refer to urology if I-PSS+ above 19. Stop T therapy.
Prostate Cancer	Baseline DRE & serum PSA. Repeat at 3 & 6 months on Testosterone. Refer to Urology: PSA rises above 4 ng/mL Abnormal DRE PSA rises > 1 ng/mL in the first 6 months PSA rises > 1.4 ng/mL/yr (use 6mo PSA) or PSA velocity >0.4 ng/mL/yr

CLINICAL PEARLS

Hepatotoxicity	LFTs are unnecessary with the use of gel, cream, pellet & IM Testosterone. Follow LFTs if oral anabolic alkylated T therapy.
Acne	H & P. Adjust dose or treat acne. Occurs because of conversion of 5-alpha reductase to DHT.
Infertility	H & P. Avoid T therapy if fertility is desired. Sperm count can go to zero.
OSA	Baseline H & P. Monitor HCT. Repeat at 3 & 6 months. Adjust pressure PRN. Optimally treating OSA does not result in recovery of Testosterone levels.
Gynecomastia & Breast Cancer	H & P. Review all medications. **Anti-androgens:** finasteride, bicalutamide. **Antibiotics:** isoniazid, ketoconazole, metronidazole. **Antihypertensives:** amlodipine, captopril, diltiazem, verapamil, nifedipine. **GI agents:** cimetidine, omeprazole. Complete sex hormone evaluation to evaluate excess estrogen from aromatization.

MRI of the sella with & w/o contrast in these conditions

- Total Testosterone < 150 ng/dL
- Hyperprolactinemia
- Low TSH
- Low LH & low FSH
- Vision changes
- Headaches
- Men with TD who are under 45

BPH with LUTS

- Unusual to observe worsening LUTS on Testosterone therapy
- Use an alpha blocker to address LUTS symptoms

Older Patients Receiving Testosterone Therapy

- Should treat at the full replacement dose to receive full benefits
- Testosterone Therapy can be used as monotherapy in men with high risk of fracture

CLINICAL PEARLS

CHOOSING THE RIGHT OPTION FOR INDIVIDUAL PATIENTS

Testosterone Cypionate	• Super-physiologic level → hypogonadal levels cause peaks & valleys & fluctuating sx • Avoid with cotton seed oil allergy. Redness/bruising at injection site common. • Tendency to significantly increase estrogen & HCT
Testosterone Cypionate	• Total dose (200 mg/mL Q14 days) split into BIW-TIW, ↓ aromatization & ↓HCT • Test peak levels after 2 months on day 3 before next injection. • Optimum level is 400-1100. • If Estradiol > 5% of TT, aromatization should be addressed w/DIM or anastrozole
Patches	• Diurnal rhythm • Adhesive is often bothersome and some men have trouble with rolling edges • Change location of patch daily (back, thigh, upper arm)
Pellets	• Applied daily. Dose is 2-10 mg/day. May require 2 patches/day. • Optimum level 400-930. • Test after 14 days of initiation of treatment or dosage change.

CHOOSING THE RIGHT OPTION FOR INDIVIDUAL PATIENTS

Gels & Creams	• Commercial and compounded products. Gel is alcohol based & creams are safflower oil based & can cause allergy • Must be mindful of risk of transference to others in the household. Wash hands before/after application. Cover. • Gel is applied to the arm, axilla or thigh. The gel should be allowed to dry completely, taking care not to shower, sweat, or otherwise remove the gel before it is absorbed 4-6 hrs after application. Individual towels & clothing should be used and never shared. Shower or wash before skin to skin contact with others.
Gels & Creams	• Applied QD-BID to maintain consistent level. Dose is 25-100 mg daily. Optimum level 400-1050. • Only 10% of gel is absorbed 25 mg has effective dose of 2.5 mg) • Test after 14 days. Do not apply on the day of test.
Pellets	• Implanted into fatty layer of skin Q4-6 months. Dosing calculators. Optimum level 400-1100. • Test at 1 month for peak and again at 90 days. Once dose determined, annual testing.
Pellets	• Consistent micro doses released daily until pellet dissolves completely. Hormone plus steric acid. • Placed under the skin with a small incision. Require in-office procedure every 4-6 months • Small risk of infection and pellet extrusion

CHOOSING THE RIGHT OPTION FOR INDIVIDUAL PATIENTS

Buccal

- The tab is placed in the mouth and is held in place above the front teeth. Gum irritation & taste changes are common.
- Increases Testosterone & Dihydrotestosterone
- BID dosing. Check liver enzymes.

Buccal

- Applied to gum. Rotate area of application. \
- 30% will experience oral irritation.
- Dose is 30 mg BID.
- Optimum level is 400-800.
- Test after 14 days just before applying next tab.

CHOOSING THE RIGHT OPTION FOR INDIVIDUAL PATIENTS

- Lifestyle
  - Dietary changes to include mostly lean proteins, nuts, legumes, vegetables and fruits.
  - Portion control.
  - Regular aerobic exercise and resistance/weight training
  - Dietary and/or supplemental Zinc
  - Weight reduction
  - Sufficient sleep
  - Decrease stress/cortisol
  - DHEA 25-50 mg QD-BID
  - Vitamin D level optimization
  - Omega 3 intake
  - CoQ10 if taking a statin
  - Possible boost with ashwagandha & ginger
  - Avoid estrogen-like compounds (BPA, parabens & other chemicals found in some types of plastic)

INITIAL LABS

- Total Testosterone (Fasting AM draw)
- Estradiol
- CBC
- PSA
- DHEA-S
- Free Testosterone and SHBG in men over 60 & if SHBG abnormality suspected
- Consider LH, FSH, Prolactin
- Consider CMP to evaluate for existing renal or kidney disease
- Consider A1C and Lipid profile to evaluate for vasculopathy

FOLLOW-UP LABS

- Total Testosterone (Fasting AM draw)
- Estradiol
- CBC
- PSA

CASE: AG

- 38 year old Caucasian male presents on gel T therapy
  - Pre-treatment TT was 310 ng/dL and 298 ng/dL. Calculated Free T was low, PSA 06.
- Pre-treatment symptoms included fatigue, depression and low libido
  - Symptoms have not improved on 8 months of T therapy
- PE: Height is 6 feet with a BMI of 42
  - Beard, no gynecomastia, no nipple discharge, normal penis, testes are 12 mL bilaterally
- TT obtained in the afternoon in the non-fasted state was 310 ng/dL, HCT 44%
- Repeat testing:
  - AM TT on a subsequent day was 295 ng/dL with a low Free T of 28 ng/dL & ⇩ SHBG
  - FSH and LH are in the very low normal range
  - Sperm analysis reveals a low sperm count

CASE: AG

1. Continue testosterone therapy at the current dose.
2. Continue testosterone therapy at the current dose, but order MRI of the sella.
3. Increase testosterone gel therapy or change type of testosterone treatment.
4. Discontinue testosterone therapy and reassess the gonadal axis in one month.

CASE: AG

- Decides not to continue T therapy because he desires fertility
- Protocol of hCG therapy started at 2000U IM MWF
- Low carbohydrate diet/weight loss advised
  - Serum testosterone in 6 weeks was 375 ng/dL, so dose of hCG was increased to 4000U IM MWF. Repeat TT was 683 ng/dL .
  - When TT is between 400-800 ng/dL, obtain a sperm analysis every 1-3 months until total sperm count is 5-10 million/mL after 6 months of adequate T production.
  - Maintain TT with stable hCG dose and continue to follow SA every 1-3 months. Repeat SA Q3 months were in the normal range and pregnancy was achieved at 14 months.
- Anticipate recovery of FSH and LH activity in one month in men between 18-50 with normal hormone potential (IM Testosterone Cypionate can slow recovery)
  - Almost all men will recover within one year, including anabolic steroid abuse
  - Sperm production lags behind FSH and LH recovery by 3-6 months

CASE: MR

- 42 yo Latino male presents with fatigue, sleep disturbances, low libido, ED, lack of spontaneous erections, concentration difficulties, loss body hair, recessive hairline on the scalp, and loss of muscle definition.
- VS normal, including BMI of 24.1
- Denies any significant past medical history, drug or alcohol use.
- Initial labs
  - TT 245 ng/dL (300-890)
  - Free T 6.9 ng/dL (4.8 – 25.7)
  - ⇩SHBG 15.2 (16.5 – 55.9)

CASE: MR

- Follow-up AM labs
  - FSH <0.3 (1.5 – 12.5)
  - LH <0.1 (1.2-8.6)
  - Prolactin 18.8 (4.0-26.0)
  - TT 110 ng/dL (300-890)
  - Estradiol <17 pg/mL (<60)
  - DHEA 205 ug/dL (82-455)
  - PSA 0.95
  - TSH 1.840 (0.4-4.100 with Free T4 1.13 (0.8-1.90) and Free T3 3.0 (2.2-4.2)

CASE: MR

- MRI of the sella with and w/o contrast
  - 6 x 4 x 6 mm circumscribed non-enhancing cyst noted in the left lateral posterior aspect of the pituitary gland
    - DDX Rathke's cleft cyst, tiny arachnoid cyst, and less likely a cystic microadenoma
    - Otherwise normal
    - Symptoms well controlled after 2 weeks on decadron

CASE: JT

- 65 yo AA male with symptomatic hypogonadism.
- Reports decreased libido, ED & decreased muscle strength
- PMH: Localized PCa with radical prostatectomy 6 years ago, margins were clear and F/U US PSA is undetectable, CAD, DVT after ankle surgery following fx (DVT occurred on the fractured leg), Osteopenia on DEXA scan
- PE is unremarkable 5'9" with BMI of 31
- Initial TT is very low at 158 ng/dL with increased FSH and LH (consistent with primary hypogonadism)

CASE: JT

1. Testosterone therapy is contraindicated.
2. Low dose replacement is safer than usual dose replacement for this patient.
3. Consideration of testosterone therapy should be delayed for 2 months.
4. He should be counseled about the controversy regarding testosterone therapy and CV disease.

CASE: JT

- DX with severe primary hypogonadism.
- He was counseled regarding the controversy surrounding T therapy and CV risk
  - Evidence is WEAK about CV risk and VTE.
  - Risk of recurrent AMI event is highest in the first month after an event, decreasing over 6 months
  - Seven studies to date with no change in number of events or with decreased number of AMI in treated cohort
  - Four studies have demonstrated a decrease in all cause mortality
  - US T Trial demonstrated no difference in number of CV events (AMI or Stroke) in either group after 1 year of T gel therapy vs placebo
    - Mean age was > 70 years of age
  - After counseling the patient, he decided to start topical gel T therapy and demonstrated an excellent response with TT of 532 ng/dL & holding

THE END

Thank you for your attention.

Questions?

- 1. Hj, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strengthofrecommendations.BMJ. 2004;328(7454):1490–1494.
- 2. Swiglo BA, Murad MH, Sch¨unemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab. 2008;93(3):666–673.
- 3. Guyatt GH, Sch¨unemann HJ, Djulbegovic B, Akl EA. Guideline panels should not GRADE good practice statements. J Clin Epidemiol. 2015;68(5):597–600.
- 4. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, Serrano V, Singh-Ospina N, Rodriguez-Gutierrez R, Salcido-Montenegro A, Benkhadra R, Prokop LJ, Bhasin S, Brito JP. The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: a systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Endocrinol Metab. 2018; 103(5):1745–1754.
- 5. Matsumoto AM, Bremner WJ. Testicular disorders. In: Melmed S, PolonskyKS,LarsenPR,KronenbergHM,eds.WilliamsTextbookof Endocrinology. 13th ed. New York, NY: Elsevier; 2016:688–777.
- 6. Bhasin S, Jameson JL. Disorders of the testes and male reproductive system. In: Kasper D, Fauci A, Longo D, Hauser S, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 19th ed. New York, NY: McGraw-Hill Education; 2015.
- 7. BhasinS,CunninghamGR,HayesFJ,MatsumotoAM,SnyderPJ, SwerdloffRS, Montori VM, Task Force: Endocrine Society. Testosteronetherapyinmenwithandrogendeficiencysyndromes: anEndocrineSocietyclinicalpracticeguideline.J ClinEndocrinol Metab. 2010;95(6):2536–2559.
- 8. Bhasin S, Travison TG, O'Brien L, MacKrell J, Krishnan V, Ouyang H, Pencina K, Basaria S. Contributors to the substantial variation in on-treatment testosterone levels in men receiving transdermal testosterone gels in randomized trials. Andrology. 2018;6(1):151–157.
- 9. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. J Clin Endocrinol Metab. 2009;94(3):907–913.
- 10. Wu FCW, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva F, Forti G, Giwercman A, Huhtaniemi IT, Kula K, Punab M, Boonen S, Vanderschueren D; European Male Aging Study Group. Hypothalamic–pituitary–testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab. 2008;93(7):2737–2745.
- 11. Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, WilliamsRE,ClarkRV,McKinlayJB.Prevalenceofsymptomatic androgen deficiency in men. J Clin Endocrinol Metab. 2007; 92(11):4241–4247.
- 12. WuFC,TajarA,BeynonJM,PyeSR,SilmanAJ,FinnJD,O'Neill TW,BartfaiG,CasanuevaFF,FortiG,GiwercmanA,HanTS,Kula K,LeanME,PendletonN,PunabM,BoonenS,VanderschuerenD, Labrie F, Huhtaniemi IT; EMAS Group. Identification of late-onset hypogonadalinmiddle-agedandolderlyman.NEnglJMed.2010; 363(2):123–135.
- 13. Finkelstein JS, Lee H, Burnett-Bowie SA, Pallais JC, Yu EW, Borges LF, Jones BF, Barry CV, Wulczyn KE, Thomas BJ, Leder BZ.Gonadalsteroidsandbodycomposition,strength,andsexual function in men. N Engl J Med. 2013;369(11):1011–1022.
- 14. FinkelsteinJS,LeeH,LederBZ,Burnett-BowieSA,GoldsteinDW, HahnCW,HirschSC,LinkerA,PerrosN,ServiasAB,TaylorAP, Webb ML, Youngner JM, Yu EW. Gonadal steroid-dependent effects on bone turnover and bone mineral density in men. J Clin Invest. 2016;126(3):1114–1125.
- 15. Bhasin S, Travison TG, Storer TW, Lakshman K, Kaushik M, Mazer NA, NguyenAH,DavdaMN,JaraH,AskiliA,AndersonS, Knapp PE, Hanks S, Mohammed N, Daou P, Miciek R, Ulloor J, Zhang A, Brooks B, Orwoll K, Hede-Brierley L, Eder R, Elmi A, Bhasin G, Collins L, Singh R, Basaria S. Effect of testosterone supplementation with and without a dual 5α-reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. JAMA. 2012;307(9):931–939.
- 16. Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB.Therelativecontributionsofaging,health,anddiseasetofactors to serum testosterone decline in men. J Clin Endocrinol Metab. 2007;92(2):549–555.
- 17. Ohlsson C, Wallaschofski H, Lunetta KL, Stolk L, Perry JR, Koster A, Petersen AK, Eriksson J, Lehtim¨ale T, Huhtaniemi IT, Hammond GL, Meggio M, Coviello AD, Ferrucci L, Heier M, Hofman A, Holliday KL, Jansson JO, K¨ah¨onen M, Karasik D, Karlsson MK, Kiel DP, Liu Y, Ljunggren O, Lorentzon M, Lyytik¨ainenLP,Metzinger7,Mellstr¨omD,MelzerD,Mikkonicl, Nauck M, Nilsson M, Penninx B, Pye SR, Vasan RS, Ramaswamy S, Rivadeneira F, Tajar A, Teumer A, Uitterlinden AG, Ulloor J, Völker U, V¨olzke H, Wichmann HE, Wu TS, Zhuang WV, Zin E, Wu FC, Ratskari O, Eriksson A, Bidlingmaier M, Harris TB, Murray A, de Jong FH, Murabito JM, Bhasin S, Vanderpui L, Haring R; EMAS Study Group. Genetic determinants of serum testosterone concentrations in men. PLoS Genet. 2011;7(10):e1002313.
- 18. BremnerWJ,VitielloMV,PrinzPN.Lossofcircadianrhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab. 1983;56(6):1278–1281.
- 19. Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serumtestosteroneandother reproductive and adrenal hormones in men. Clin Endocrinol (Oxf). 2007;67(6):853–862.
- 20. CaronisLM,DwyerAA,HaydenD, AmosF,PitteloudN,Hayes FJ. Abrupt decrease in serum testosterone levels after an oral glucoseloadinmen:implicationsforscreeningfortypogonadism. Clin Endocrinol (Oxf). 2013;78(2):291–296.
- 21. Lehtihet M, Arver S, Bartusevicine I, Pousette A. S-testosterone decrease afters mixed mealin healthymen independent of SHBG and gonadotrophin levels. Andrologia. 2012;44(6):405–410.
- 22. SprattDI,O'DeaLS,SchoenfeldD,ButlerJ,RaoPN,CrowleyWF Jr. Neuroendocrine-gonadal axis in men: frequent sampling of LH, FSH, and testosterone. Am J Physiol. 1988;254(5 Pt 1): E658–E666.
- 23. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: utility, limitations, and pitfalls in measuring testosteroneanEndocrineSocietypositionstatement.JClinEndocrinol Metab. 2007;92(2):405–413.
- 24. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A Reappraisal of testosterone's binding in circulation: physiological and clinical implications. Endocr Rev. 2017;38(4): 302–324.
- 25. Antonio L, Wu FCW, O'Neill TW, Pye SR, Ahern TB, Laurent MR, Huhtaniemi IT, Lean MEJ, Keevil BG, Rastrelli G, Forti G, Bartfai G, Casanueva FF, Kula K, Punab M, Giwercman A, Claessens F, Decallonne B, Vanderschueren D; European Male Ageing Study Study Group. Low free testosterone is associated with hypogonadal signs and symptoms in men with normal total testosterone. J Clin Endocrinol Metab. 2016;101(7):2647–2657.
- 26. VosPJ,MijnhoutGS,RondeelJMM,BaronW,GroeneveldPHP. Sex hormone binding globulin deficiency due to a homozygous missense mutation. J Clin Endocrinol Metab. 2014;99(9): E1798–E1802.
- 27. Anawalt BD, Hotaling JM, Walsh TJ, Matsumoto AM. Performance of total testosterone measurement to predict free testosterone for the biochemical evaluation of male hypogonadism. J Urol. 2012;187(4):1369–1373.

- 28. ZakharovMN,BhasinS,TravisonTG,XueR,UlloorJ,VasanRS, Carter E, Wu F, Jasuja R. A multi-step, dynamic allosteric model of testosterone's binding to sex hormone binding globulin. Mol Cell Endocrinol. 2015;399:190–200.
- 29. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999;84(10):3666–3672.
- 30. Sartorius G, Ly LP, Sikaris K, McLachlan R, Handelsman DJ. Predictive accuracy and sources of variability in calculated free testosterone estimates. Ann Clin Biochem. 2009;46(Pt 2): 137–143.
- 31. Travison TG, Vesper HW, Orwoll E, Wu F, Kaufman JM, Wang Y, Lapauw B, Fiers T, Matsumoto AM, Bhasin S. Harmonized reference ranges for circulating testosterone levels in men of four cohort studies in the United States and Europe. J Clin Endocrinol Metab. 2017;102(4):1161–1173.
- 32. AraujoAB, Dixon JM,Suarez EA, Murad MH,GueyLT, Wittert GA. Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011;96(10):3007–3019.
- 33. Bulliard J-L, Chiolero A. Screening and overdiagnosis: public health implications. Public Health Rev. 2015;36(1):8.
- 34. Wilson JMG. Current trends and problems in health screening. J Clin Pathol. 1973;26(8):555–563. 35. Bawor M,Bami H, Dennis BB, PlaterC, WorsterA, VarenbutM, Daiter J, Marsh DC, Steiner M, Anglin R, Coote M, Pare G, Thabane L, Samaan Z. Testosterone suppression in opioid users: a systematic review and meta-analysis. Drug Alcohol Depend. 2015;149:1–9.
- 36. Reid IR. Serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med. 1987;106(4):639–640.
- 37. CowardRM,RajanahallyS,KovacJR,SmithRP,PastuszakAW, Lipshultz LI. Anabolic steroid induced hypogonadism in young men. J Urol. 2013;190(6):2200–2205.
- 38. KanayamaG,HudsonJI,DeLucaJ,IsaacsS,BaggishA,WeinerR, Bhasin S, Pope HG Jr. Prolonged hypogonadism in males following withdrawal from anabolic-androgenic steroids: an underrecognized problem. Addiction. 2015;110(5):823–831.
- 39. Rasmussen JJ, Selmer C, Østergren PB, Pedersen KB, Schou M, Gustafsson F, Faber J, Juul A, Kistorp C. Former abusers of anabolic androgenic steroids exhibit decreased testosterone levels and hypogonadal symptoms years after cessation: a case-control study. PLoS One. 2016;11(8):e0161208.
- 40. Arver S, Sinha-Hikim I, Beall G, Guerrero M, Shen R, Bhasin S. Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss. J Androl. 1999;20(5):611–618.
- 41. Riggs BL, Khosla S, Melton LJ III. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev. 2002;23(3):279–302.
- 42. MorleyJE,CharltonE,PatrickP,KaiserFE,CadeauP,McCready D, Perry HM III. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000;49(9): 1239–1242.
- 43. Moore C, Huebler D, Zimmermann T, Heinemann LA, Saad F, Thai DM. The Aging Males' Symptoms scale (AMS) as outcome measure for treatment of androgen deficiency. Eur Urol. 2004; 46(1):80–87.
- 44. Smith KW, Feldman HA, McKinlay JB. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. Clin Endocrinol (Oxf). 2000;53(6):703–711.
- 45. Gelhorn HL, Dashiell-Aje E, Miller MG, DeRogatis LR, Dobs A, Seftel AD, Althof SE, Brod M, Revicki DA. Psychometric evaluation of the Hypogonadism Impact of Symptoms Questionnaire. J Sex Med. 2016;13(11):1737–1749.
- 46. O Mohamed,[1] R E Freundlich,[1] H K Dakik,[1] E D Grober,[2] B Najari,[3] L I Lipshultz,[1] and M Khera The quantitative ADAM questionnaire: a new tool in quantifying the severity of hypogonadism. Int J Impot Res. 2010 Jan; 22(1): 20–24.