Is Testosterone Right For Me?

A case study of a 35-year-old male

youngmenshealthsite.org

quora.com

Disclaimer

This lecture and the cited scientific literature, when referring to men/males, is referring to individuals born biological males.

Objectives

- Using a case study to guide our discussion
  - Define testosterone deficiency (TD)
  - What laboratory tests are needed when assessing TD
  - What else needs to be considered when making a TD diagnosis and when determining the need for treatment
  - Discuss treatment options

Debunking TTh Myths

Testosterone Therapy Myths

Testosterone therapy does NOT cause prostate cancer

Testosterone therapy does NOT increase CVD

Morgentaler A, Traish AM. Eur Urol. 2009; 55(2): 310-320.
Khera M, et al. Eur Urol. 2014; 65(1): 15-23.
Morgentaler A, et al. Mayo Clin Proc. 2015; 90(2): 224-251.
Miner M, et al. Clin Endocrinol (Oxf). 2018; 89(1): 3-10.

Case Study

Kevin, a 35-year-old male asks: is testosterone therapy (TTh) right for me?

Kevin, A 35-Year-Old Male

- CC: Kevin, a 35-year-old male presents with decreased energy, vitality, fatigue, brain fog, anxiety, difficulty with sleep (he does not snore) and cannot lose belly fat. He complains of decreased libido. He states that he recently developed erectile dysfunction manifested by difficulty achieving and maintaining an erection. His erections are not as strong as previous. In addition, he has lost muscle mass and despite aggressive training, he has been unsuccessful. Further, he states his work performance is slipping. Denies a history of snoring. Seeks solutions.
- PMH: Used anabolic steroids as a teenager for ~ 9 months, developed a varicocele (scrotal varicose veins) requiring surgical removal. In his late 20's he received pellets for "low T" and in 2019, he did a weight loss challenge, lost weight, and TT increased. In 2020 received HCG for a bit and a T troche. He currently is not taking any T supplementation

Kevin, A 35-Year-Old Male

- FH: He had 3 children in his 20's, not on TTh; otherwise his FH is unremarkable
- SH: He is happily married, works in sales in a high stress industry; he exercises regularly and does not smoke or drink alcohol. His diet is "OK," when he pays attention
- ROS: He has gut issues that necessitated an extensive GI work-up, which is when he was diagnosed with irritable bowel syndrome. He is HLA DQ2 (+)(-) and DQ8 (-)(-). He is not gluten or dairy free.
- PE: 5'10" tall, 170 lbs., BMI: 24.4, waist to hip ratio > 1 (abnormal). BP 145/90 and his resting HR is 80.
- Additional testing: testicular ultrasound to assess T volume: 8cc (< 10cc indicative of HPG axis dysregulation)

Check if you have any of the following:

- ❑ *1. Do you have a decrease in libido (sex drive)?*
- ❑ *2. Do you have a lack of 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?*

If you checked question **1** or **7** or ***any 3 other questions***, you may have low testosterone. A simple blood test can determine your testosterone level. **Talk with your doctor to see if you should be tested.**

Morley JE, et al. Metabolism. 2000; 49(9): 1239-1242.

ADAM Questionnaire: Validated screening tool for males aged ≥40 years

- Kevin checked boxes
  - 1 and 7
  - 2, 3, 5, 6, 8, 10
- Kevin should be tested for TD

What Tests Do We Do?

Serum is the gold-standard for testosterone testing and monitoring

What Tests Do We Do?

- Serum laboratory testing
  - CBC, CMP, SHBG
    - CBC, CMP, and SHBG at baseline, 1-, 4-, 8-, and 12-months, 2-3x a year
  - Total testosterone, calculated free testosterone
    - At baseline, 1-, 4-, 8-, and 12-months, 2-3x a year
  - Estradiol using LC-MS/MS
    - At baseline, 1-, 4-, 8-, and 12-months, 2-3x a year
  - FSH, LH, prolactin
    - Prolactin: initially
    - FSH: initially (unless on Clomid then more regularly)
    - LH: baseline, 1-, 4-, 8-, and 12-months
  - Other
    - TFT's, vitamin D, pregnenolone, progesterone, etc.
    - Have a high index of suspicion for metabolic disease, OSA

What Tests Do We Do?

- PSA, digital rectal exam, testicular volume
  - Baseline, 4- and 12-months (PSA, DRE)
- DUTCH testing
  - Test: baseline, 4- and 12-months, 2x a year
  - HPA axis
    - Saliva
    - Urine
  - Hormones
    - To evaluate hormone metabolism initially and on TTh,
    - Evaluate total androgen production and activity, and
    - To optimize detoxification pathways

Kevin's 2021 Hormone Labs

03.2021

- CBC: Hb/Hct: 15.1/42.9
- CMP: FBS: 90
- HbA1c: 5.7%
- TT: 300ng/dL (250-1100)
- FT-C: 65.9pg/mL (> 65-100pg/mL)
- E2: 25pg/mL (20-40, LC-MS/MS)
- SHBG: 16nmol/L (10-50)
- Prolactin: 8ng/mL (3-18)
- FSH: 5mIU/mL (1.6-8)
- LH: 2.3mIU/mL (1.5-9.3)

09.2021

- CBC: unchanged
- CMP: unchanged
- HbA1c: 5.7%
- TT: 290ng/dL (250-1100)
- FT-C: 63.5pg/mL (> 65-100pg/mL)
- E2: 23pg/mL (20-40, LC-MS/MS)
- SHBG: 16nmol/L (10-50)
- FSH: 5mIU/mL (1.6-8)
- LH: 2.3mIU/mL (1.5-9.3)
- PSA: 0.6ng/mL (1-1.5)

Kevin's 2021 Hormone Labs

03.2021

- CBC: Hb/Hct: 15.1/42.9
- SHBG: 26nmol/L (10-50)
- Prolactin: 8ng/mL (3-18)
- FSH: 5mIU/mL (1.6-8)
- LH: 2.3mIU/mL (1.5-9.3)

09.2021

- CBC: unchanged
- FSH: 5mIU/mL (1.6-8)
- LH: 2.3mIU/mL (1.5-9.3)
- PSA: 0.6ng/mL (1-1.5)

Clinical Pearl: In men with TD, central adiposity, and low SHBG think metabolic disease (IR). In 1/3 of these men, as opposed to an elevated E2 secondary to aromatase enzyme upregulation, E2 will be unexpectedly normal, this is hypogonadotropic hypogonadism

Kevin's 2021 Hormone Labs

03.2021

- CBC: Hb/Hct: 15.1/42.9
- CMP: FBS: 90
- HbA1c: 5.2%
- E2: 25pg/mL (20-40, LC-MS/MS)
- SHBG: 26nmol/L (10-50)
- Prolactin: 8ng/mL (3-18)
- FSH: 5mIU/mL (1.6-8)
- LH: 2.3mIU/mL (1.5-9.3)

09.2021

- CBC: unchanged
- CMP: unchanged
- HbA1c: 5.3%
- E2: 25pg/mL (20-40, LC-MS/MS)
- SHBG: 26nmol/L (10-50)
- FSH: 5mIU/mL (1.6-8)
- LH: 2.3mIU/mL (1.5-9.3)
- PSA: 0.6ng/mL (1-1.5)

Clinical Pearl: In a male with borderline criteria, testicular volume and PSA may be helpful

Questions

- Does Kevin meet diagnostic criteria for TD?
- If Kevin meets diagnostic TD criteria, what, in addition to altered HPG signaling, needs to be considered?
- What additional tests will be helpful, either with the diagnosis or treatment?
- What treatment options should be considered?

Questions

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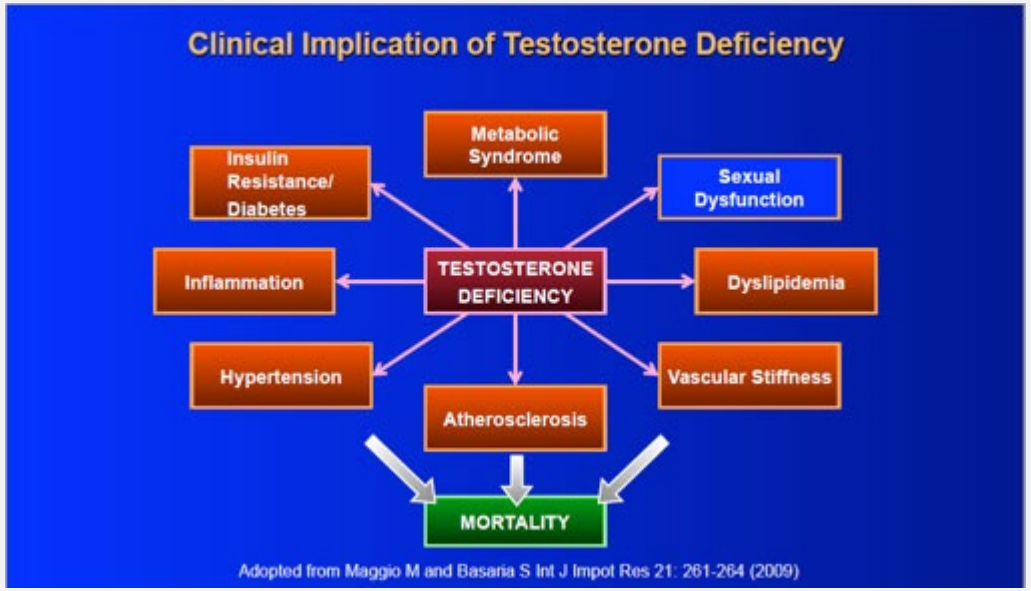
TD: Making the Diagnosis



What Do The Guidelines Say?

- American Urological Association (AUA): TT < 300ng/dL
- British Society for Sexual Medicine (BSSM): TT < 230ng/dL
- Canadian Medical Association Journal (CMAJ): TT No specific cutoff
- International Society for Sexual Medicine (ISSM): TT < 230ng/dL
- European Association of Urology (EAU): TT < 231ng/dL
- Endocrine Society Practice Guidelines: TT < 300ng/dL
- European Menopause and Andropause Society (EMAS): TT < 350ng/dL
- Key opinion leaders with TD symptoms
  - Morgentaler, Khera, Maggi, Zitzmann: a TT < 350ng/dL
  - Khera: a TT < 400ng/dL in a young symptomatic male

TD: Making the Diagnosis

- In healthy males, testosterone decreases by ~ 1-2% per year
- The most common and reliable symptoms are sexual symptoms
  - Decreased libido is a primary TD symptom and may occur without any other symptoms
  - In men > 50 decreased libido strongly suggests TD, without other obvious causes
  - Other sexual symptoms include: erectile dysfunction, difficulty achieving or maintaining an erection, etc.
- Non-sexual TD symptoms include
  - Fatigue, decreased energy, decreased vitality, depressed mood, irritability, “brain fog,” decreased motivation, etc.

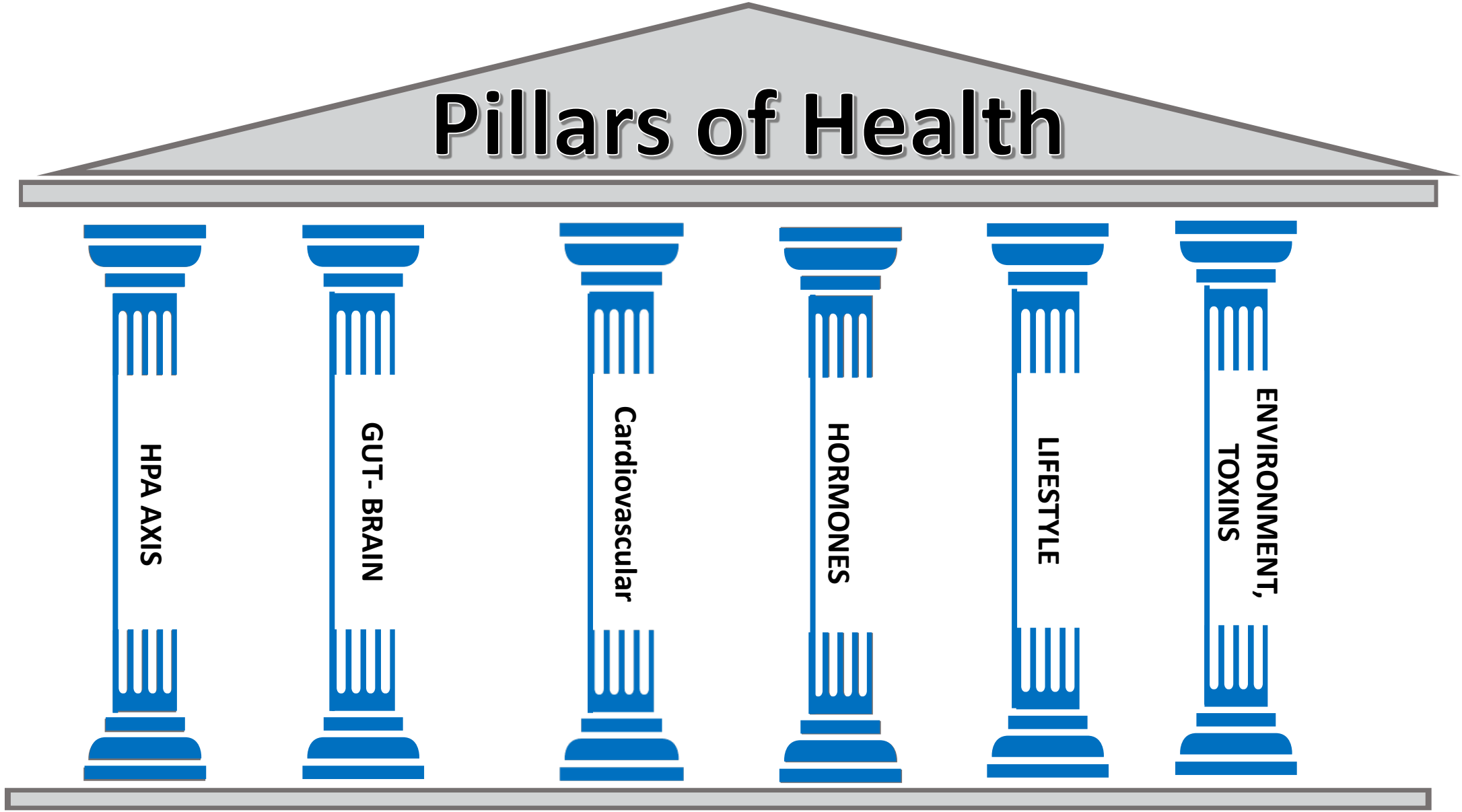
TD: Making the Diagnosis

- TD signs include
  - Loss of muscle mass, decreased BMD, and/or anemia
  - Decreased testicular volume
- Laboratory Testing
  - Total Testosterone < 300-350ng/dL is a reasonable threshold, but not absolute
    - However, multiple cofounding factor including SHBG level and androgen receptor sensitivity as measured by CAG repeats (> 24 repeats = decreased AR sensitivity, genedx.com)
      - CAG = cytosine, adenine, guanine; mean #: AA ~ 18-20, Caucasians ~ 21-23, East Asians ~ 22-23
  - Calculated Free T (FT-C) threshold levels of < 65-100pg/mL have been recommended
    - Need SHBG and albumin
  - A TT < 200-250ng/dL is associated with adverse health outcomes, to include decreased BMD

TD: Making the Diagnosis

- Testosterone should be measured in the AM
  - Always measure a morning specimen x 2
  - In healthy young males, T has a diurnal pattern
  - In men > 40, this diurnal pattern may be lost
- Optimal total testosterone levels
  - > 500ng/dL to < 1,000ng/dL, with a goal of 500ng/dL to 800ng/dL

Risk Factors Matter



Key Points

In a male > 50 years old, with SS consistent with TD (ADAM), low TT and/or FT-C, evaluate and treat any underlying etiologies and consider TTh

In a male < 50 years old, with SS consistent with TD (ADAM), with primary TD (elevated LH and low TT and/or FT-C), after ruling out other possible etiologies, TTh is the treatment of choice

In a male < 50 years old, with SS consistent with TD (ADAM), with secondary TD (low or normal LH, low TT and/or FT-C), evaluate and treat any underlying etiologies and recommend against TTh as the first choice, use other options: HCG, Clomid, nutraceuticals

Questions

- **Does Kevin meet diagnostic criteria for TD?**
- If Kevin meets diagnostic TD criteria, what, in addition to altered HPG signaling, needs to be considered?
- What additional tests will be helpful, either with the diagnosis or treatment?
- What treatment options should be considered?

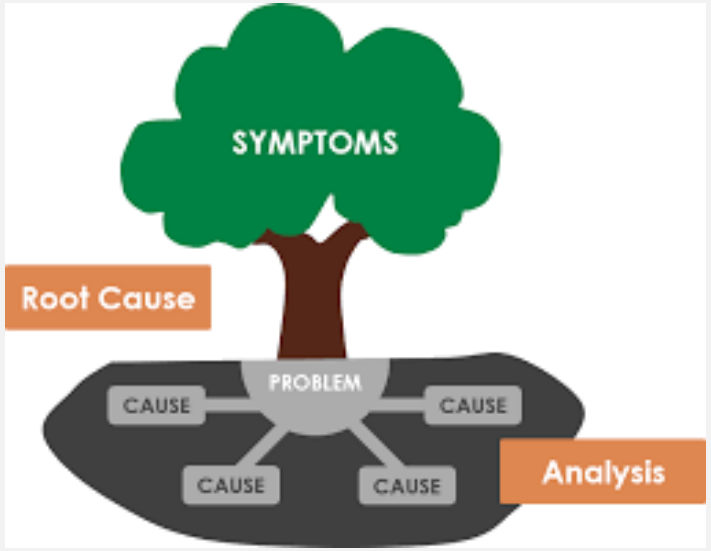
Does Kevin Meet TD Diagnostic Criteria? 9.13.2021 Labs

- Testosterone: Yes
  - Total: 290ng/dL
  - Free T-C: 63.5pg/mL
- Symptoms: Yes, positive ADAM questionnaire
  - Sexual: decreased libido, erectile dysfunction, no morning erections
  - Non-sexual: brain fog, fatigue, loss of vigor, irritability, etc.
- Signs: Yes
  - Decreased muscle mass: Yes
  - BMD: normal
  - Anemia: no

Questions

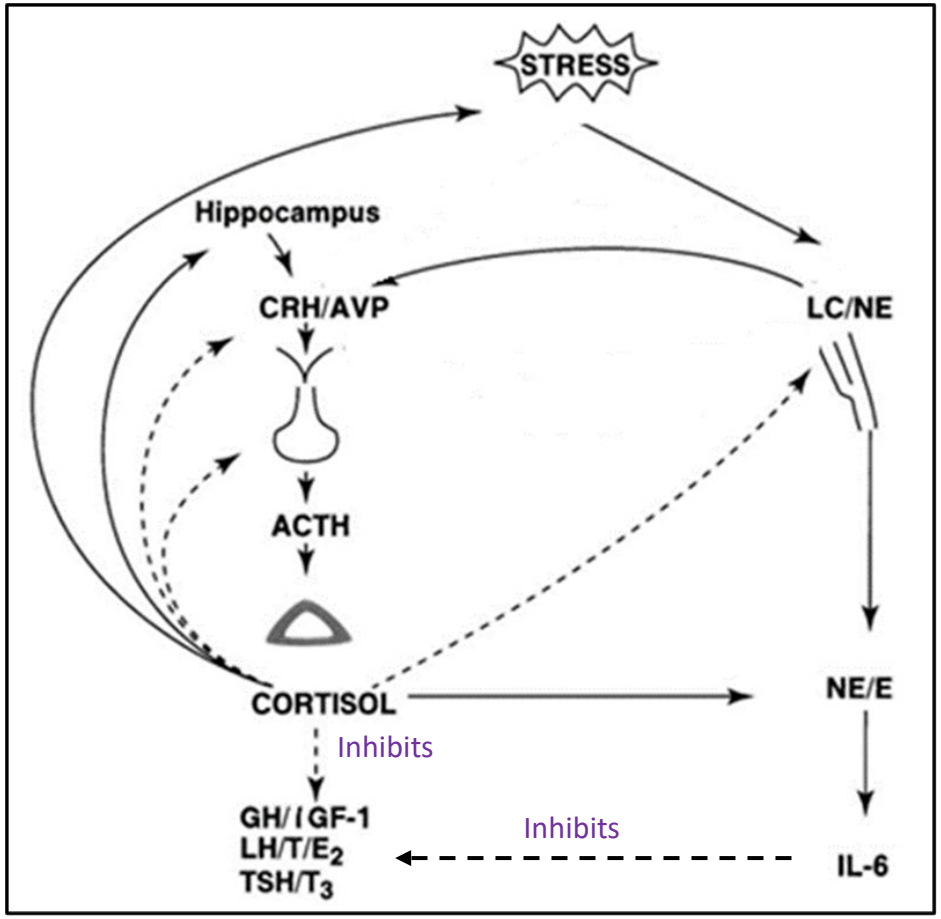
- Does Kevin meet diagnostic criteria for TD? **YES**
- **Since Kevin meets diagnostic TD criteria, what, in addition to altered HPG signaling, needs to be considered?**
- What additional tests will be helpful, either with the diagnosis or treatment?
- What treatment options should be considered?

Root Cause Analysis



HPA and HPG Axes

- Chronic Stress, HPA axis dysfunction, and the HPG axis
  - Stress → ↑CRH, which suppresses gonadotrophin releasing hormone (GnRH), FSH, and LH
  - Elevated cortisol inhibits FSH, LH, and leads to gonadal tissue receptor resistance, thus decreasing T levels, and T's effectiveness
  - Chronic stress increases inflammation, which also effects testicular function, decreasing LH and T



Tsigos C, Chrousos GP . J Psychosom res. 2002; 53(4): 865-871.
Pasquali R. Ann N Y Acad Sci. 2012; 1264(1): 20-35.

Gut and Sex Hormones

- The gut mediates hormone metabolism and hormone-related diseases
  - A balanced microbiome is diverse, with > 90% of species within the Firmicutes and Bacteroidetes phyla, and has a lower F/B ratio
  - β-glucuronidase secreting microbes modulate systemic E and T levels
  - Dysbiosis reduces bacterial diversity, increases the F/B ratio, decreases or increases β-glucuronidase
    - Low β-glucuronidase secreting bacteria leads to low T states
    - High β-glucuronidase secreting bacteria leads to estrogen-dominant states
      - Endometriosis, uterine fibroids, endometrial hyperplasia and cancer
  - Gut's 5α- and 5β-reductase activity impacts Pg metabolism

Baker J, et al. 2017; 103: 45-53.
Tremellen K. Basic Clin Androl. 2016; 26(7): 1-13.

Gut and Sex Hormones

- Sex hormone and Gut health: A bidirectional relationship
  - First study to assess the association between serum hormone levels, GM, and bacterial taxa
  - 57 participants: 31 males, 26 females, looked at serum T men, serum E2 in women
  - Divided into 3 groups based on serum levels: low, medium, and high
    - Low: T < 355ng/dL, E2 < 5pg/mL; Medium: T < 455ng/dL, E2 between 5.0-60pg/mL
    - High: T > 455ng/dL, E2 > 60pg/mL
  - Results: Sex hormone levels linked to changes in gut microbiome diversity
    - In both high serum hormone groups, there was greater diversity than in the medium and low groups
- Conclusion: Sex hormone levels may impact gut health and vice versa

Shin JH, et al. Research Microbiol. 2019; 170(4-5): 192-201.

What Do We Know About Kevin?

- Kevin meets diagnostic criteria for TD
- Kevin probably has HPA axis dysfunction with increased inflammation, which is impacting his testosterone production, signaling, and tissue responsiveness
- Kevin has gut dysbiosis, with increased visceral fat, a permeable gut, some degree of metabolic endotoxemia, which increases inflammation and decreases T production, etc.

Inflammation, Metabolic Endotoxemia, and TD

Gut Endotoxin Leading to a Decline IN Gonadal Function (GELDING) theory for obesity related male hypogonadism

- First theory linking obesity, endotoxemia, and TD
- There is minimal supporting human data; however, there is abundant animal data and data in women supporting this theory

Tremellen K. Basic Clin Androl. 2016; 26(7): 1-13.

Gut Endotoxin Leading to a Decline IN Gonadal Function (GELDING) Theory

- Theory posits: obesity, a poor diet ⇨ increased gut permeability, and chronic low-grade inflammation ⇨ impaired testicular function
  - It is not low T's decreased immunosuppressive effects that increases inflammation
- Mechanism
  - Obesity and associated poor diet lead to increased gut permeability
  - Facilitates LPS translocation to systemic circulation
    - May be the key inflammatory trigger
  - LPS decreases testicular T production, both directly and indirectly
    - Direct: inhibits Leydig cell steroidogenesis
    - Indirect: decreases both LH (T) and FSH (spermatogenesis) drive

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Gut Endotoxin Leading to a Decline IN Gonadal Function (GELDING) Theory

- Chronic stress ⇨ increased gut permeability, and chronic low-grade inflammation ⇨ impaired testicular function
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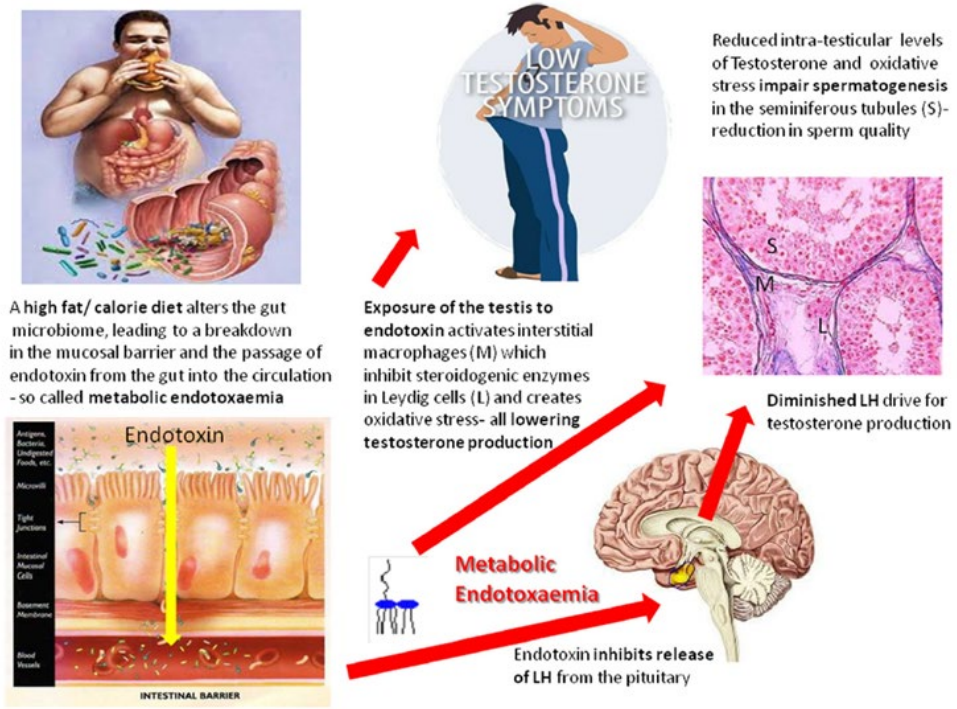
GELDING Theory, a Root Cause

High saturated fat diet is a trigger as is chronic stress



- Under normal conditions, macrophages necessary for Leydig cell development – provide growth and differentiation factors
- With inflammation:
  - Macrophages produce proinflammatory cytokines: IL-1β, IL-6, and TNF-α, and ROS
  - Leydig cells also produce proinflammatory cytokines: IL-1β, IL-6, and TNF-α
  - Leydig cells have TLR4 receptors
    - TLR4 bind LPS, bind to Leydig cell TLR4 receptors and directly inhibit T production
- ⇧ gut permeability and chronic low-grade inflammation → TD

Tremellen K. Basic Clin Androl. 2016; 26(7): 1-13.

GELDING Theory, a Root Cause

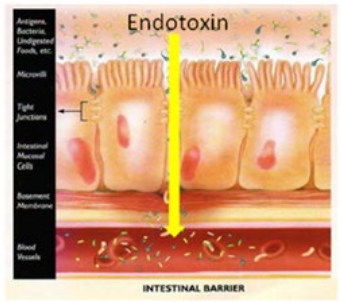
High saturated fat diet is a trigger as is chronic stress

Reduced intra-testicular levels of Testosterone and oxidative

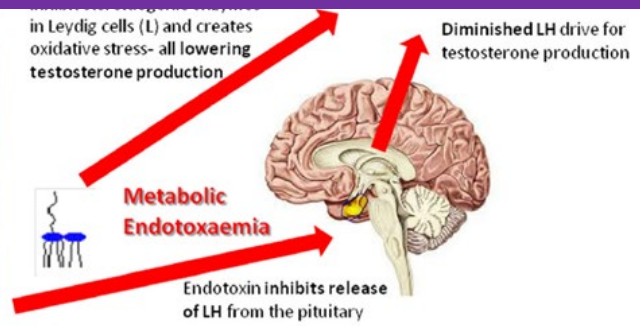
- Under normal conditions, macrophages necessary for Leydig cell development – provide growth and differentiation factors

Evaluate and treat the HPA axis and the gut, in addition to TD

- so called **metabolic endotoxaemia**



in Leydig cells (L) and creates oxidative stress- all lowering testosterone production



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The Gold-Standard

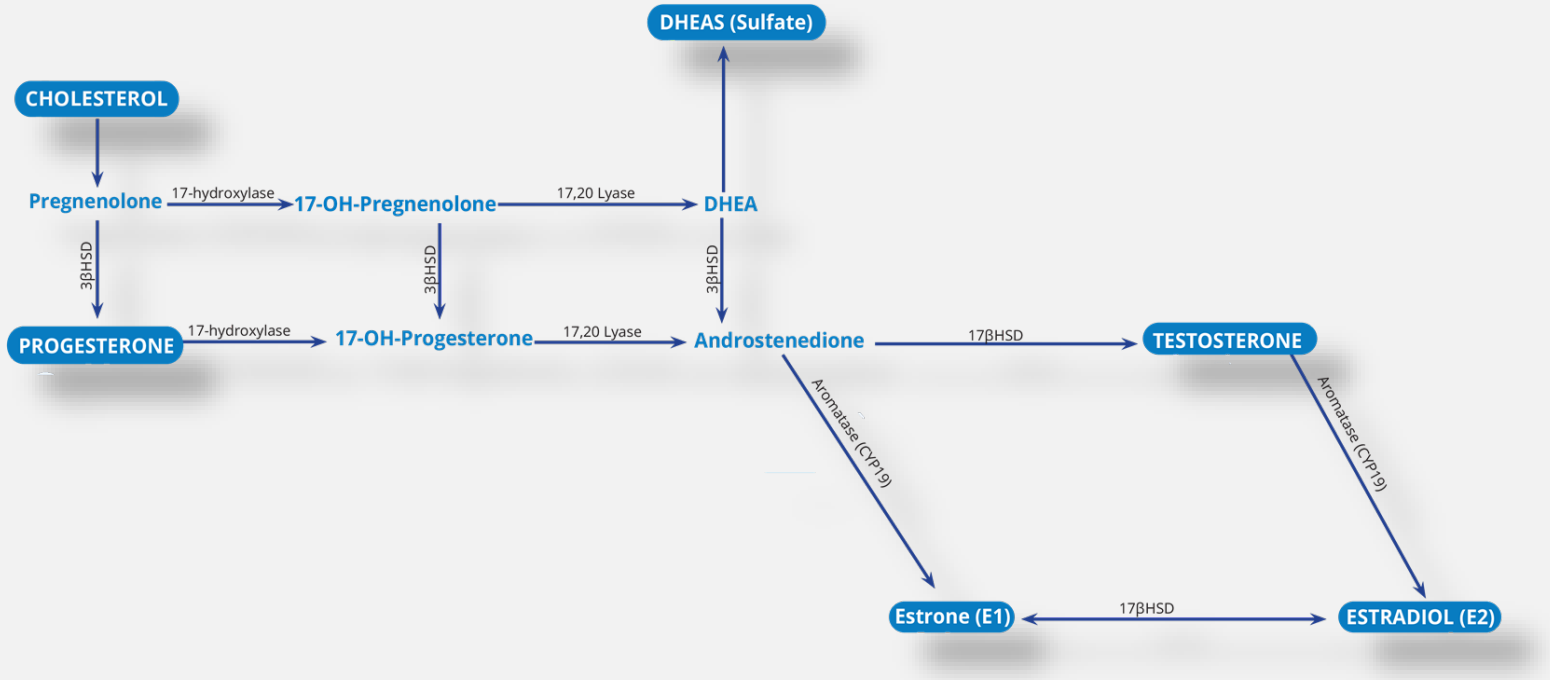
Before choosing a test other than the gold-standard, you must ask: has the test been validated against the gold-standard and/or are there outcome studies documenting its clinical utility?

The Gold-Standard

Before choosing a test other than the gold-standard, you must ask: has the test been validated against the gold standard and/or are there outcome studies documenting its clinical utility?

Serum is the gold-standard for testosterone testing and monitoring TTh. However, urine adds comprehensiveness re: estrogen metabolism, androgen tissue exposure, and detoxification.

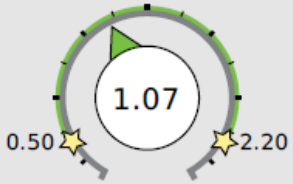
DUTCH PLUS


DHEAS (Sulfate)
CHOLESTEROL
Pregnenolone
17-hydroxylase
17-OH-Pregnenolone
17,20 Lyase
DHEA
3βHSD
3βHSD
3βHSD
PROGESTERONE
17-hydroxylase
17-OH-Progesterone
17,20 Lyase
Androstenedione
17βHSD
TESTOSTERONE
Aromatase (CYP19)
Aromatase (CYP19)
Estrone (E1)
17βHSD
ESTRADIOL (E2)

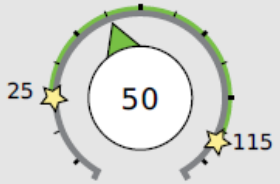
Kevin's DUTCH PLUS

Key (how to read the results):

Sex Hormones



Estradiol(E2)



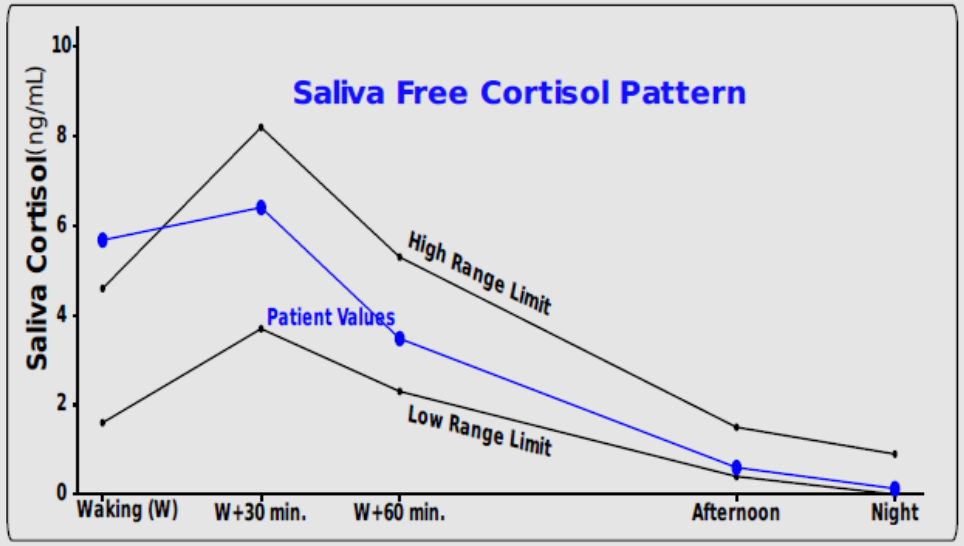
Testosterone

Testosterone

Age	Range
18-25	50-115
26-40	40-95
41-60	30-80
>60	25-60

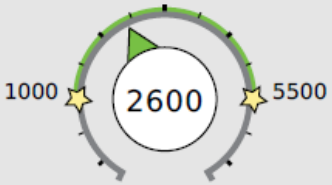
Adrenal Hormones

See pages 4 and 5 for a more complete breakdown of adrenal hormones

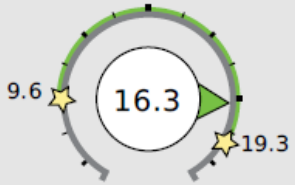


Total DHEA Production

Age	Range
20-39	3000-5500
40-60	2000-4000
>60	1000-2500

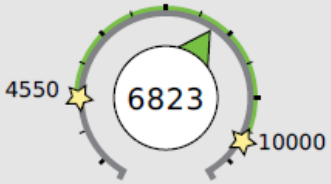


Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)



Saliva Cortisol Total
(Sum of 5 values)

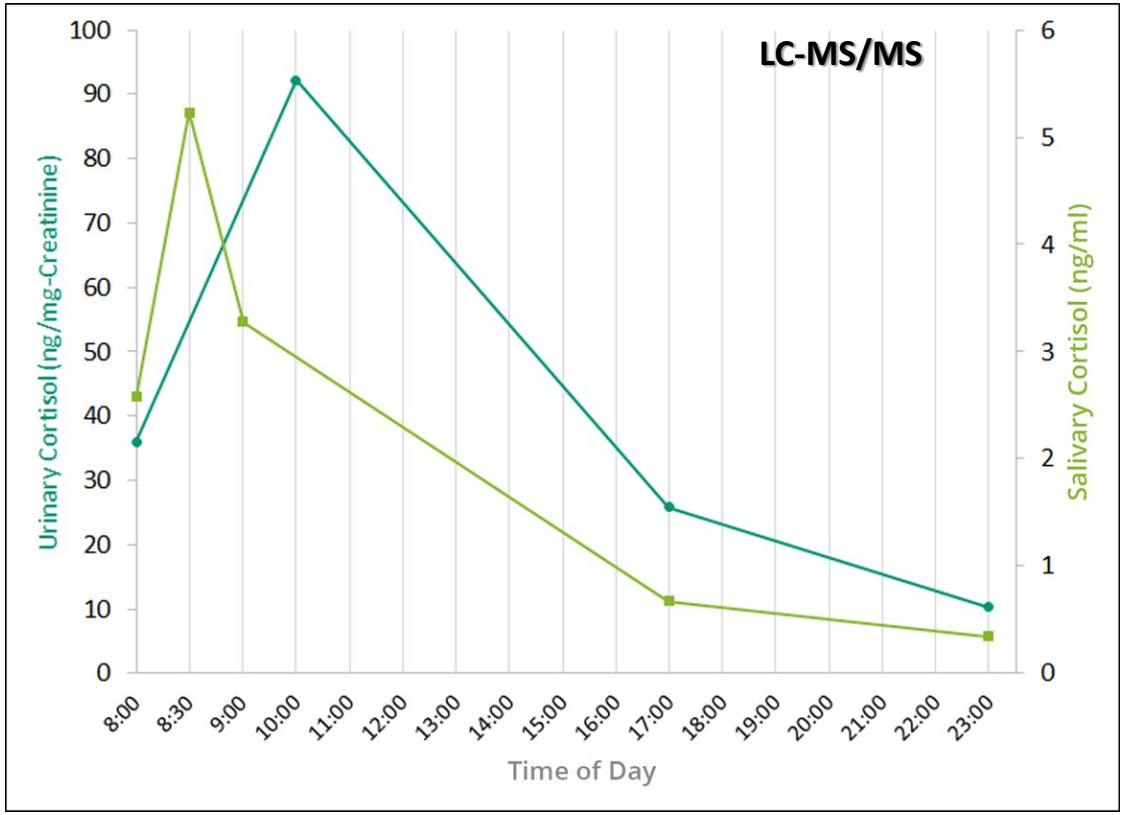
cortisol metabolism



Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

A Commercially Available Validated Urine Test



- Study Objectives:
  - Determine the utility of dried urine to measure cortisol and cortisol metabolites
  - Is the 4-spot dried urine representative of 24-hour liquid urine
  - Can the diurnal pattern be observed in urine
- Study group:
  - 68 individuals with both saliva and urine diurnal cortisol measurements on the same day
- Conclusion:
  - 4-spot dried urine a viable alternative to liquid urine for measuring cortisol and metabolites
  - 4-spot dried urine is good surrogate for the salivary diurnal pattern

Newman M, et al. J Clin Transl Endocrinol. 2020; 100243.

Cortisol Metabolites

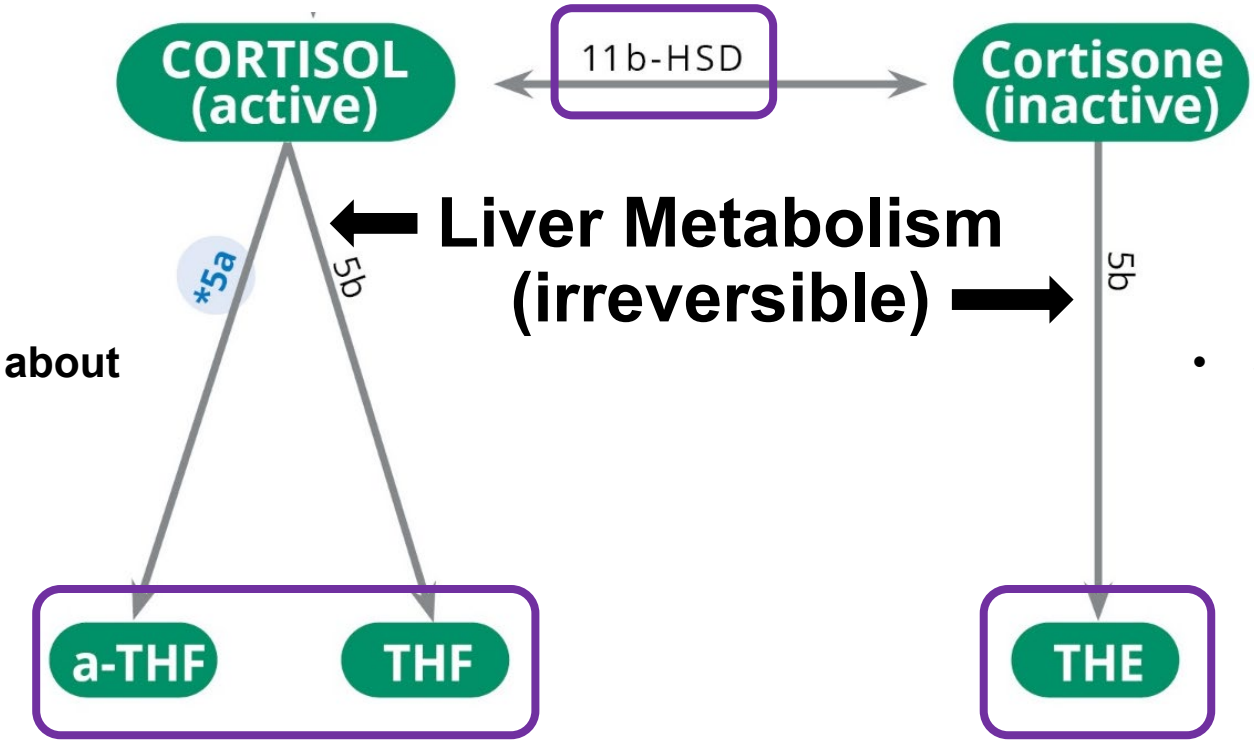
Activation to Cortisol

- **Liver**
- **Adipose**
- Gonads
- Brain
- Vascular smooth muscle

11β-HSD1 ⇄ 11β-HSD2

Deactivation to Cortisone

- **Kidneys**
- Colon
- Salivary gland

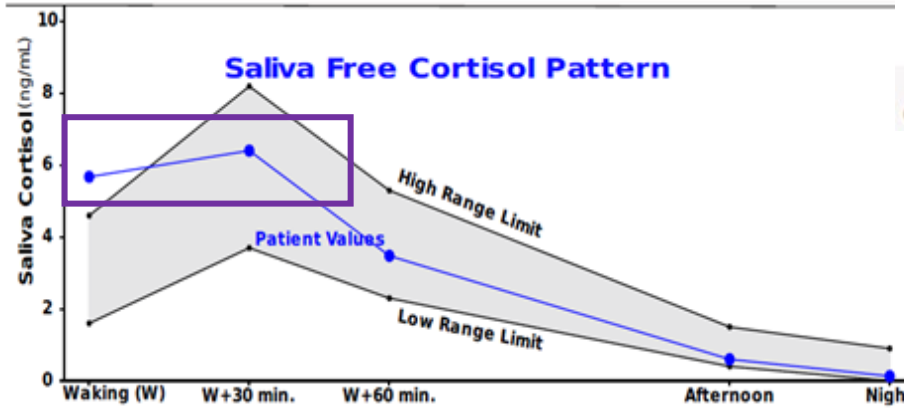


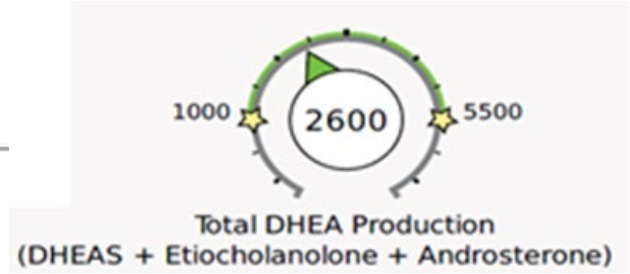
- **5α metabolism informs about global metabolism**
- **5β metabolism informs about liver metabolism**

Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

Kevin's HPA Axis Assessment: Loss of Resilience

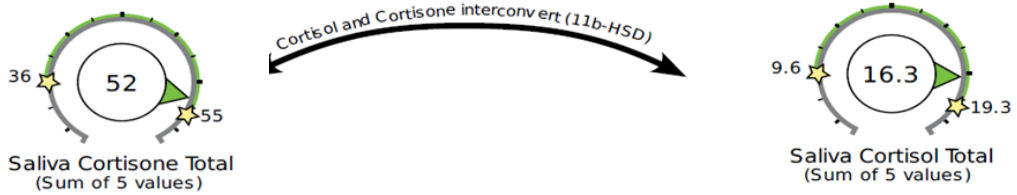
The Cortisol Awakening Response (CAR) was **0.73ng/mL** (expected range 1.5-4.0) or 12.9% (range 50-160%)

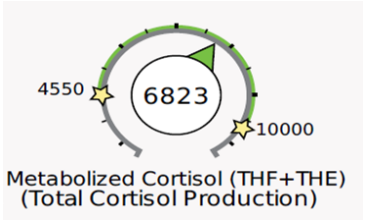


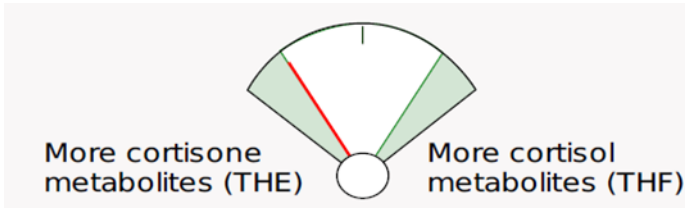


Total DHEA Production

Age	Range
20-39	3000-5500
40-60	2000-4000
>60	1000-2500

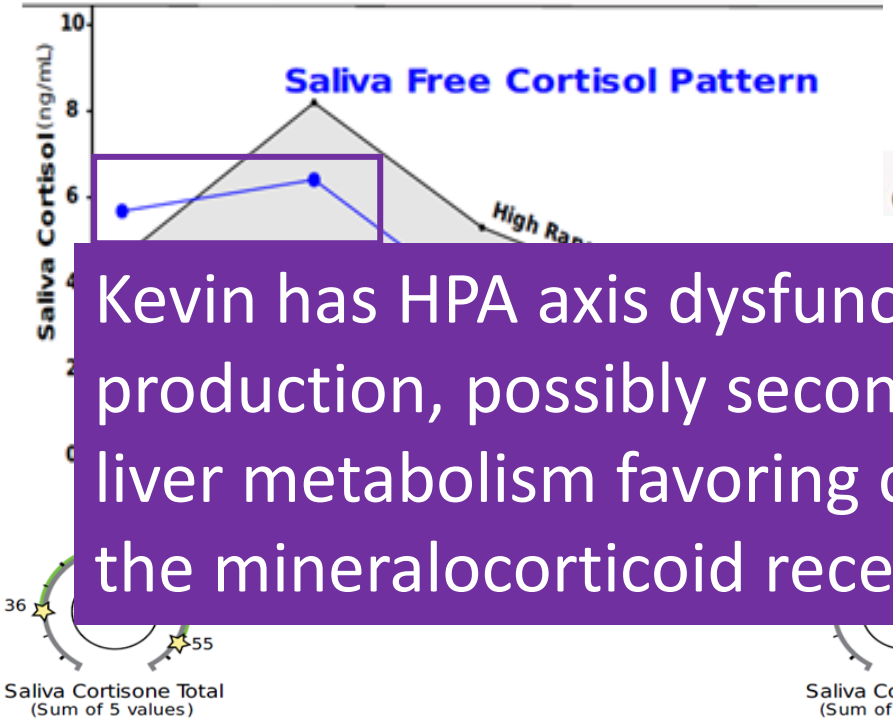






- Cortisol Awakening Response: decreased resilience
  - Is this accurate or was 1st point later than awakening?
  - If accurate – then CAR low
- DHEA total: worsening HPA axis dysfunction
  - Low, consistent with decreased resiliency
- Is visceral adiposity increasing 11β-HSD1 activity resulting in more cortisol? Possibly
- Is the liver trying to deactivate cortisol to cortisone, 11β-HSD1 is bidirectional?
  - Liver metabolism favoring 5β-reductase activity with cortisone metabolites
- Is the kidney deactivating cortisol to cortisone (11β-HSD2 activity)? Maybe

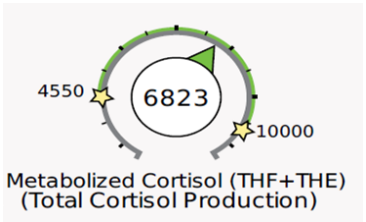
Kevin's HPA Axis Assessment: Loss of Resilience

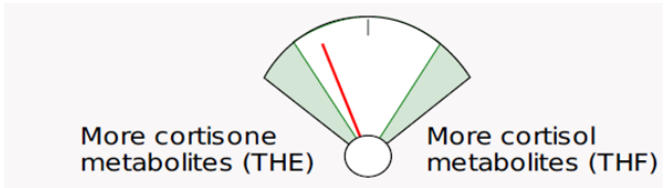


Total DHEA Production

Age	Range
20-39	3000-5500
40-60	2000-4000
>60	1000-2500

Kevin has HPA axis dysfunction with loss of resiliency, increased cortisol production, possibly secondary to adipose 11β-HSD1 upregulation and liver metabolism favoring cortisone metabolites and kidney protecting the mineralocorticoid receptor (11β-HSD2 activity)





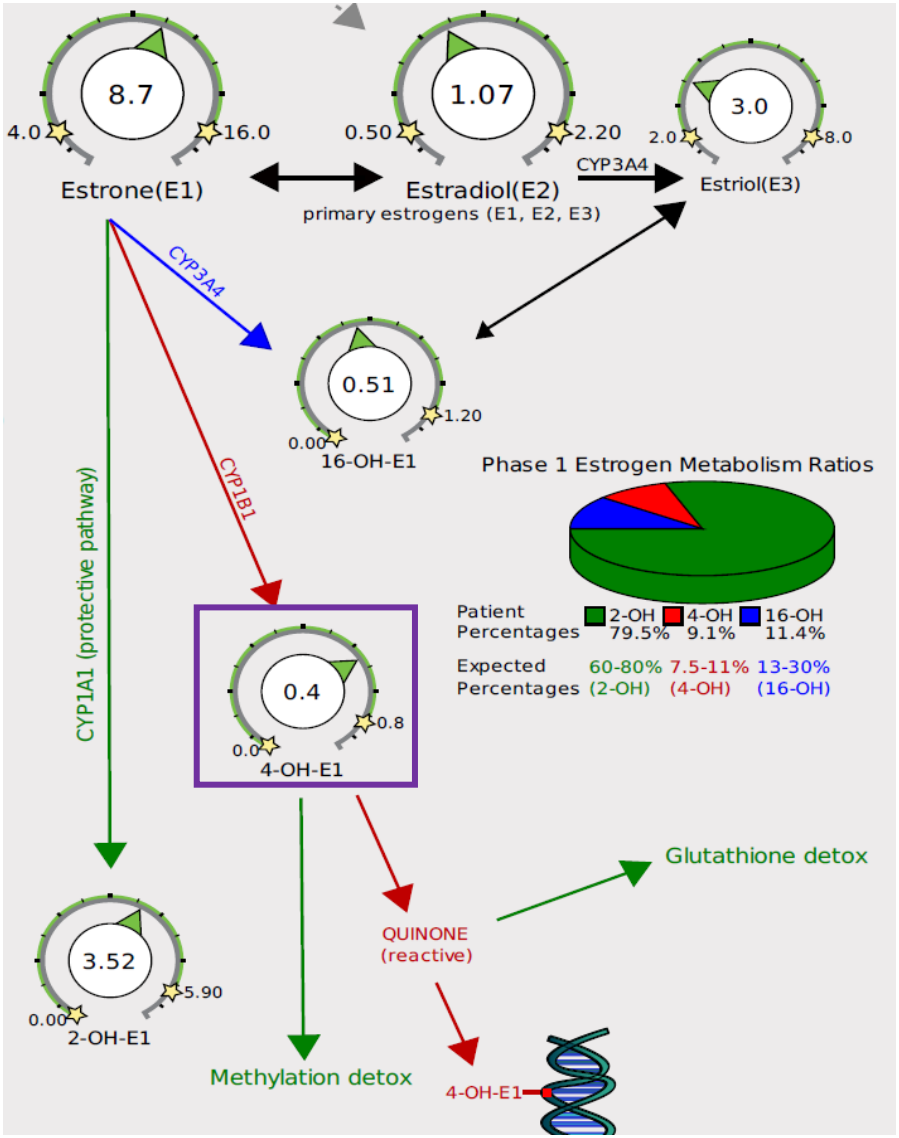
- DHEA total: worsening HPA axis dysfunction
  - Low, consistent with decreased resiliency
- Is visceral adiposity increasing 11β-HSD1 activity resulting in more cortisol? Is the liver trying to deactivate cortisol to cortisone, 11β-HSD1 is bidirectional?
- Liver metabolism favoring 5β-reductase activity with cortisone metabolites

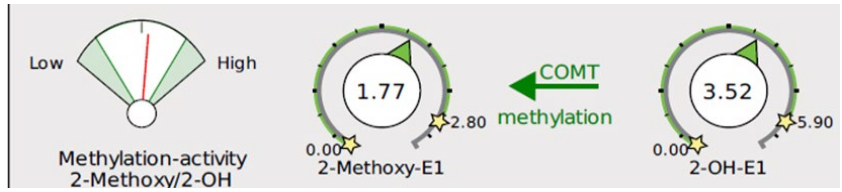
Key Point

Estrogen metabolism in men is as important as estrogen metabolism is in women

Poor estrogen detoxification in men is associated with hormonally driven cancers, similar to women

Kevin's E Metabolism

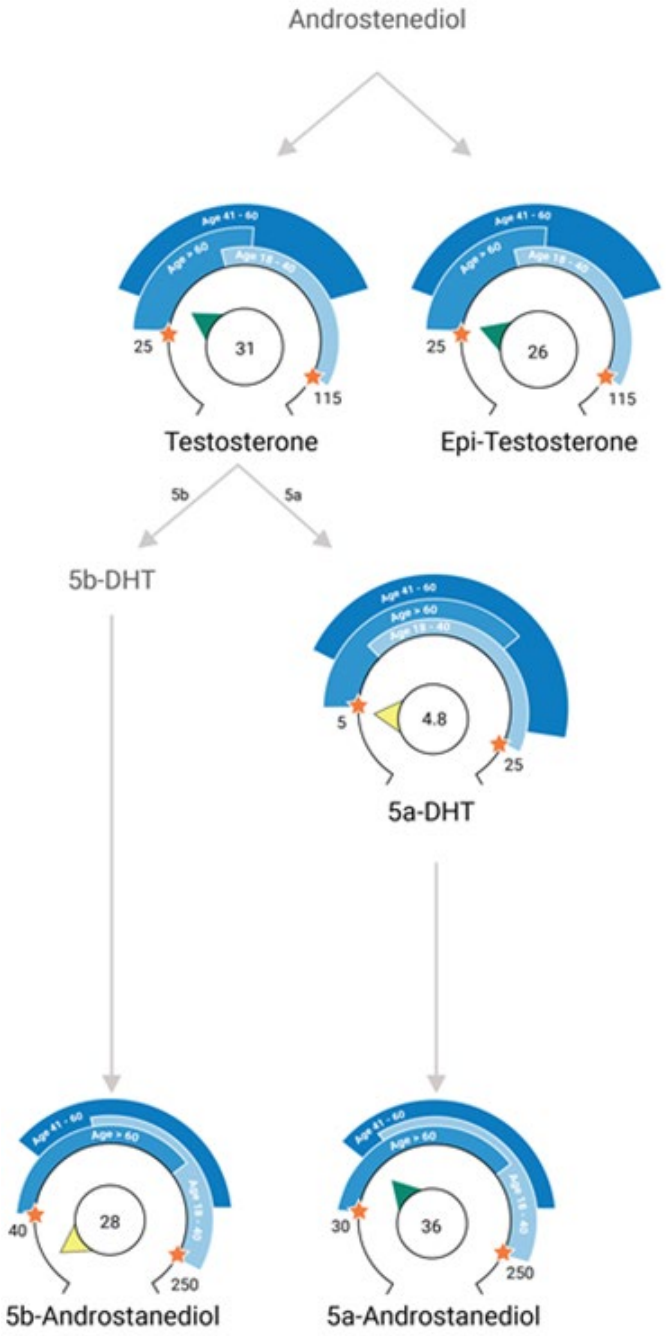




Kevin's serum E2 = 23pg/mL

Estrogens and Metabolites (Urine)				
Estrone(E1)	Within range	8.7	ng/mg	4 - 16
Estradiol(E2)	Within range	1.07	ng/mg	0.5 - 2.2
Estriol(E3)	Low end of range	3.0	ng/mg	2 - 8
2-OH-E1	Within range	3.52	ng/mg	0 - 5.9
4-OH-E1	Within range	0.4	ng/mg	0 - 0.8
16-OH-E1	Within range	0.51	ng/mg	0 - 1.2
2-Methoxy-E1	Within range	1.77	ng/mg	0 - 2.8
2-OH-E2	Within range	0.21	ng/mg	0 - 0.6
4-OH-E2	Within range	0.1	ng/mg	0 - 0.3
2-Methoxy-E2	Within range	0.3	ng/mg	0 - 0.8
Total Estrogen	Within range	19.6	ng/mg	10 - 34

- In men, E2 is 100% metabolized from testosterone
- E2 is important in men for sexual function, BMD, etc.
- Optimal serum E2 levels range from 20-40pg/mL (goal 30-35pg/mL) using an LC- or GC-MS/MS assay
- Serum E2 levels > 15pg/mL prevent marked and significant bone loss



What about T metabolism and T excretion?

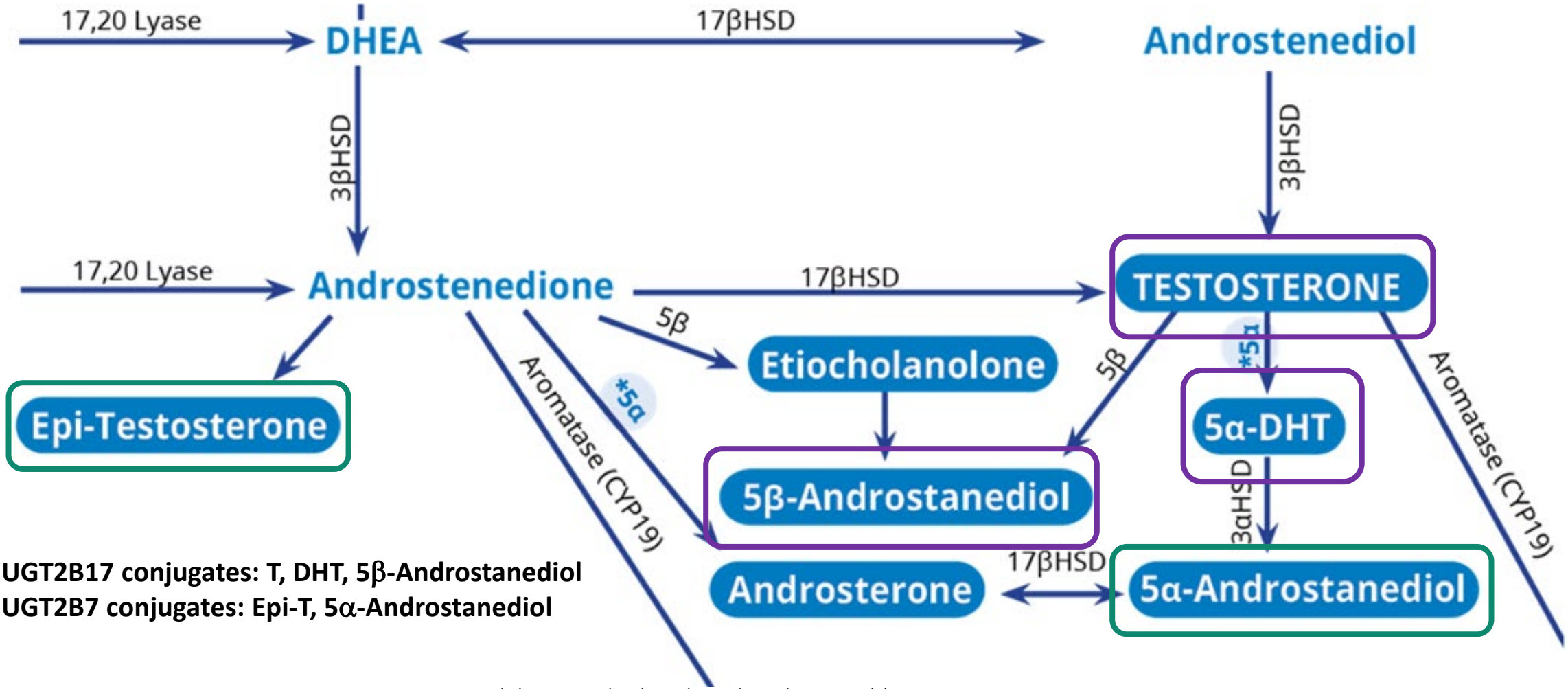
T's more complicated!

Schiffer L, et al. Mol Cell Endocrinol. 2018; 465: 4-26.
Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

Testosterone Phase 2 Detoxification

- Urine testing assumes normal phase II metabolism
- T is subject to phase II SNPs that may limit urine's clinical utility
  - T glucuronidation doesn't always happen normally
  - Interpretation may be challenging, unless you understand the nuances
  - UGTs (uridine diphosphoglucuronosyl transferases) play a key role in androgen metabolism and homeostasis

UGT SNPs



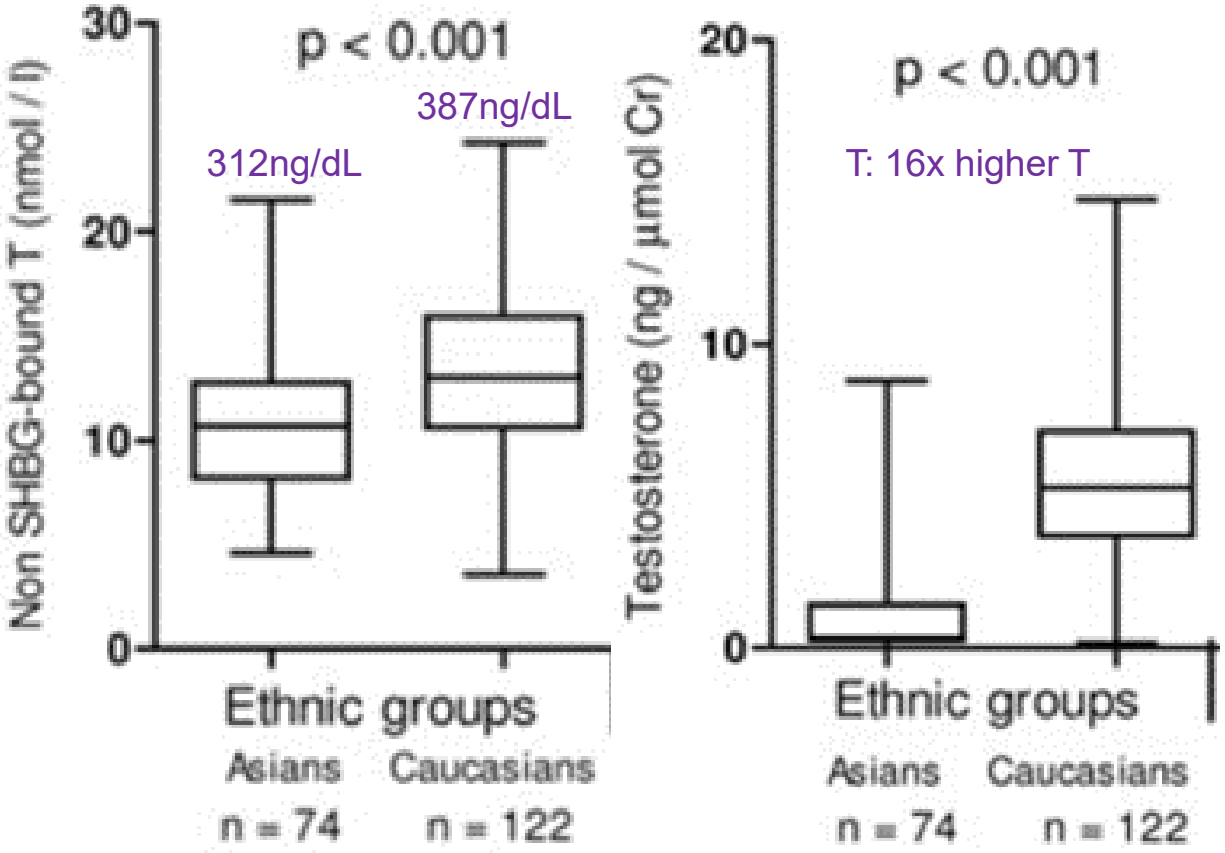
- **UGT2B17 conjugates: T, DHT, 5β-Androstanediol**
- **UGT2B7 conjugates: Epi-T, 5α-Androstanediol**

Jakobsson J, et al. J Clin Endocrinol Metab. 2006; 91(2): 687-693.
Stein T, et al. Drug Metab Dispos. 2009; 37(2): 417-423.
Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

UGT SNP and Urine Testing

Large Differences in Testosterone Excretion in Korean and Swedish Men Are Strongly Associated with a UDP-Glucuronosyl Transferase 2B17 Polymorphism

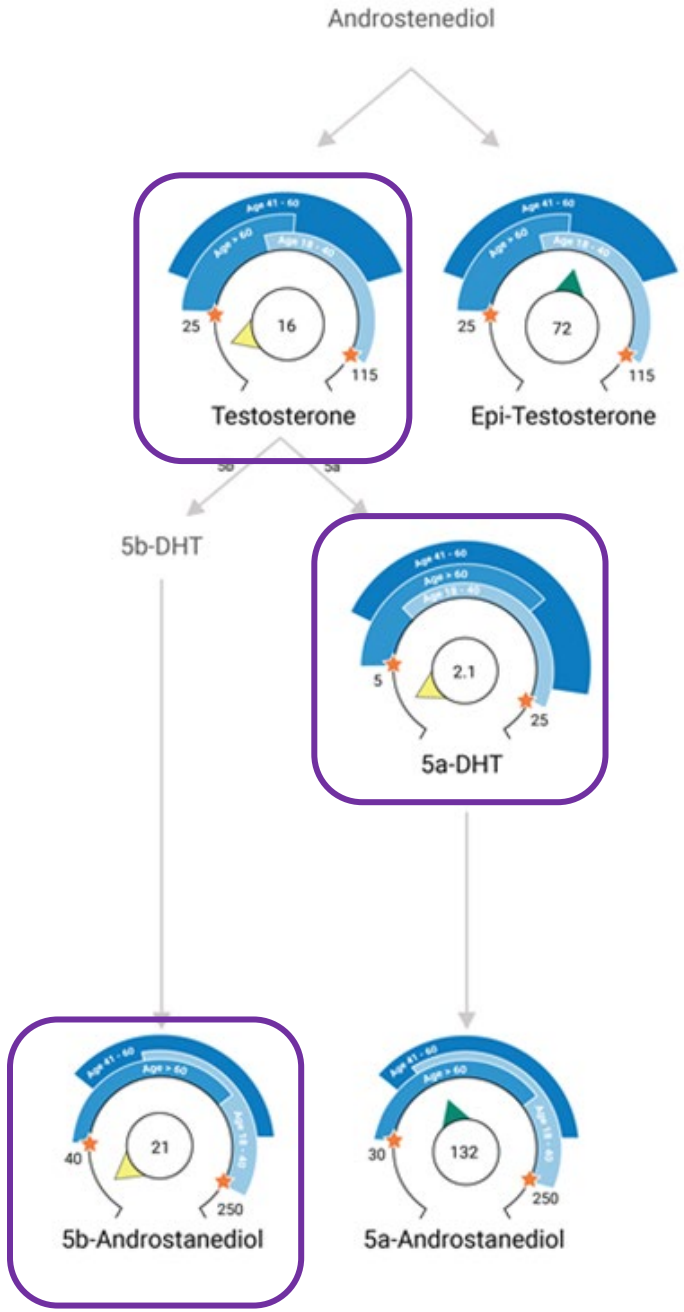
Jenny Jakobsson, Lena Ekström, Nobuo Inotsume, Mats Garle, Mattias Lorentzon, Claes Ohlsson, Hyung-Keun Roh, Kjell Carlström, and Anders Rane



- Study:
  - 122 Caucasian men and 74 Korean men
  - Assessed urinary T excretion patterns and serum T concentrations in relation to UGT2B17 SNP
- Results:
  - Caucasian male serum T levels were significantly higher than Korean male serum T levels
  - Urinary T excretion was 16x higher in Caucasians
  - Serum T significantly correlated with urine T excretion in both groups
  - Epi-T urinary excretion was the same in both groups
  - **UGT2B17 SNP (+/+) was 7.2 times higher in Korean men than Caucasian men (66.7% vs 9.3%)**
- Conclusions
  - UGT2B17 SNP occurs frequently (> 60%) in Korean men, whereas it occurs in < 10% of Caucasian men
  - SNP explains difference in urinary T excretion

Jakobsson J, et al. J Clin Endocrinol Metab. 2006; 91(2): 687-693.

How do we translate this into clinical practice?



UGT2B17 SNP

- Findings:
  - **(+) SNP: T, DHT, and 5β-Androstanediol are falsely low**
  - **(+) SNP: Epi-T and 5α-Androstanediol are normal**
  - **SNP occurs in women too**
- Male or female on TTh:
  - Serum is the primary tool
  - Urine is a useful adjunct: metabolites, etc.
  - In individuals of Asian descent urine may not reliable

Jakobsson J, et al. J Clin Endocrinol Metab. 2006; 91(2): 687-693.
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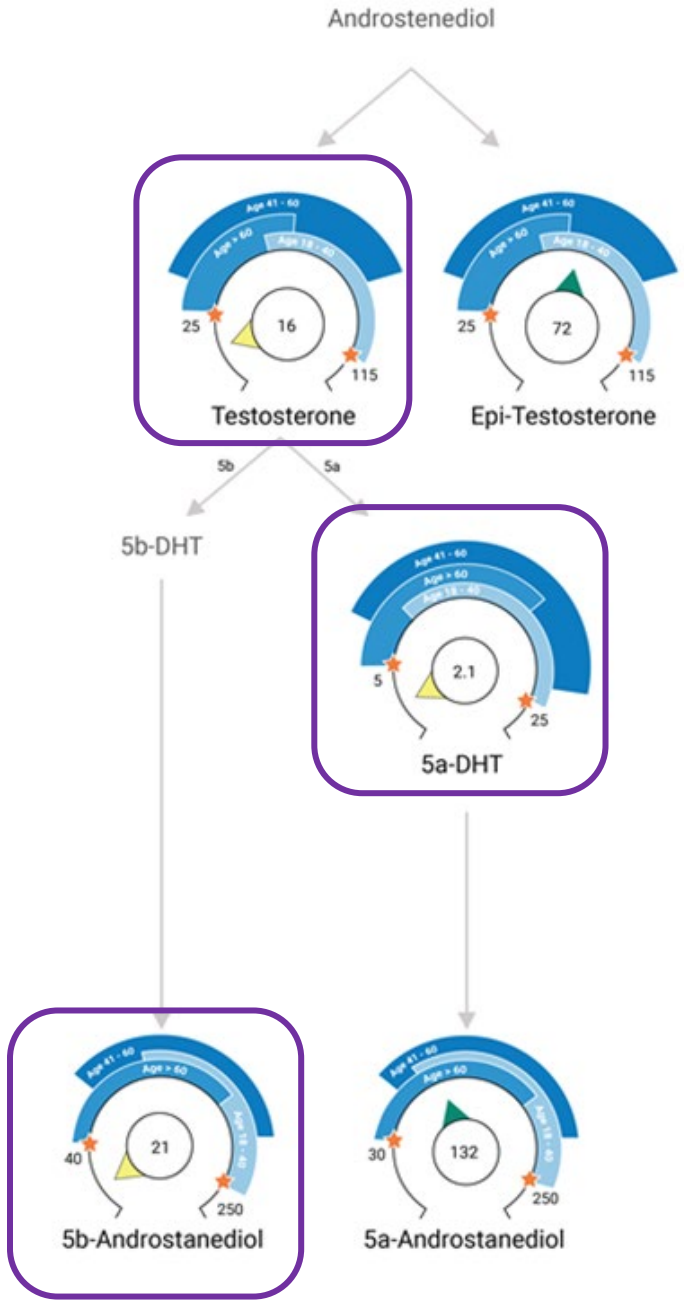

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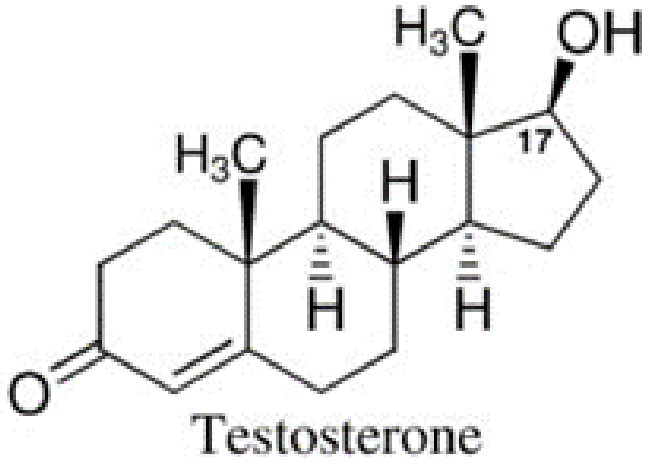
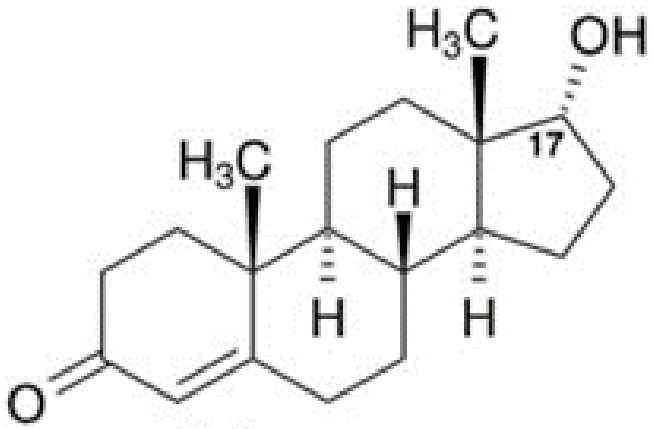
What is Epi-T?

Jakobsson J, et al. J Clin Endocrinol Metab. 2006; 91(2): 687-693.
Stein T, et al. Drug Metab Dispos. 2009; 37(2): 417-423.
Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

Epi-Testosterone



Testosterone



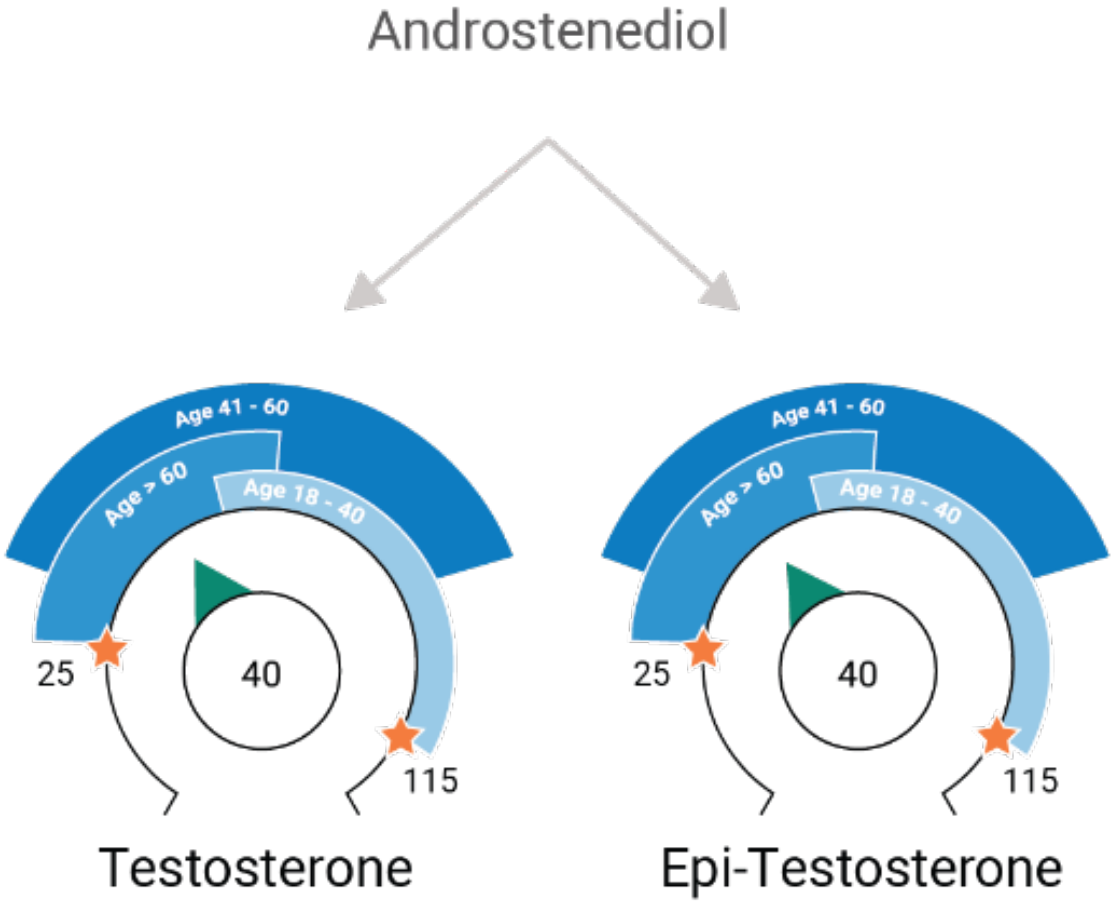
Epitestosterone

- An epimer of T; structurally identical but not mirror images
- Epi-T is also made by the testes in similar concentrations to T
- Epi-T is not androgenic
- A useful marker for identifying the UGT2B17 SNP
  - T is falsely low with (+) SNP; Epi-T normal
- In men: an approximate measure of gonadal T production and gonadal suppression
- In women: T from ovaries, adrenals, and peripheral conversion; literature not as clear on Epi-T interpretation

Kicman AT, et al. Clin Endocrinol (Oxf). 1999; 50(5): 661-668.
Stein T, et al. Drug Metab Dispos. 2009; 37(2): 417-423.

Epi-T with TTh

Before TTh, Epi-T and T have similar concentrations



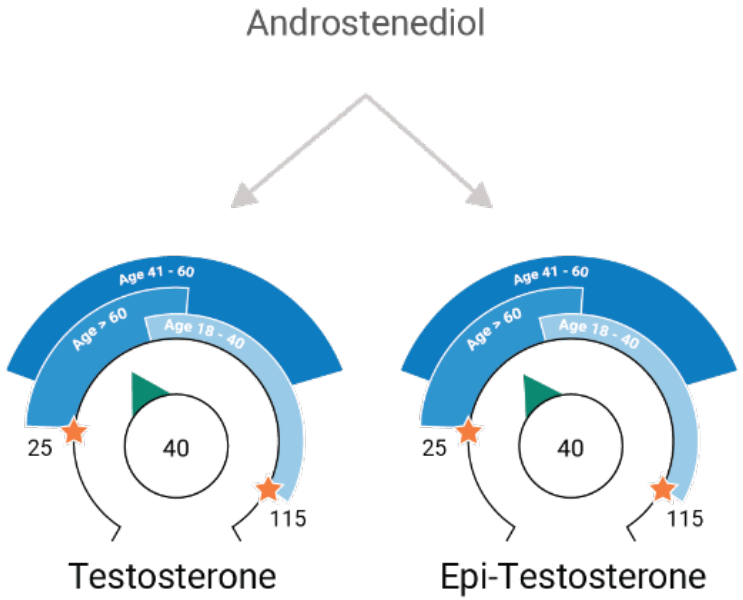
Typical Aging Male

Epi-T with TTh

Before TTh, Epi-T and T have similar concentrations

With TTh, Epi-T decreases to the extent that LH and gonadal androgen production is suppressed

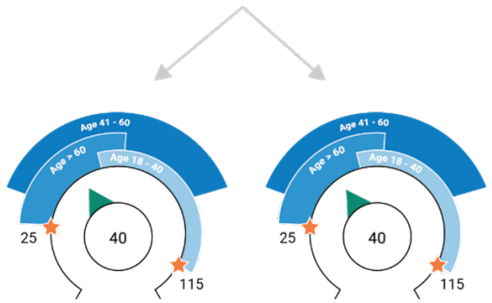
Average Aging Male



Testosterone	
Age	**Range**
18-25	50-115
26-40	40-95
41-60	30-80
>60	25-60

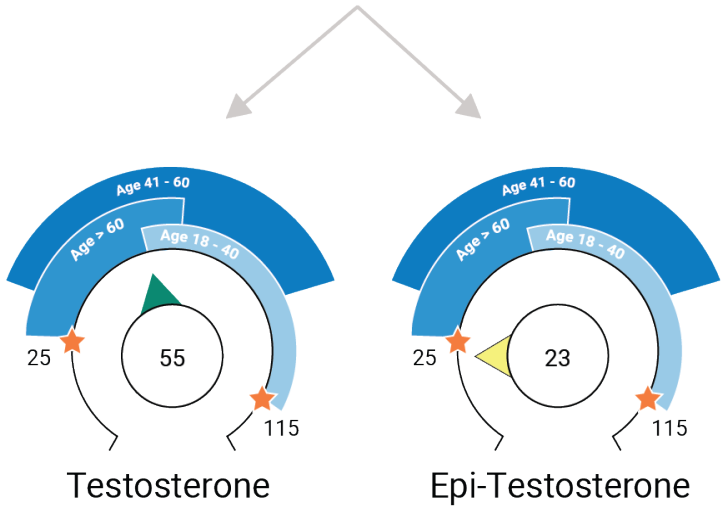
Epi-T with TTh

Androstenediol



25mg Gel

Androstenediol

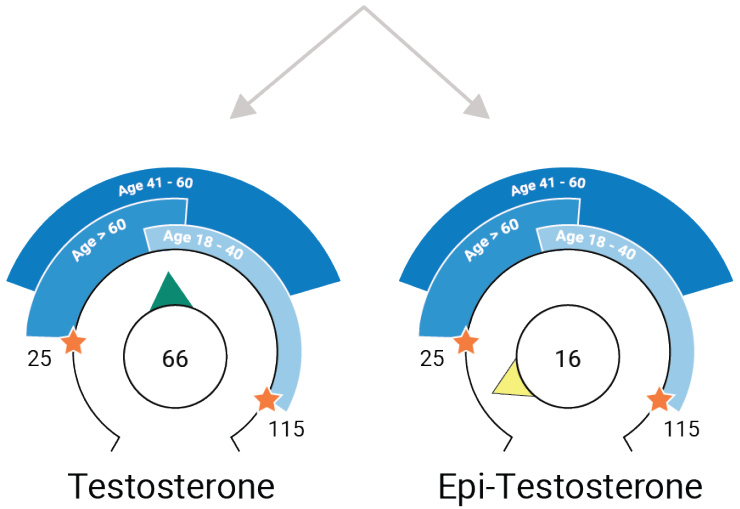


Testosterone

Age	Range
18-25	50-115
26-40	40-95
41-60	30-80
>60	25-60

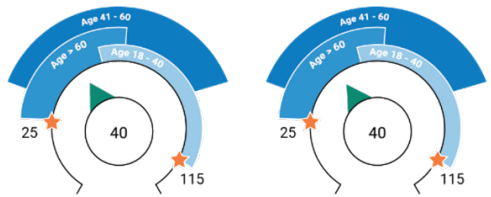
50mg Gel

Androstenediol



Epi-T with T Gel

Androstenediol

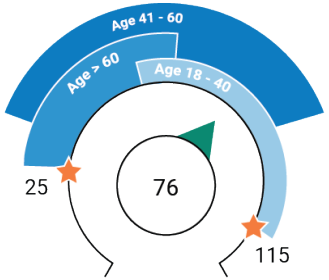


Testosterone

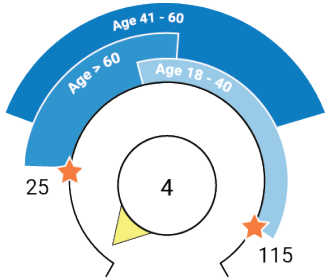
Epi-Testosterone

100mg Gel

Androstenediol



Testosterone



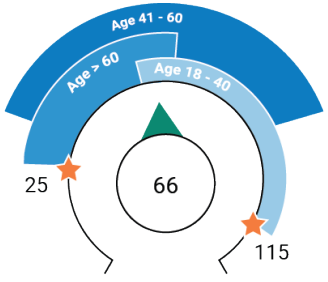
Epi-Testosterone

Testosterone

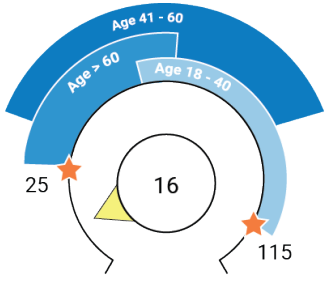
Age	Range
18-25	50-115
26-40	40-95
41-60	30-80
>60	25-60

50mg Gel

Androstenediol



Testosterone

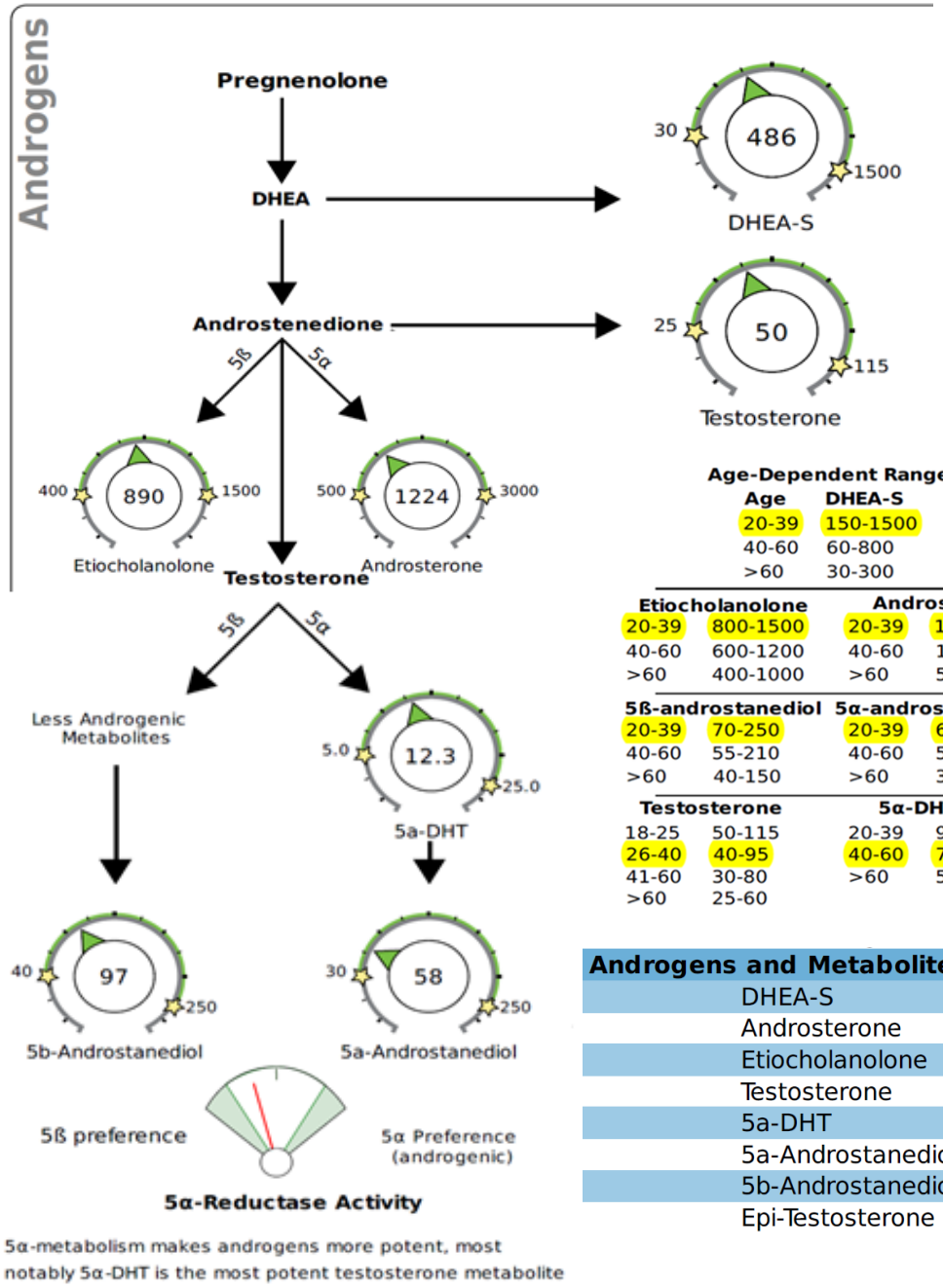


Epi-Testosterone

Kevin's Androgen Metabolism

Kevin's serum TT = 290ng/dL, FT-C = 63.5ng/dL

- No evidence of a UGT 2B17 SNP
- T and all T metabolites are low, consistent with low production, tissue exposure, and metabolism
- Favors 5β-reductase enzyme activity, which is less androgenic
- Urine is consistent with serum, Kevin indeed has TD



Age-Dependent Ranges

Age	DHEA-S
20-39	150-1500
40-60	60-800
>60	30-300

Etiocholanolone		Androsterone	
20-39	800-1500	20-39	1500-3000
40-60	600-1200	40-60	1000-2000
>60	400-1000	>60	500-1000

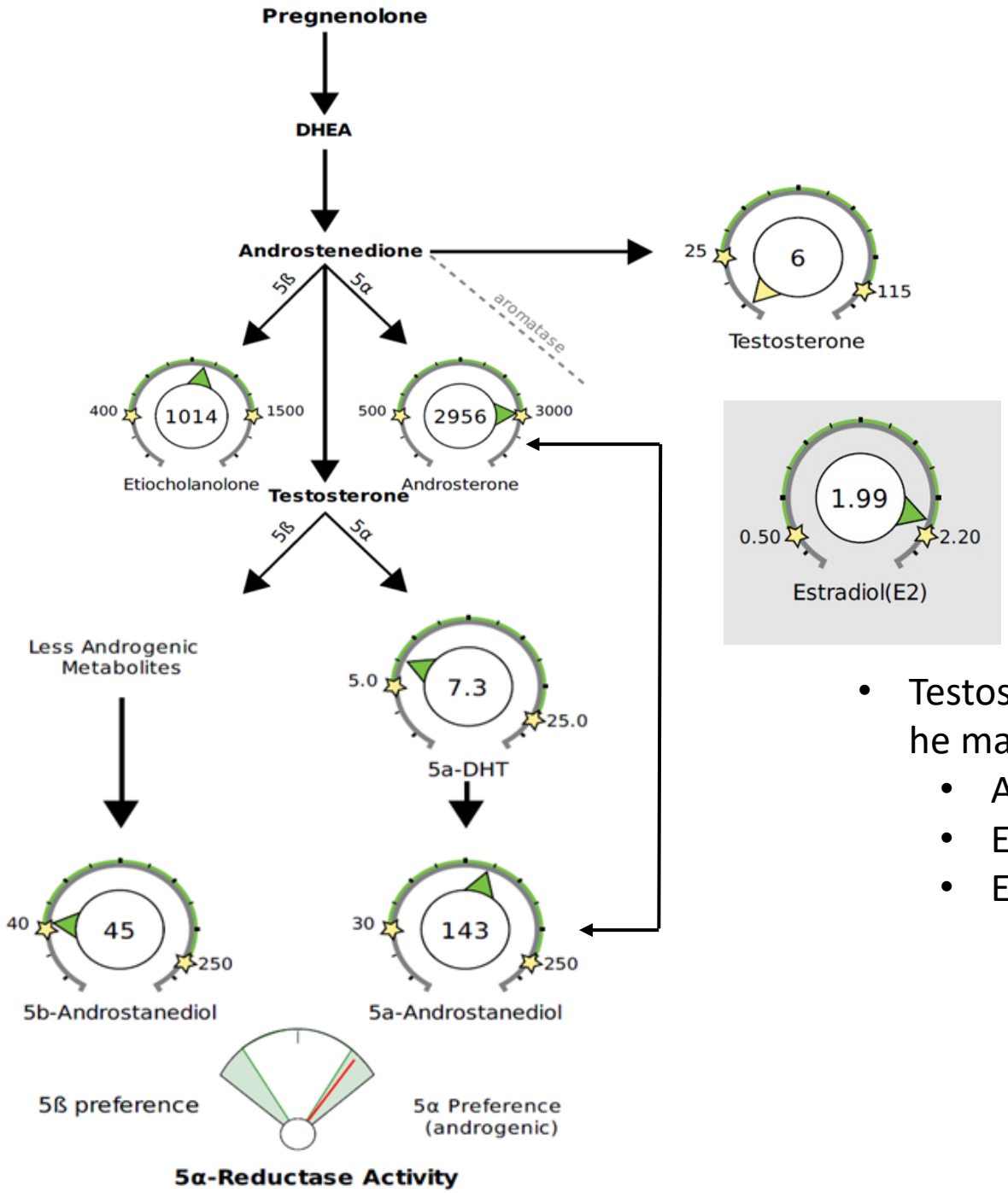
5ß-androstanediol		5α-androstanediol	
20-39	70-250	20-39	60-250
40-60	55-210	40-60	50-180
>60	40-150	>60	30-130

Testosterone		5α-DHT	
18-25	50-115	20-39	9-25
26-40	40-95	40-60	7-20
41-60	30-80	>60	5-16
>60	25-60		

Androgens and Metabolites (Urine)				
DHEA-S	Within range	486.0	ng/mg	30 - 1500
Androsterone	Within range	1224.0	ng/mg	500 - 3000
Etiocholanolone	Within range	890.0	ng/mg	400 - 1500
Testosterone	Within range	49.6	ng/mg	25 - 115
5a-DHT	Within range	12.3	ng/mg	5 - 25
5a-Androstanediol	Low end of range	58.1	ng/mg	30 - 250
5b-Androstanediol	Within range	97.0	ng/mg	40 - 250
Epi-Testosterone	Below range	17.5	ng/mg	25 - 115

Kevin's Organic Acid Results

Category	Test		Result	Units	Normal Range	
Nutritional Organic Acids						
Vitamin B12 Marker (may be deficient if high) - (Urine)						
	Methylmalonate (MMA)	Above range	3.2	ug/mg	0 - 3	
Vitamin B6 Markers (may be deficient if high) - (Urine)						
	Xanthurenate	High end of range	2.0	ug/mg	0 - 2.1	
	Kynurenate	Within range	6.0	ug/mg	0 - 9.3	
Glutathione Marker (may be deficient if low or high) - (Urine)						
	Pyroglutamate	Within range	65.8	ug/mg	43 - 85	
Neurotransmitter Metabolites						
Dopamine Metabolite - (Urine)						
	Homovanillate (HVA)	Within range	11.2	ug/mg	4.8 - 19	
Norepinephrine/Epinephrine Metabolite - (Urine)						
	Vanilmandelate (VMA)	Within range	6.5	ug/mg	2.8 - 8	At higher end of range
Melatonin (*measured as 6-OH-Melatonin-Sulfate) - (Urine)						
	Melatonin* (Waking)	Within range	30.6	ng/mg	10 - 85	Would like to see higher
Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)						
	8-OHdG (Waking)	Within range	2.5	ng/mg	0 - 8.8	



What If This Was Kevin's Androgen Metabolites?

- Testosterone is low, but patient is making sufficient T, but he may still have TD (serum TT and SS)
  - Androsterone is also a T metabolite
  - E2 is high and E2 is 100% synthesized from T
  - Epi-T high end of normal

What Do We Know about Kevin?

- Kevin definitely meets diagnostic criteria for TD
- Kevin has HPA axis dysfunction with decreased resilience, increased inflammation, which is impacting his testosterone production, signaling, and tissue responsiveness
- Kevin has gut dysbiosis, a permeable gut, some degree of metabolic endotoxemia, which increases inflammation and decreases T production, etc.
- Kevin's E metabolism and detoxification are OK, but may need to be addressed
- Kevin's androgen metabolism favors the less androgenic 5β-reductase, his T and all its metabolites are low, and he does not have a UGT 2B17 SNP

Kevin’s Treatment

stockadobe.com

Age, LH, Prolactin

- Primary Hypogonadism
  - T Replacement

LH RR (1.5-9.3mIU/mL) **LH**

- Secondary Hypogonadism

> Upper limits of RR

Could be at the lower end of RR or within the RR

Low Total Testosterone

3 - 18 Normal

Prolactin

> 18 High

- Work-up
  - MRI Brain to rule out prolactinoma
    - Cabergoline (dopamine agonist)
  - Chronic renal?
  - Hypothyroid?
  - Cortisol?

Lifestyle
- 8-hours restful sleep, movement
- Higher protein, Mediterranean eating

Nutraceuticals
- Eurycoma, Tribulus, Testofen, Thai Ginseng, Zinc

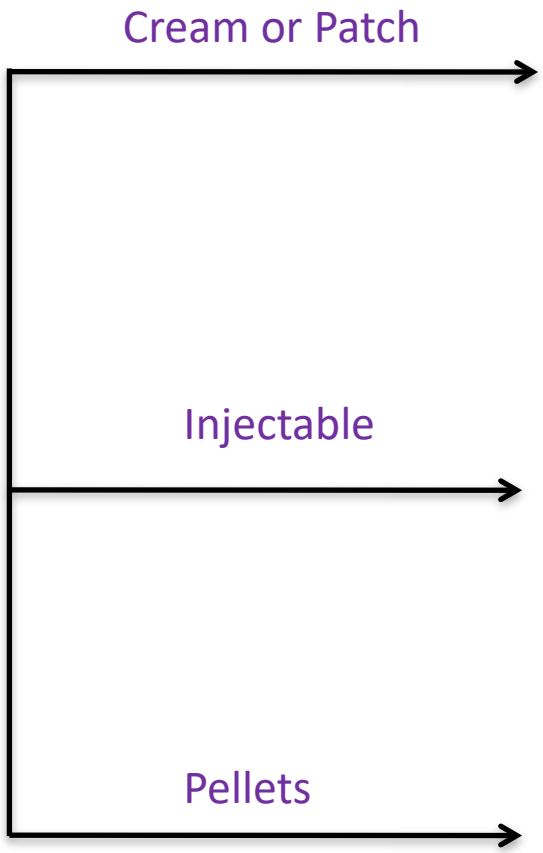
Age < 55
- Clomid: 5-15mg 3x week, most common
- HCG: 1000 IU 2x week x 6-8 weeks
  - 250 IU 6 d/w x 6-8 weeks
  - 500 IU 3 d/w x 3 weeks, then 500 IU 2d/w x 3 weeks
- Kisspeptin: 10mg at HS 5 d/w x 6 months

Age > 55
- Testosterone therapy (TTh)

** In men with secondary TD, especially younger men, don't forget to check for heavy metals, biotoxin illness, etc.

** Avoid glandulars with (+) TPO antibodies

Testosterone Options



- Testosterone patch
  - 2.5 and 5mg patches, starting dose is 5mg/day
- Topical Testosterone
  - AndroGel: 50mg/d; if using compounded cream you may need higher dose
- Keep it above the belt and rotate sites: chest/abd/flank/shoulders
- Labs in 1-month, 4-months, 8-months, 12-year, then 2x year is typical

- IM or Sub-Q (more comfortable for patient and as effective)
- Propionate (shortest acting) 10-25mg 2-3x week
  - Can use to dose pellets: for every 25mg place two 75mg pellets
- Enanthate
- Cypionate (most common) 25-50mg biweekly

- Pellets - viable option
  - Consider cost
  - Dosing adjustments: patients do not need as much as you think!

**Check PSA before and after initiation
**PSA increase > 0.75ng/mL worrisome PC

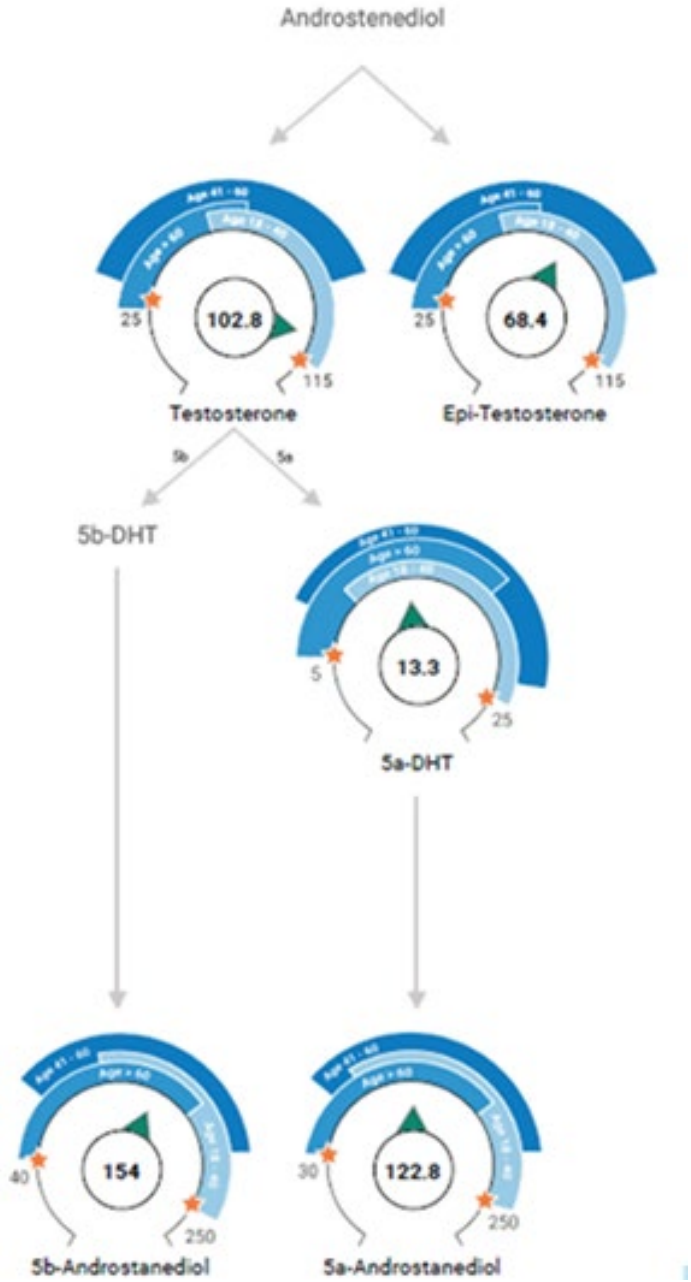
Raising T levels in Men

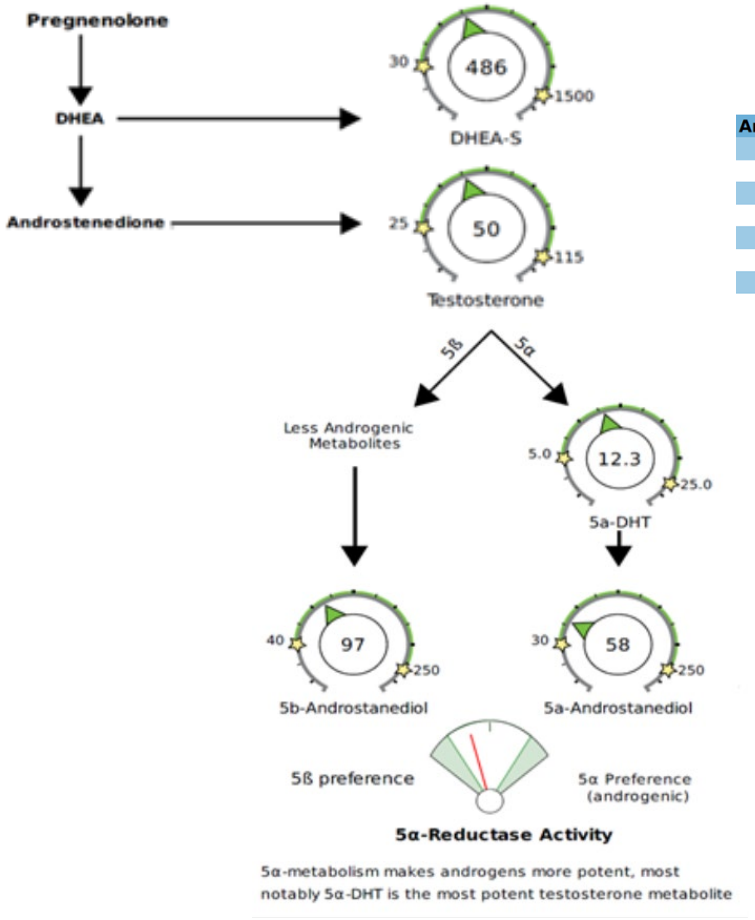
- Regardless of delivery, a serum T level > 500ng/dL improves sexual function, body composition, and BMD
  - AndroGel 50-100mg/d; T pellets: 400-900mg (avg: ~ 750mg)
  - Testosterone Undecanoate 750-1000mg initially, then at 6-weeks, then Q10-12 weeks
- Serum total E2 levels should be maintained between 20-40pg/mL (LC-MS/MS), goal 30-35pg/mL for optimum benefit
  - Sexual function, BMD, etc.
- Young men on Clomid or HCG
  - After 1 year of treatment + lifestyle changes, there will be a percentage of males who no longer require therapy
  - Stop treatment for 3-months and re-evaluate patient

Kevin's Treatment Plan

Target Organ	Treatment
HPA Axis	• Sleep hygiene and gentle exercise • Holy Basil 50mg BID and increase to 100mg BID slowly • Magnesium 10mg/kg elemental magnesium at HS
Gut Dysbiosis/IR	• Probiotic BID • Plant-based Mediterranean style eating that is gluten/dairy free • Intermittent fasting • ALA 300-600mg BID
Testosterone Deficiency	• Clomid 25mg M, W, F re: check labs in 4 weeks • DIM 1 capsule BID x 3 months
Miscellaneous	• Multivitamin • Complex methylated B vitamins • Consider IV hydration with methyl B's, vitamins, AA, glutathione, and phosphatidyl choline

Kevin's 4-Month Follow-up Androgens





Androgens and Metabolites (Urine)				
DHEA-S	Within range	486.0	ng/mg	30 - 1500
Androsterone	Within range	1224.0	ng/mg	500 - 3000
Etiocholanolone	Within range	890.0	ng/mg	400 - 1500
Testosterone	Within range	49.6	ng/mg	25 - 115
5a-DHT	Within range	12.3	ng/mg	5 - 25
5a-Androstanediol	Low end of range	58.1	ng/mg	30 - 250
5b-Androstanediol	Within range	97.0	ng/mg	40 - 250
Epi-Testosterone	Below range	17.5	ng/mg	25 - 115

Kevin's 4-Month Follow-up Androgens

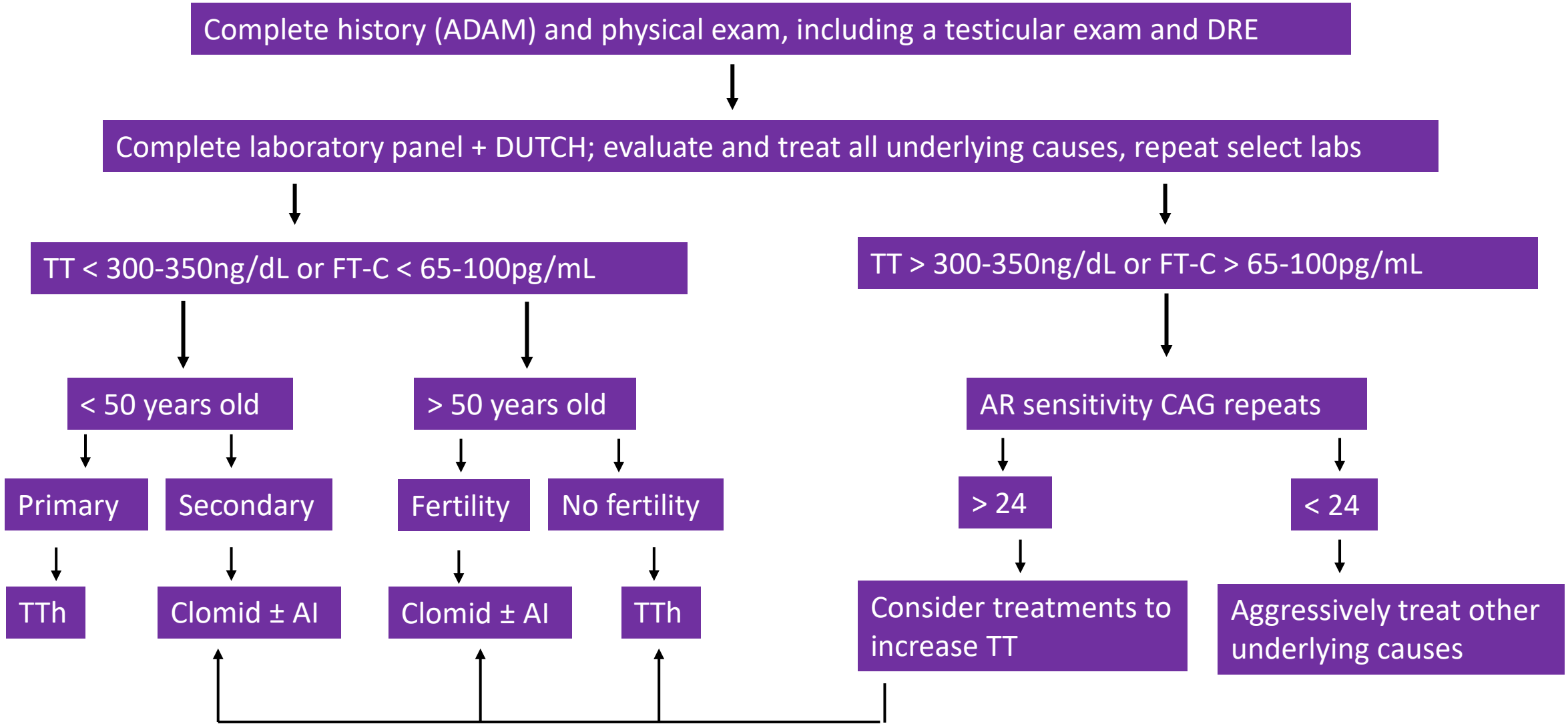
9.2021

- CBC: 15.1/42.9
- CMP: FBS: 90
- HbA1c: 5.7%
- TT: 290ng/dL (250-1100)
- FT-C: 63.5pg/mL (> 65-100pg/mL)
- E2: 23pg/mL (20-40, LC-MS/MS)
- SHBG: 16nmol/L (10-50)
- FSH: 5mIU/mL (1.6-8)
- LH: 2.3mIU/mL (1.5-9.3)
- PSA: 0.6ng/mL (1-1.5)
- Testicular volume: 8 cc

10.2021

- CBC: Hb/Hct: 15.3/43.2
- CMP: FBS: 70
- HbA1c: 5.1%
- TT: 700ng/dL (250-1100)
- FT-C: 188pg/mL (> 65-100pg/mL)
- E2: 30pg/mL (20-40, LC-MS/MS)
- SHBG: 23nmol/L (10-50)
- FSH: 5mIU/mL (1.6-8)
- LH: 1.0mIU/mL (1.5-9.3)
- PSA: 1.0ng/mL (1-1.5)
- Testicular volume: 15cc

My Approach To Males with Suspected TD

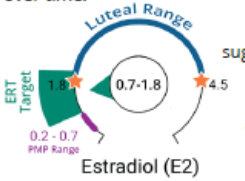


MONITORING (B)HRT WITH LAB TESTING

Tutorials available at www.dutchtest.com/videos/hormone-tutorials

PRECISION ANALYTICAL INC.
CREATORS OF THE DUTCH TEST®

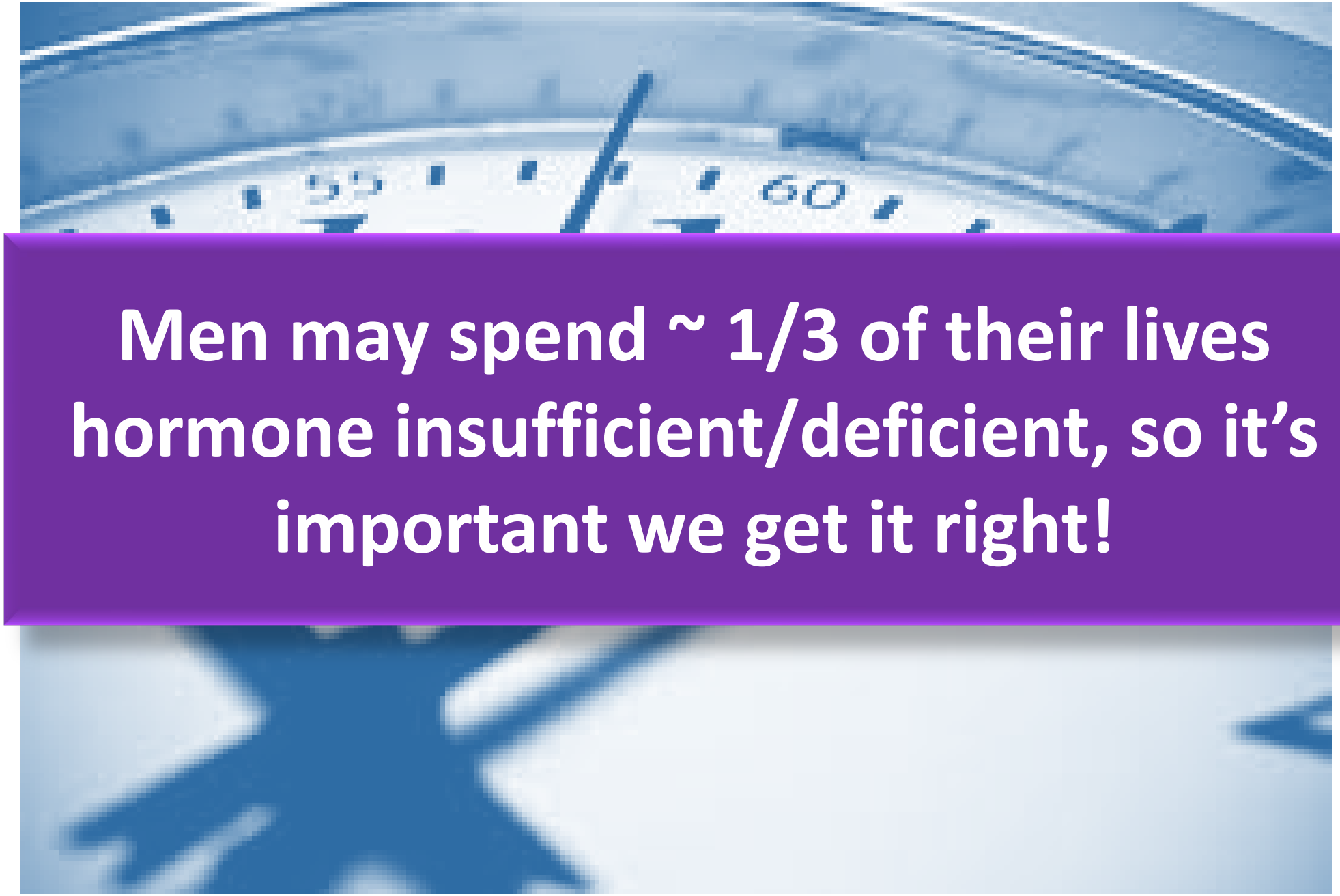
Can serum or DUTCH, as a standalone test, effectively monitor HRT? ✔ Yes ✘ No ? Maybe

Oral Progesterone (OMP)	Estradiol (E2) Patches	E2 Gels & Creams (Skin)	Vaginal E2 & Testosterone (T)	Vaginal Progesterone (Pg)	Transdermal (TD) Testosterone	Testosterone Injections & Pellets
✔ DUTCH	✔ DUTCH	✔ DUTCH	✔ DUTCH	✘ DUTCH	? DUTCH	? DUTCH
The DUTCH Test® provides useful feedback when using OMP in women with PMP sleep disturbances. 5a (more active) and 5b metabolites are measured to individualize OMP dosing. OMP's sleep effects are via its 5a metabolites, predominately allopregnanolone binding to the GABA receptor. No lab test reflects OMP's effect on the endometrium.	Values between the top of the postmenopausal range and the lower limit of the premenopausal range correlate with patient clinical improvement (bone density, hot flash relief, etc.). Doses that push levels to the middle of the premenopausal range and beyond may be excessive. DUTCH is preferred over serum because in addition to metabolites, dried urine averages out the daily up and down E2 patterns. This is particularly helpful with gels and creams that may have serum values that change rapidly over time.  The aggregate clinical data suggests that a serum (LC-MS/MS) E2 level of ~20-40pg/mL improves clinical outcomes (VMS, VVA, BMD). This approximates a DUTCH value of ~ 0.7-1.8ng/mg.		The DUTCH Test® is unique in that it removes potential contamination, and monitoring is helpful with E2 and T. Very low doses may impact local tissue without increasing lab values. For local (not systemic) E2 therapy, keep urine E2 in PMP range.	Pg is measured indirectly in urine by measuring pregnanediols. These metabolites may be underrepresented when Pg is taken vaginally. Serum Pg seems to increase to a higher degree than urine metabolites with vaginal Pg application.	Levels generally parallel changes in serum and clinical outcomes (increased lean body mass, erythrocytosis, etc. in men). Epi-testosterone (Epi-T) values can be used to assess gonadal suppression due to TRT (Epi-T levels in men decrease as TRT increases and are <10ng/mg with complete suppression).	Injections and pellets increase levels, as expected, but the increase may exceed what is seen in serum testing. DUTCH allows for monitoring both the dosing of hormones as well as metabolic patterns.
			Vaginal E2, Pg, and T are systemically absorbed. If placed in the top 1/3 of the vagina, a higher dose will get to the uterus (uterine 1st pass effect), which may be helpful for Pg, but not E2.		Urine testosterone does not correlate as reliably to T serum values, compared to E2 and other tests. Urine testing is best suited as a complimentary test to serum for T and should not be used solely for TRT decisions.	
✘ SERUM	✔ SERUM	? SERUM	✔ SERUM	? SERUM	✔ SERUM	✔ SERUM
Results go up and down quickly. If taken at bedtime, levels return to baseline within a few hours. Results can also be inaccurate due to progesterone metabolites cross-reacting with immunoassay tests.	Serum testing is well suited for use with these types of therapies. Results increase with increased dosing in a fairly linear fashion. Most recommendations are to push serum E2 levels to 20-40pg/mL for clinical impact.	The only published data for E2 creams shows serum results move up and down within a few hours, so serum testing can easily underestimate clinical impact. DUTCH results average out the daily up and down pattern and may be a better option.	Serum results rise quite dramatically with what may seem like modest doses due to the high uptake of hormones across the mucosal membrane. However, values may rise and fall quickly, so be careful with the interpretation of both low and high results.	Serum values increase with dosing and likely represent systemic exposure to Pg. However, the uterine first-pass effect loads the uterus with high levels of Pg (which may be desirable) and serum does not reflect uterine hormone levels.	A great deal of published research shows that serum levels reflect clinical changes in both men and women taking TD T. Be aware of potential up and down patterns throughout the day, but serum is the best tool for monitoring doses of TD T in both men and women.	Serum testing is well suited for use with these types of therapies. Results increase with increased dosing in a fairly linear fashion. Test injections halfway between doses or right before a dose.

✘ SALIVA	The literature does not support salivary testing's use for monitoring TD hormone creams. The saliva data is limited and, in fact, there are no saliva testing outcome studies using TD creams, injections, estradiol patches, oral estradiol, or vaginal hormones. While salivary testing is the gold standard for free cortisol measurement, avoiding its use for monitoring HRT is advised. For situations where saliva testing may parallel the clinical impact, DUTCH or serum testing are better options (see above).
✘ Oral Estradiol, Estradiol Pellets, or Sublingual Hormones	Though not recommended, if you choose to use either oral estradiol or estradiol pellets, serum testing can monitor both, whereas urine should only be used with pellet therapy. Sublingual hormones may be used in some situations but lab monitoring is not helpful in optimizing doses.
✘ Transdermal Progesterone	In PMP women, the evidence does not support TD Pg's use to protect the endometrium. When prescribed, laboratory monitoring is not helpful for TD Pg dosing.

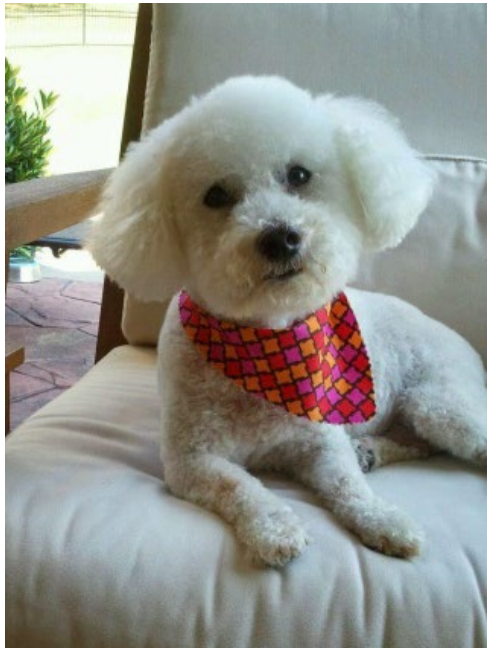
Final Thoughts

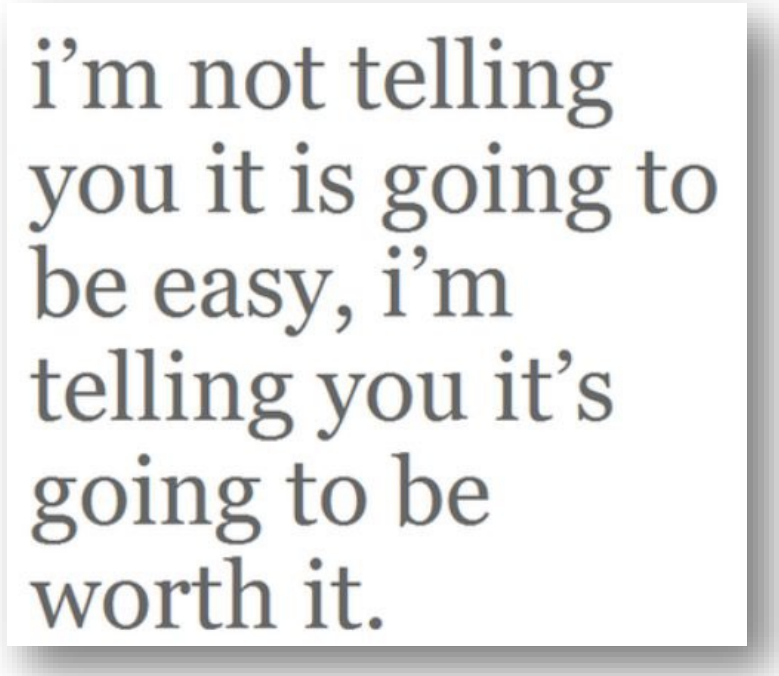
- In males who meet diagnostic criteria for TD, don't stop there
- Address the HPA axis, the gut, etc. ⇨ the whole person
- What ever therapy you choose, start low, go slow, and set expectations
- Laboratory monitoring is key, don't just treat
- Learn and understand hormone metabolomics, it is essential to a successful hormone practice
- Ask yourself: are your decisions evidence-based?
- Are you questioning the absolutes and asking: where is the evidence?



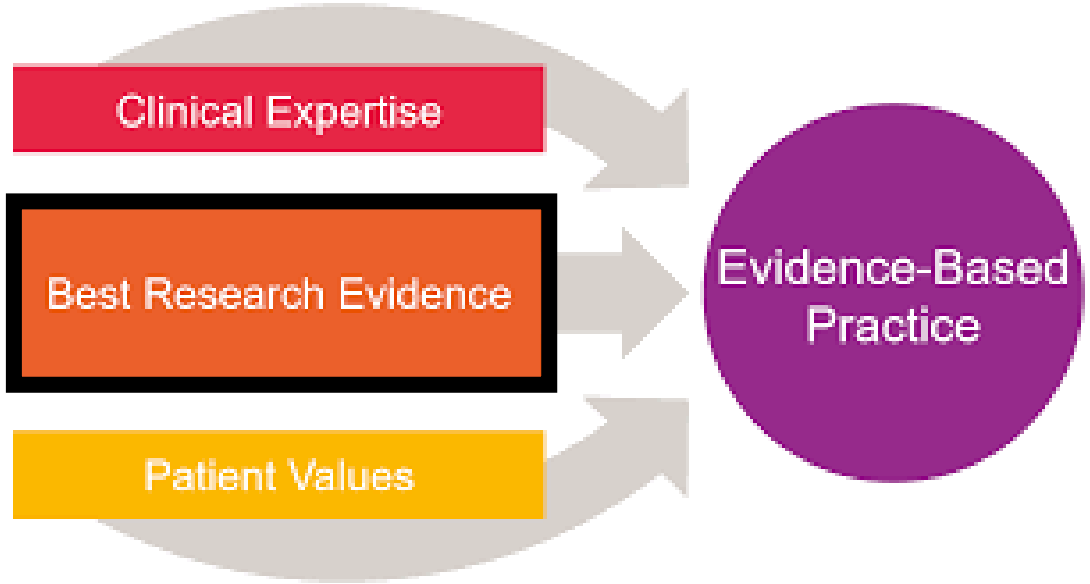
Men may spend ~ 1/3 of their lives hormone insufficient/deficient, so it's important we get it right!

Doreen Saltiel, MD JD FACC FAARFM ABAARM
Peak Health and Wellness
Asheville, NC





Questions?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Best Research Evidence
Patient Values
Evidence-Based Practice

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