# A Primary Care Approach to the Evaluation and Treatment of Male Hypogonadism

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# Learning Objectives

1. Identify patients with an increased likelihood of experiencing male hypogonadism based on their clinical presentation and/or risk factors
2. Outline the evaluation to diagnose and classify male hypogonadism
3. Consider the indications, benefits, contraindications, and potential risks of testosterone therapy to determine which patients are appropriate candidates
4. Individualize testosterone treatment according to the distinct clinical profiles of the available testosterone formulations as well as each patient's preferences and healthcare goals

# Section 1

## Why Male Hypogonadism Matters

# Male Hypogonadism or Testosterone Deficiency (TD)

## DEFINITION

- A clinical syndrome characterized by deficiency of testosterone (T) and/or spermatozoa
- Diagnosis requires symptoms of low T *and* measured low T

## ETIOLOGY

- Pathology at 1 or more levels of the hypothalamic-pituitary-testicular axis

## CLASSIFICATION

- Primary: defect at testicular level
- Secondary: defect at the hypothalamus or pituitary

Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

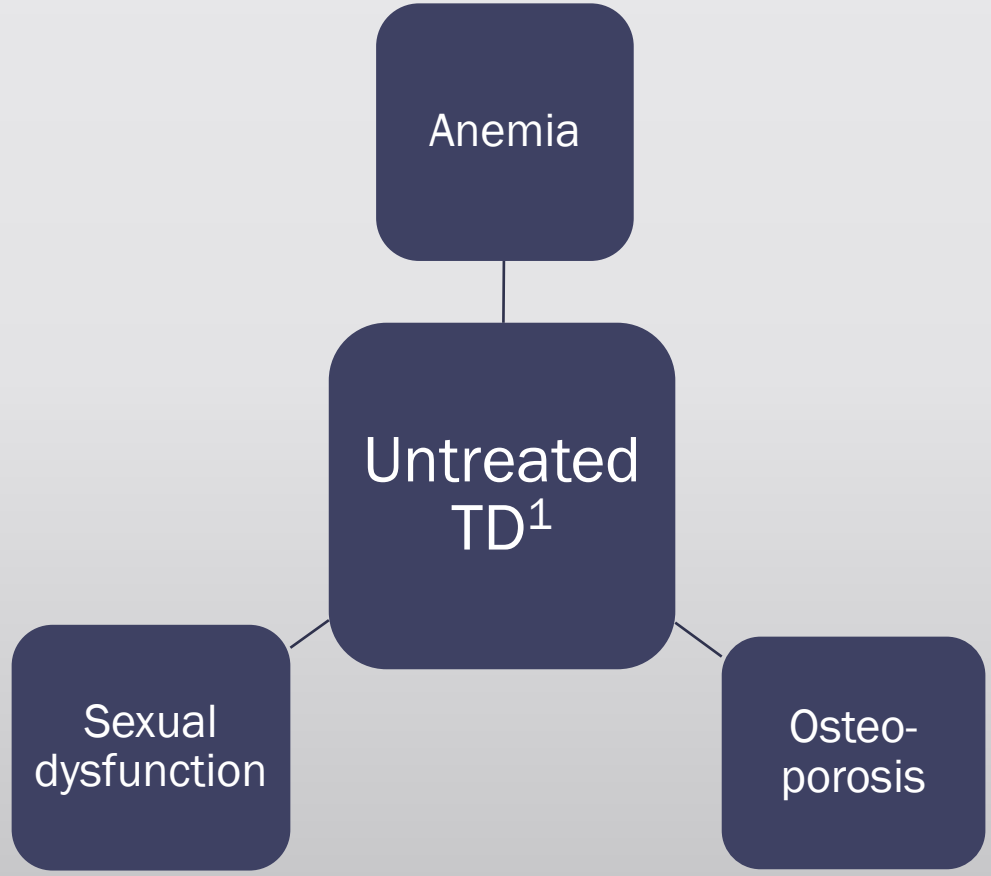
# Testosterone Deficiency: How Common Is It?

- Low levels of testosterone increases with age: about 35% of males >45 years of age have low measured testosterone (not necessarily symptomatic)[1]
- Symptomatic testosterone deficiency prevalence estimated at ~6%-12% of healthy males ages 40-70[2]
- Associated with obesity or type 2 diabetes mellitus (T2DM), affecting 30%-50% of males with these diagnoses[1]
- Will be increasingly prevalent in our growing elderly population[3]

1. Endocrine Society. Accessed June 1, 2023. https://www.endocrine.org/patient-engagement/endocrine-library/hypogonadism 2. Rivas AM et al. *Proc (Bayl Univ Med Cent).* 2014;27(4):321-324. 3. Dandona P. *Int J Clin Pract.* 2010;64(6):682-696.

# Failure to Treat Testosterone Deficiency (TD)

- In addition to symptoms from TD causing patients distress, untreated TD may predispose to long-term health problems[1]
- TD associated with increased risk of all-cause and cardiovascular death, although between-study heterogeneity is noted[2]




1. Al-Sharefi A. *Br J Gen Pract.* 2020;70(696):364-365. 2. Araujo AB. *J Clin Endocrinol Metab*. 2011;96(10):3007-3019.

# Section 2

## Evaluation for Testosterone Deficiency

# Recognizing TD Can Be Challenging

## SIGNS AND SYMPTOMS

- Often nonspecific
- May overlap with symptoms of concurrent conditions, such as obesity, T2DM

## PRESENTATION

Affected by:

- Age
- Severity and duration of testosterone deficiency
- Variations in androgen sensitivity
- Previous testosterone therapy

Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# Signs and Symptoms Suggestive of TD

## SPECIFIC

- Incomplete or delayed sexual development
- Loss of axillary and pubic hair
- Small testes (<6 mL)

## SUGGESTIVE

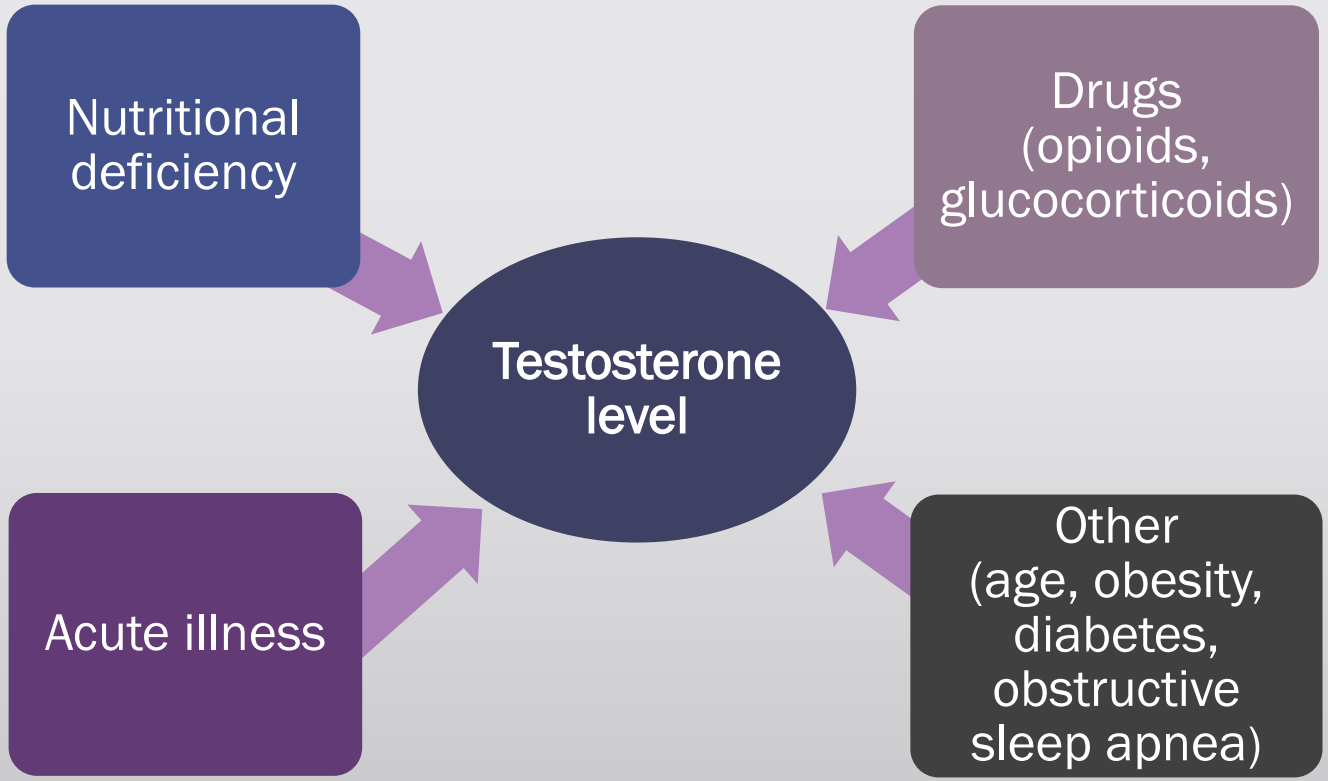
- Reduced libido
- Decreased spontaneous erections/erectile dysfunction
- Gynecomastia
- Low sperm count
- Low bone mineral density (BMD)
- Hot flashes

## NONSPECIFIC

- Decreased energy
- Depressed mood
- Poor concentration
- Sleep disturbance
- Mild unexplained anemia
- Reduced muscle bulk
- Increased body fat

Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# Modulators of Testosterone Level




When investigating low testosterone levels, include evaluation to exclude:

- Systemic illness
- Eating disorders
- Excessive exercise
- Sleep disorders
- Use of recreational drugs
- Use of certain medications, like androgen deprivation therapy (ADT)

1. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744. 2. Smith SJ, et al. *Adv Nutr*. 2021 Jun 1;12(3):744-765.

# Patient Findings Rendering Increased Risk of TD[1,2]

Consider measuring **total testosterone** in patients with these findings even in the absence of symptoms or signs associated with testosterone deficiency

| | |
|---|---|
| Unexplained anemia | Bone density loss |
| Alcohol/marijuana abuse | Chronic narcotic, anabolic steroid use |
| Diabetes | Male infertility |
| Exposure to chemotherapy | Pituitary dysfunction |
| Exposure to testicular radiation | Chronic corticosteroid use |
| End-stage renal disease | HIV/AIDS with weight loss |
| Organ failure | Comorbid illness associated with aging |

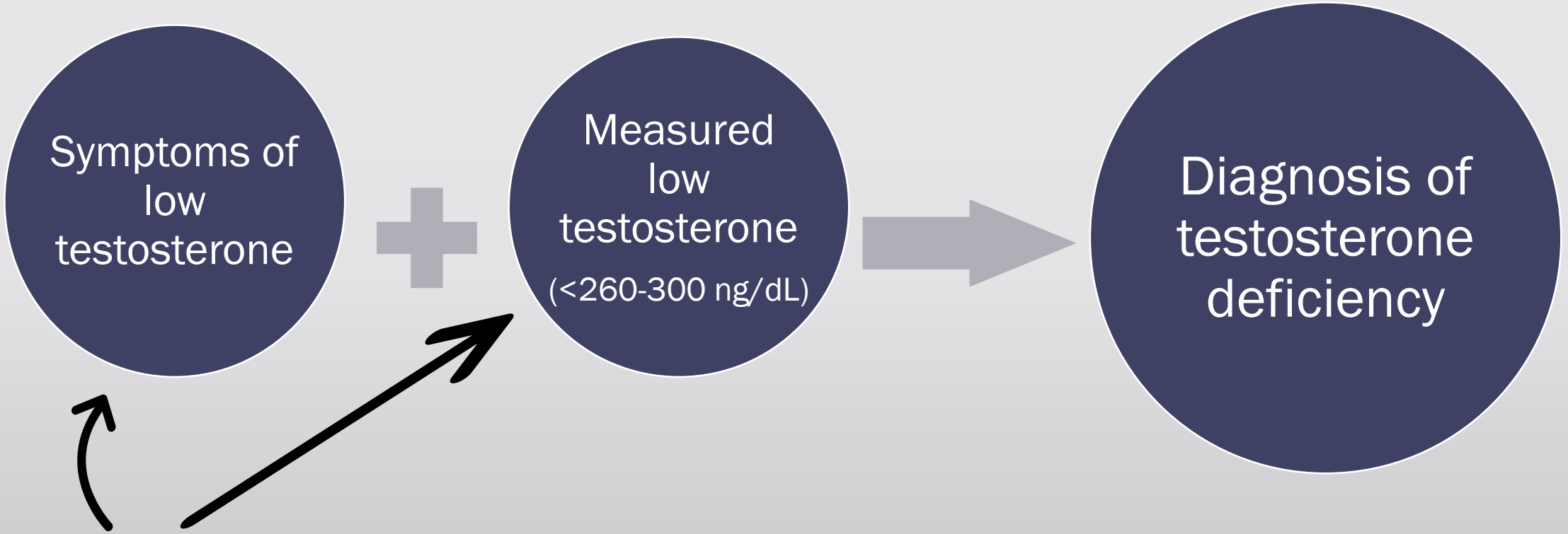
1. Mulhall JP. *J Urol.* 2018;200:423-432. 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# Targeted Physical Exam for Signs of TD

- General body habitus
- Virilization status (body hair patterns and amounts in androgen-dependent areas)
- Body mass index and waist circumference
- Presence of gynecomastia
- Testicular evaluation for presence, size, consistency, masses
- Varicocele presence
- Prostate size and morphology

Mulhall JP. *J Urol.* 2018;200:423-432.

# Diagnosis of Testosterone Deficiency[1,2]




Both are required to correctly make the diagnosis of testosterone deficiency

1. Mulhall JP. *J Urol.* 2018;200:423-432. 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# Endocrine Society/AACE Clinical Practice Guideline

## GUIDANCE

- Measure testosterone levels of men with any of the primary or other symptoms suggestive of hypogonadism

## PRIMARY SYMPTOMS

- Reduced libido
- PDE5 inhibitor failure for erectile dysfunction
- Reduced muscle mass
- Depressed mood
- Decreased energy
- Low bone mass

## SUGGESTIVE

- Incomplete sexual development, aspermia
- Gynecomastia
- Loss of body hair
- Small testes
- Mild anemia
- Hot flashes

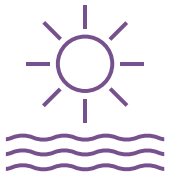
Dandona P. *Int J Clin Pract. 2010;64(6):682-696.*

# Measuring for Testosterone Deficiency

## Consensus Approach

Total testosterone <260-300 ng/dL supports testosterone deficiency[1,2]

Measure testosterone with an accurate and reliable method[2]



Measure testosterone during the morning peak after an overnight fast[1,2]

Confirm low testosterone concentrations with repeat measurement[1,2]

1. Mulhall JP. *J Urol.* 2018;200:423-432. 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# What's the Deal with Free Testosterone?

**Total testosterone = Unbound (free) testosterone + Protein-bound testosterone**

- Most T is bound to sex hormone-binding globulin (SHBG) and albumin proteins
- Measure free T in men with conditions that alter SHBG levels or have total T concentrations that are borderline low (eg, 200-400 ng/dL)
- Like measurement of total T, free T measurements are subject to interassay variability

## Decreased SHBG

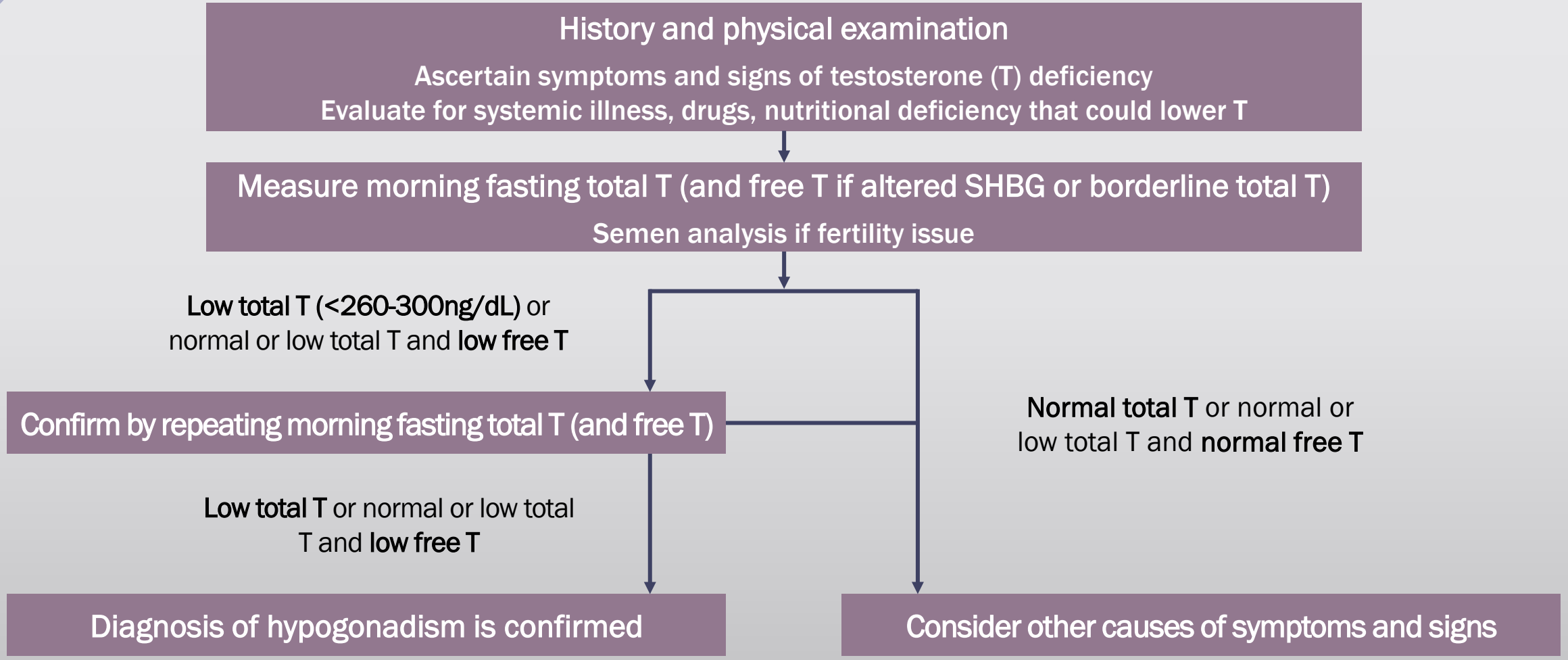
- Obesity
- Diabetes
- Use of glucocorticoids
- Nephrotic syndrome
- Hypothyroidism
- Acromegaly

## Increased SHBG

- Aging
- HIV
- Cirrhosis and hepatitis
- Some medications (anticonvulsants, estrogens)

Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# Summary: Diagnostic Evaluation for TD




Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

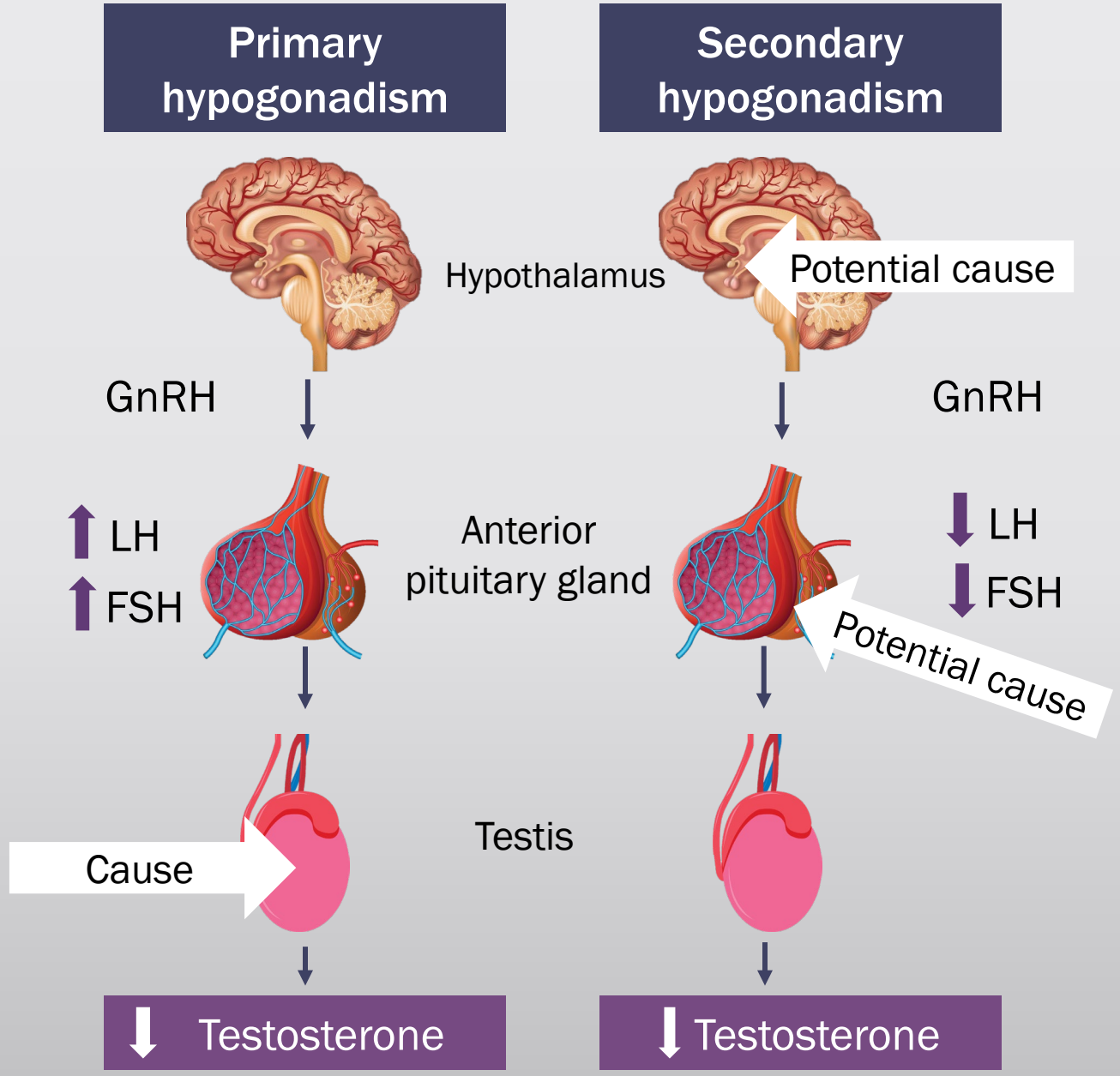
# Section 3

## Diagnosis of Testosterone Deficiency Is Established — Now What?

# Distinguishing Subtypes of Hypogonadism (HG)

Measure LH and FSH to distinguish a defect

- **Primary HG (~20%):** defect at the level of the testes
- **Secondary HG (~80%):** defect at the level of the pituitary or hypothalamus[1-3]
  - LH low or “inappropriately normal”
  - FSH low or “inappropriately normal”




1. Al-Sharefi A. *Br J Gen Pract.* 2020;70(696):364-365. 2. Dandona P. *Int J Clin Pract.* 2010;64(6):682-696. 3. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.
4. Tajar A et. al. *The Journal of Clinical Endocrinology & Metabolism.* 2010;95(4):1810–1818

# Causes of Primary and Secondary HG

## PRIMARY HYPOGONADISM ~20%

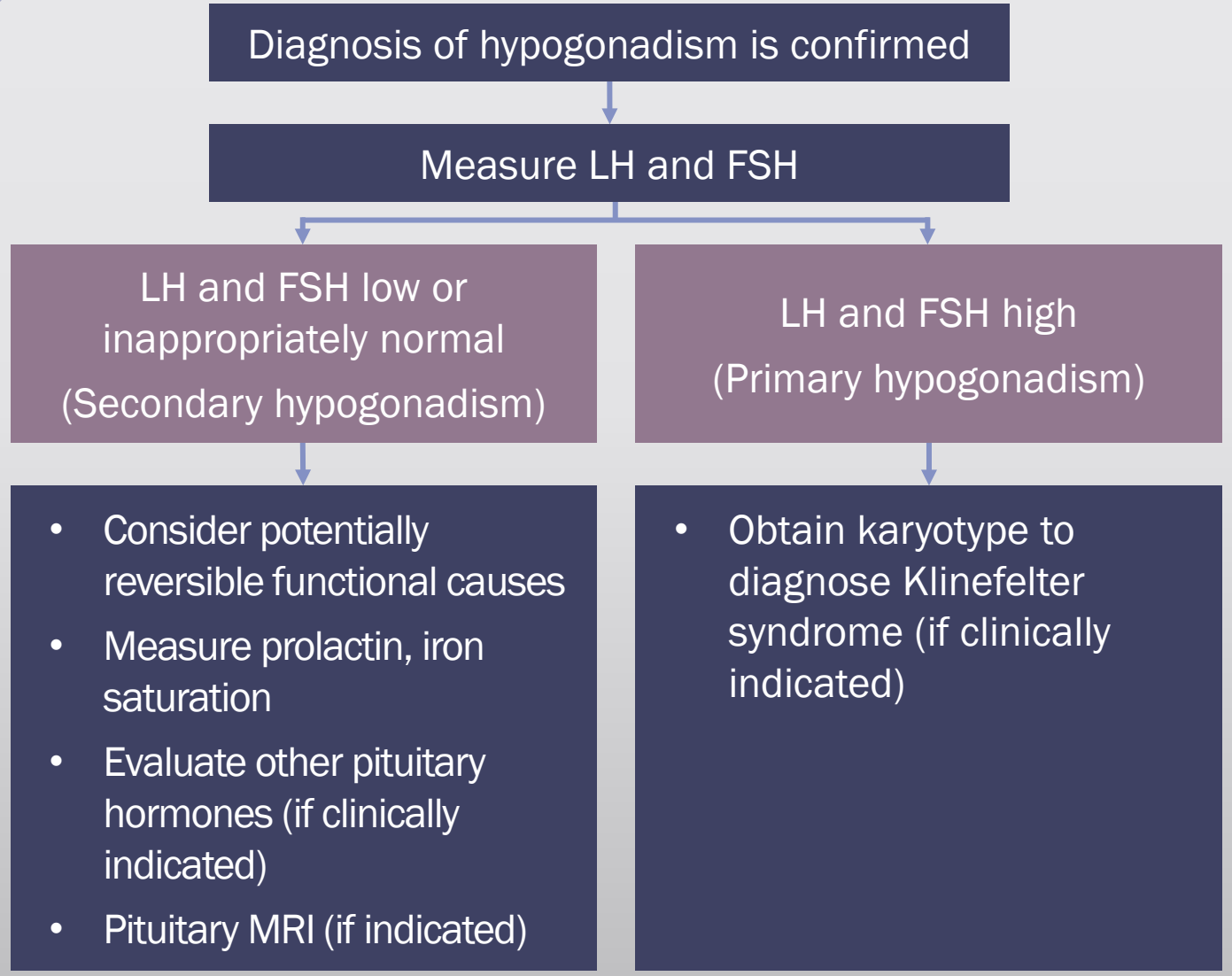
- Aging
- Congenital anorchidism
- Cryptorchidism
- Mumps orchitis
- Klinefelter syndrome
- Androgen receptor/ Sertoli cell defect syndromes
- Radiation/chemotherapy
- Testicular trauma
- Autoimmune syndromes

## SECONDARY HYPOGONADISM ~80%

- Aging
- Kallmann syndrome
- Prader-Willi syndrome
- Pituitary tumors, abscesses
- Hyperprolactinemia
- Cranial trauma
- Radiation treatment
- Various medications
- Alcohol abuse
- Chronic infections (HIV)
- Hemochromatosis
- Systemic disease

1. Dandona P. *Int J Clin Pract.* 2010;64(6):682-696. 2. Tajar A et. al. *The Journal of Clinical Endocrinology & Metabolism.* 2010;95(4):1810–1818.

# Further Testing for Evaluation of HG




Men with HG who are interested in fertility should have a reproductive health evaluation prior to consideration of testosterone therapy, including[2]:

- Testicular exam
- FSH
- Semen analysis
- Karyotype testing, as appropriate

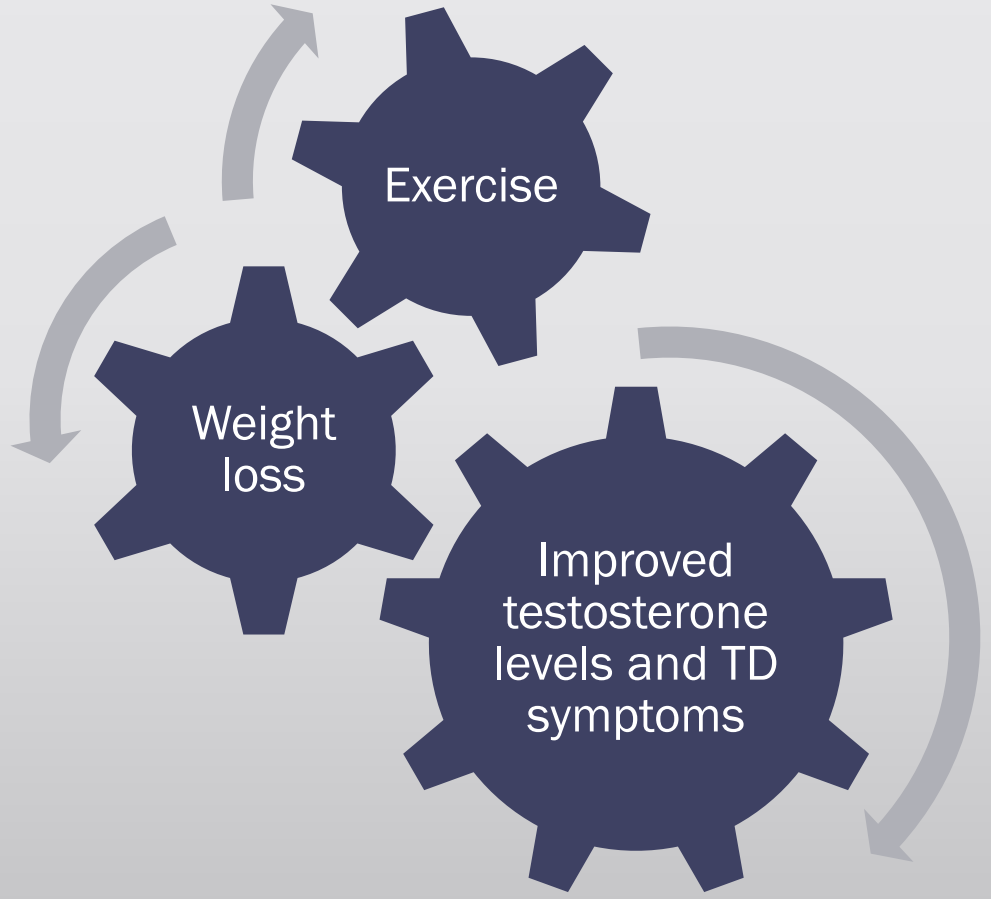
1. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744. 2. Mulhall JP. *J Urol.* 2018;200:423-432.

# Section 4

## Treatment of Testosterone Deficiency

# Lifestyle Modification for TD

- Weight loss and increased physical exercise are associated with improvement of obesity-associated functional TD and related sexual symptoms[1,2]
- All patients with TD should be counseled regarding the benefits of lifestyle modification[1,2]
- Elevated BMI + low testosterone could increase cardiovascular risk
  - Benefits of lifestyle modification should be counseled concurrent with testosterone therapy[2]




1. Corona G. *World J Mens Health.* 2020;38(3):256-270. 2. Mulhall JP. *J Urol.* 2018;200:423-432.

# Testosterone Therapy in Adults

## GOALS OF TREAMENT

- Improve symptoms of testosterone deficiency

## POTENTIAL BENEFITS OF TREATMENT

- Improved sexual function/activity in men (libido, erections, nocturnal erections)
- Improved energy and mood
- Increased muscle mass, decreased fat mass
- Improved bone mineral density (BMD)
- Resolution of unexplained anemia

Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# Pretreatment Testing

Hematocrit: If >50%, consider withholding therapy[1,2]

Prostate-specific antigen (PSA): Guidelines vary on age to initiate testing

- American Urological Association: Men >40 years[1]
- Endocrine Society: Men >55 years with earlier testing for those at high risk for prostate cancer[2]

1. Mulhall JP. *J Urol.* 2018;200:423-432. 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# Testosterone Therapy Cautions[1,2]

## CONTRAINDICATIONS

- Metastatic prostate cancer or breast cancer
- Unevaluated prostate nodule, elevated PSA
- Elevated hematocrit
- Severe BPH symptoms
- Uncontrolled congestive heart failure
- Desire for fertility in the near term

## PRECAUTIONS

- Potential increased risk of prostate cancer debated; recent evidence **does not support** a link[3]
- Conflicting data regarding risk for VTE and acute cardiovascular events
- Risk of transference with gels/creams

## ADVERSE EFFECTS

- Low frequency of serious adverse events in RCT with treatment doses
- Erythrocytosis
- Acne, oily skin
- Breast tenderness
- Detection of subclinical prostate cancer
- Growth of metastatic prostate cancer
- Reduced sperm production and fertility

RCT, randomized clinical trial; BPH, benign prostatic hypertrophy; VTE, venous thromboembolism

1. Mulhall JP. *J Urol.* 2018;200:423-432. 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

3. Lincoff AM et al. *N Engl J Med.* 2023;389(2):107-117.

# Counseling Patients About Testosterone Therapy

Despite the overall efficacy and safety of testosterone therapy demonstrated in clinical trials, concerns exist about the potential impact of therapy[1]

## PROSTATE CANCER

- Lack of direct evidence linking testosterone therapy to development of prostate cancer[1-3]
- Increases risk of subclinical prostate cancer detection because of increased surveillance[3]

## CARDIOVASCULAR EVENTS

- Low testosterone is a risk factor for cardiovascular disease[2]
- No conclusive evidence that testosterone supplementation increases cardiovascular risk in men with HG[1-4]

## OTHER TOPICS[1-3]

- Effects on spermatogenesis and fertility
- Increased risk of polycythemia

1. Dobs AS. *Int J Gen Med*. 2022;15:7719-7733. 2. Mulhall JP. *J Urol.* 2018;200:423-432. 3. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744. 4. Lincoff AM et al. *N Engl J Med.* 2023;389(2):107-117.

# TRAVERSE Study (2023)
# Cardiovascular Outcomes in Males with TD

- Population: 5,246 males with cardiovascular disease (CVD) or at risk for CVD, with symptoms of hypogonadism and low testosterone (<300 ng/dL)
- Intervention: Randomized to daily transdermal 1.62% testosterone gel or placebo gel
- Mean follow-up: 33 months
- Main outcomes: Occurrence of major adverse cardiac events (MACE*)
- Important Findings:
  - Primary outcome: No increased risk of MACE
  - Secondary outcome: No increased risk of composite of MACE + coronary revascularization procedures#
  - Adverse Effects:
    - No increased risk of prostate cancer
    - Higher incidence of atrial fibrillation, acute kidney injury, and pulmonary embolism in the testosterone group

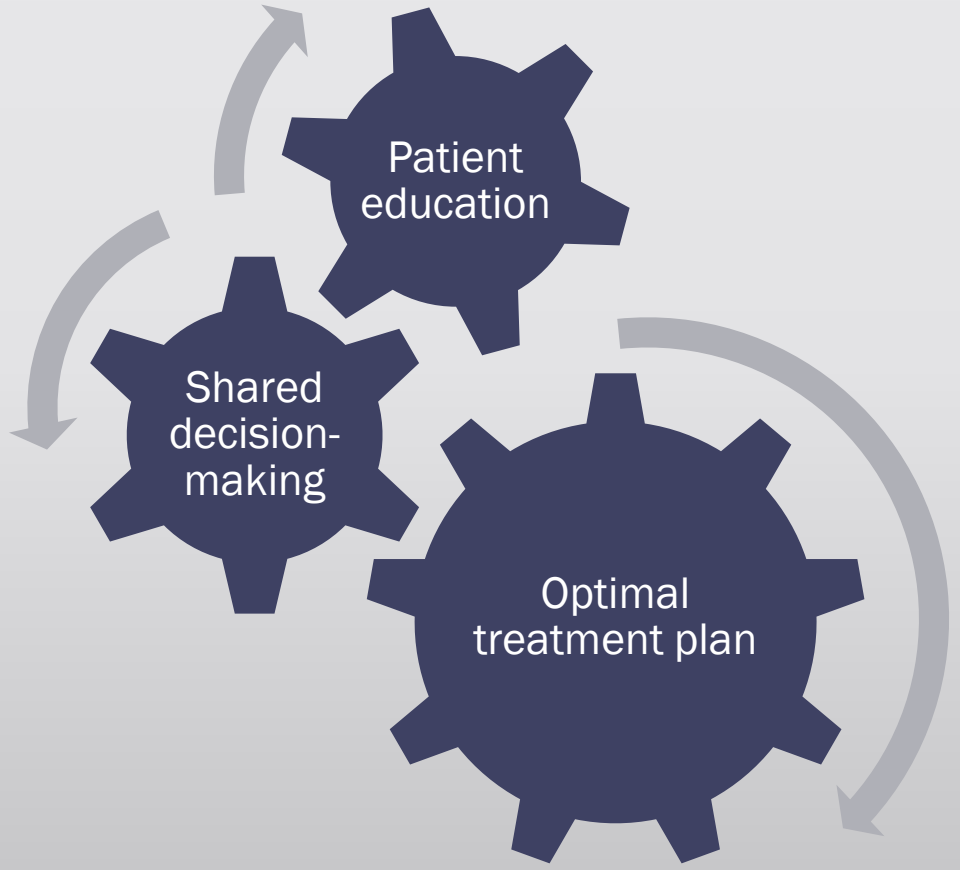
*MACE includes death from cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke

# Coronary revascularization procedures includes percutaneous coronary intervention or coronary–artery bypass grafts

Lincoff AM et al. *N Engl J Med.* 2023;389(2):107-117.

# Patient Education and Shared Decision-Making[1-3]

- Approach to treatment should be individualized for each patient with decision-making shared between clinician and patient
- Patient education is key to informed decision-making
  - Potential risks and benefits of therapy
  - Gaps in risk assessment data
    - Monitoring for prostate cancer
    - Testosterone therapy for men with prostate cancer history
    - Effects of therapy on cardiovascular disease
  - Range of treatment options
  - Consideration of patient-specific characteristics, such as goals, preferences, comorbidities is key




1. Dobs AS. *Int J Gen Med*. 2022;15:7719-7733. 2. Mulhall JP. *J Urol.* 2018;200:423-432. 3. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

# Testosterone Formulations: Transdermal

| Administration | Dosing | Benefits | Side effects and risks |
|---|---|---|---|
| **Gels**[1-4] | • Once daily | • Ease of use | • Generally well tolerated<br>• Skin irritation<br>• Variable plasma concentration in some<br>• Transference (absorption from skin-to-skin contact with females/children) |
| **Patch**[1,2,4] | • Once daily | • Ease of use | • Skin reaction at application site frequent<br>• Higher rate of inadequate T levels |

1. StatPearls. Accessed June 1, 2023. https://www.ncbi.nlm.nih.gov/books/NBK534853/ 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744. 3. Dobs AS. *Int J Gen Med*. 2022;15:7719-7733. 4. Bhat SZ. *touchREV Endocrinol.* 2022;18(2):133-140.

# Testosterone Formulations: Parenteral

| Administration | Dosing | Benefits | Side effects and risks |
|---|---|---|---|
| **Intramuscular[1-4] (short-acting)** | • Cypionate or Enanthate<br>• Weekly or every 2 weeks | • Relatively inexpensive<br>• Self administered or given in the office<br>• Flexibility in dosing | • Mood, energy, libido fluctuations<br>• Required IM injection, pain<br>• Undecanoate is not typically a first-line choice, requires large IM injection volume |
| **Intramuscular[1-4] (long-acting)** | • Undecanoate<br>• First dose at weeks 0 and 4, then every 10 weeks | • Less frequent admin, but dosing less flexible than short-acting | |
| **Subcutaneous implanted pellet[1-4]** | Long-acting, every 3-6 months | • Infrequent administration | • Surgical incision for insertion<br>• Rarely, local infection, skin allergy |
| **Subcutaneous injection device[1,3,4]** | • Enanthate, weekly self administered auto-injector | • Relatively painless<br>• Fewer fluctuations than IM | • Generally well tolerated<br>• Small increases in systolic BP, labeling includes a box warning<br>• Expensive |

1. StatPearls. Accessed June 1, 2023. https://www.ncbi.nlm.nih.gov/books/NBK534853/ 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744. 3. Dobs AS. *Int J Gen Med*. 2022;15:7719-7733. 4. Bhat SZ. *touchREV Endocrinol.* 2022;18(2):133-140.

# Testosterone Formulations: Oral and Intranasal

| Administration | Dosing | Benefits | Side effects and risks |
|---|---|---|---|
| **Oral capsules**[1-4] | • Undecanoate<br>• Short-acting, Dosed 2x daily with food | • Convenience of oral administration<br>• Easy reversibility | • Requires admin with fatty meal<br>• Liver toxicity (older alkylated formulations only)<br>• Elevated BP<br>• Expensive |
| **Intranasal gel**[1-4] | • Short-acting<br>• Dosed 2-3x daily | • Rapid absorption<br>• Bypasses first-past metabolism | • Multiple daily doses<br>• Local nasal effects |

1. StatPearls. Accessed June 1, 2023. https://www.ncbi.nlm.nih.gov/books/NBK534853/ 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744. 3. Dobs AS. *Int J Gen Med*. 2022;15:7719-7733. 4. Bhat SZ. *touchREV Endocrinol.* 2022;18(2):133-140.

# Monitoring Therapy: Measuring Testosterone Levels

- Measure initial follow-up total testosterone level based on the formulation:
  - Transdermal, intranasal, oral: 1-4 weeks after treatment onset
  - IM or SC injections: After 3-4 cycles of treatment
  - Long-acting IM undecanoate: Between the first two 10-week injections
  - SC pellets: 2-4 weeks after pellet placement to determine whether additional pellets required, and after 10-12 weeks
- The AUA recommends adjusting dosing to achieve total T in the **mid-normal range of 450-600 ng/dL**
- However, some men won't achieve adequate response until total T in **upper levels of normal 650-1000 ng/dL**
- Measure total T levels every 6-12 months thereafter while on treatment

**Stop treatment after 6 months if no symptomatic benefits occur despite confirmation that total T levels are adequate or robust**
(Consider extending treatment trial if patient is under stress or in poor health at the time of this assessment)

IM, intramuscular; SC, subcutaneous; AUA, American Urological Association

1. StatPearls. Accessed June 1, 2023. https://www.ncbi.nlm.nih.gov/books/NBK534853/ 2. Bhasin S. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744. 3. Dobs AS. *Int J Gen Med*. 2022;15:7719-7733.

# Additional Monitoring While on Therapy

- Each follow-up visit: evaluate signs and symptoms of testosterone deficiency and formulation-specific adverse events
- For those electing to have prostate monitoring, PSA and digital rectal exam 3-12 months after treatment onset
- Check hematocrit 1-2x in first year, then annually
- Check PSA 1-2x in first year, then annually

PSA, prostate specific antigen

Morgentaler A, et al. *Sexual medicine reviews*. 2019 Oct;7(4):636-49.

# Section 5

## Patient Puzzles:
## What Should I Do Next?

# Patient Case #1

## Ray, 44-year-old man

- Longstanding history of class 1 obesity and 6-year history of T2DM
- Symptoms of decreased energy, reduced libido
- Medications: Lisinopril, metformin, dulaglutide
- FH: Obesity, hypertension, diabetes
- BP: 148/90 mm Hg; BMI: 31.6 $kg/m^2$
- Abdominal adiposity, gynecomastia present, testes soft with reduced volume bilaterally on exam
- First morning fasting testosterone: 200 ng/dL, confirmed with second measurement; low bone mineral density

**What is the treatment plan for Ray?**

Ray, age 44

# Audience Response Question

What are the benefits of lifestyle modification for weight reduction and increased exercise for patients like Ray?

1. Increased testosterone levels
2. May reduce the risk for CVD
3. Improved mood and energy level
4. No apparent benefit anticipated

# Key Takeaways

- Low T occurs in an estimated ~35% of men >45 years old, and the incidence of TD is anticipated to increase
- Failure to treat TD may predispose to long-term health issues
- Diagnosis of TD requires symptoms of low testosterone *and* properly measured low testosterone
- Measure LH and FSH to distinguish between subtypes of hypogonadism
- A wide variety of testosterone therapies are available in oral, transdermal, injectable, intranasal, and subdermal forms
- Contraindications to T include elevated hematocrit, metastatic prostate or breast cancer, elevated PSA, severe BPH, and desire for fertility in near future
- Individualize treatment of TD using shared decision-making to consider risks and benefits

# Thank You!
# Questions?