Testosterone and the Prostate

E. David Crawford, MD

Professor of Surgery (Urology) and Radiation Oncology

Head, Urologic Oncology

E. David and Vicki M. Crawford Endowed Chair in Urologic Oncology

University of Colorado Health Sciences Center

Denver, Colorado

Men with low T when diagnosed with prostate cancer have a lower GS?

- 1. True
- 2. False
- 3. Unsure

ARS: Testosterone replacement therapy(TRT) has been shown to flair prostate cancer in men on Active Surveillance ?

- 1. Yes
- 2. No
- 3 Not sure

Testosterone Treatment

Potential Benefits

- Increase sexual interest
- Improve erectile function
- Increase muscle mass/strength
- Decrease central fat
- Increase bone density
- Improve cognition
- Improve mood/well-being
- Improve physical performance/activity
- Decrease fractures
- Improve QOL
- Increase life expectancy

Potential Risks

- Increase risk and severity of prostate cancer
- Exacerbate benign prostatic hyperplasia
- Polycythemia
- Exacerbate sleep apnea
- Fluid retention
- Coronary artery disease
- Gynecomastia
- Priapism
- Acne

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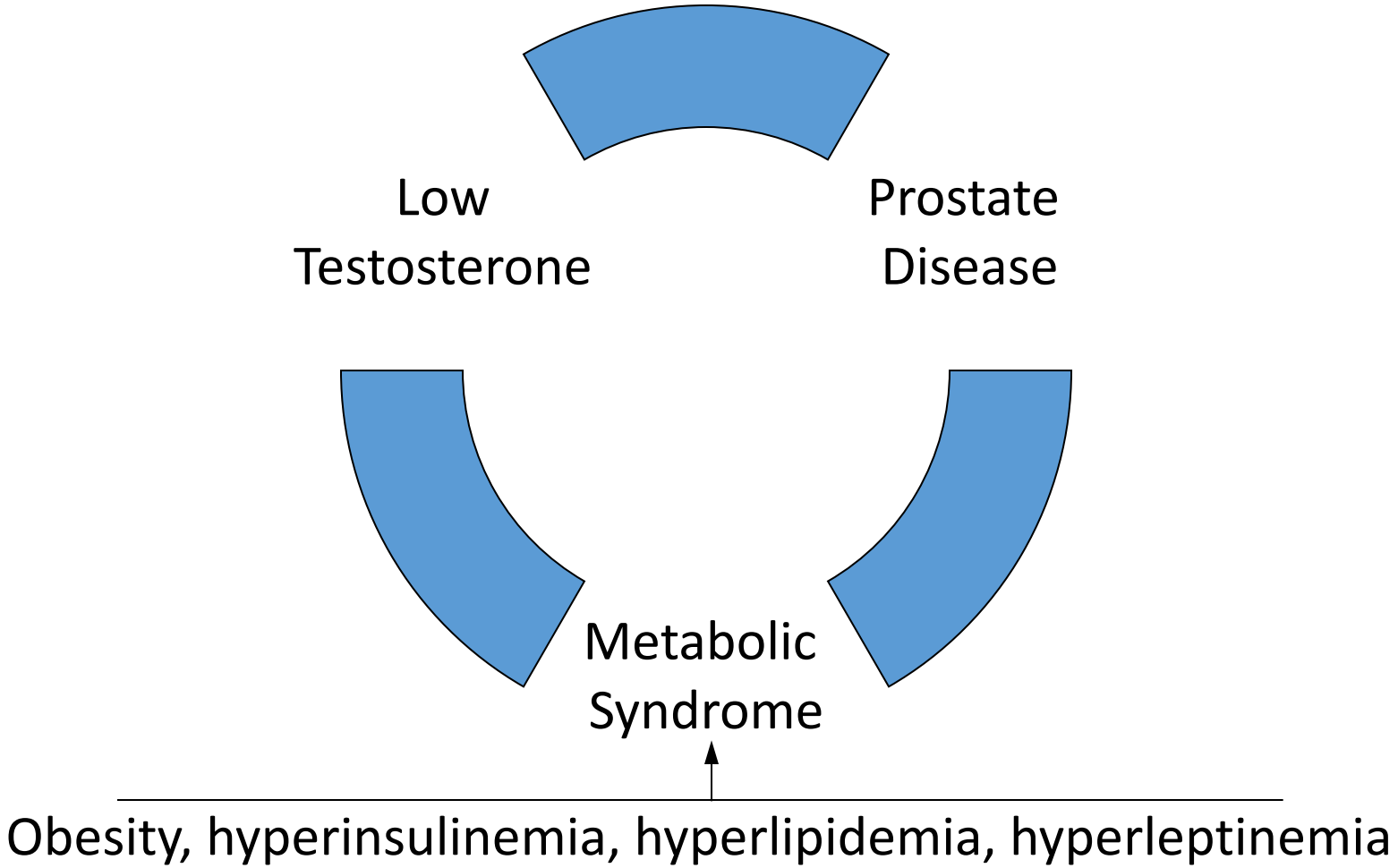
Increase risk and severity of prostate cancer

Testosterone Treatment



Testosterone Substitution
and Possible Prostate Changes

- **Increases in PSA levels?**
- **Increases in prostate volume?**
- **Stimulation of growth in previously undiagnosed tumors?**

- ***No data to support testosterone substitution as a cause of prostate cancer***

Basaria S, Dobs AS. *Drugs Aging*. 1999;15(2):131-142.
Hajjar RR et al. *J Clin Endocrinol Metab*. 1997;82(11):3793-3796.
Rhoden EL, Morgentaler A. *N Engl J Med*. 2004;350(5):482-492.

Testosterone and the Prostate

- **Prostate development, differentiation, and maintenance are known to be closely linked to the bioavailability of testosterone and other related sex hormones**

- **Huggins, 1941**
  - **Deprivation of testosterone slowed the progression of prostate cancer**

Testosterone and the Prostate

Clinical concern:

Testosterone risk of converting an occult cancer into a clinical cancer?

Testosterone and the Prostate

If castration makes PCa cells die, then shouldn’t raising testosterone (T) make cancer cells grow?

Testosterone and the Prostate

BUT…

Men dying from prostate cancer are all castrated!

Testosterone and Prostate Cancer

Time for reevaluation
based on evidence!

- One of the principles of Evidence-based Medicine is that concepts that fail to withstand scientific scrutiny are to be discarded

- Such a time has come for the belief that T causes enhanced growth of prostate cancer (PCa)

A. Morgentaler, MD
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

Testerone and Prostate Cancer: An Historical Perspective on a Modern Myth

Morgentaler A. *Eur Urol.* 2006;50(5);935-939.

Huggins' Heritage From a 1967 Review Article:

"Orchiectomy or the administration of estrogens resulted in regression of PCa

"Whereas, in untreated prostates, testosterone enhanced the rate of growth of cancer"

Huggins C. *Cancer Res.* 1967;27(1):1925-1930.

However . . .

The logic: “testosterone favors PCa growth” is completely inconsistent

There is robust data supporting this view

Huggins and Hodges reported that daily injections of testosterone propionate caused **acid phosphatase** levels to increase. LHRH Flair!!!

Although 3 men were injected, results were provided for only 2 of them.

One of these 2 had already been castrated.

In the remaining patient, acid phosphatase levels rose during 18 days of T treatment, but fluctuated widely before and afterward, reaching the same peak levels 3 weeks after T discontinuation.

Huggins C, Hodges CV. *Cancer Res*. 1941:293-297.

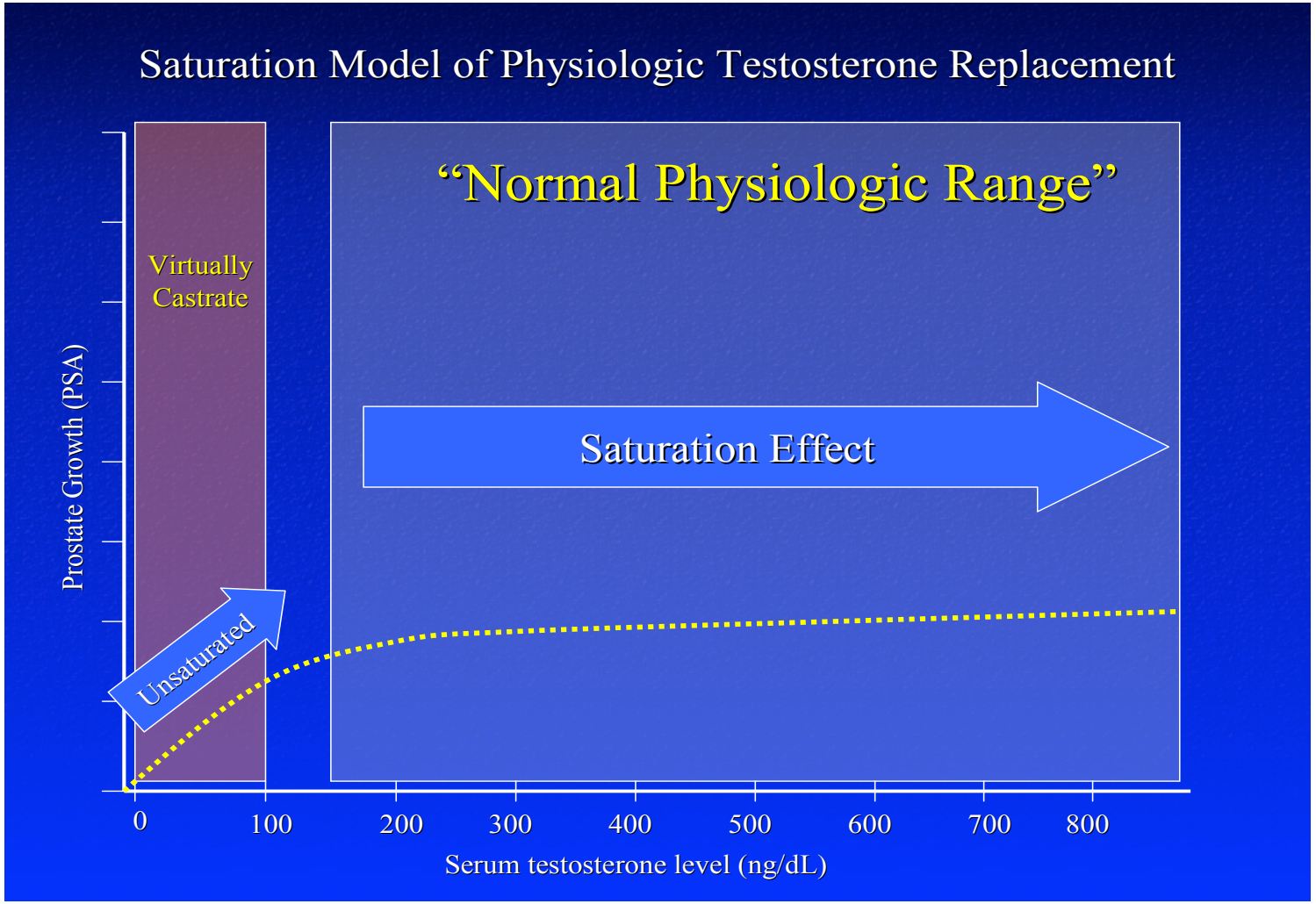
The original assertion that testosterone caused prostate cancer in untreated patients was thus based on equivocal acid phosphatase results in a single individual!!

The US Institute of Medicine:

"In summary, the influence of T on prostate carcinogenesis and other prostate outcomes remains poorly defined"

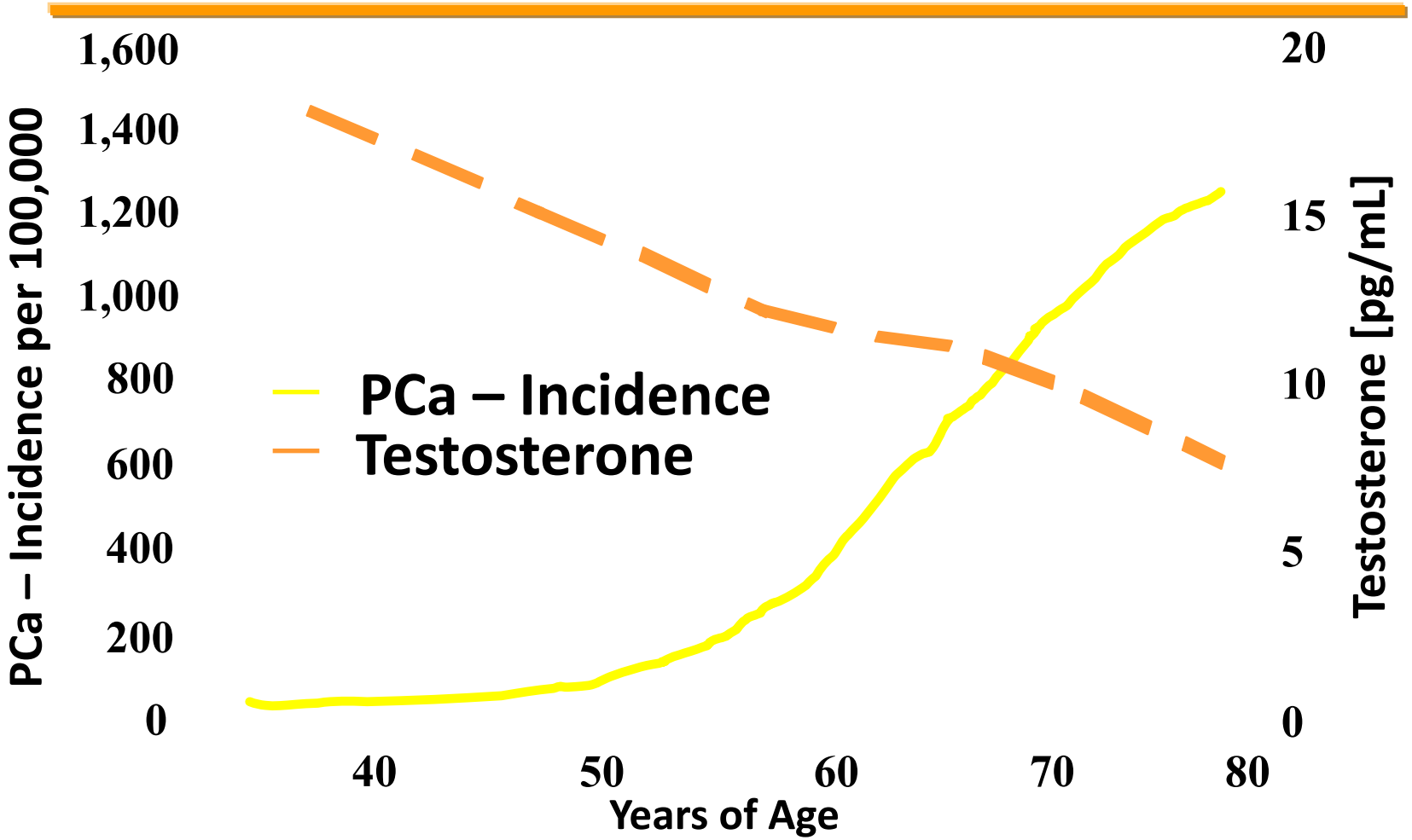
Liverman CT, Blazer DG, eds. *Testosterone and Aging: Clinical Research Directions.* Washington DC: National Academies Press; 2004.

Prostate Saturation Model



Morgentaler A, Traish AM. *Eur Urol*. 2008;55:310-320

Incidence Of Prostate Cancer Testosterone



Miller B. *J Natl Cancer Inst.* 1993;85(13):1023.
Madersbacher et al. *Urologe A.* 2001:540.

Occult Cancer
in Men With Low Testosterone

- 77 men with low total or free serum testosterone, normal DRE, and PSA <4 ng/mL
- All underwent sextant ultrasound-guided prostate biopsy
- 11 (14%) had biopsies positive for prostate cancer
- Expected (published) prevalence of positive biopsies in men with normal DRE and PSA <4 ng/mL is 1.8% to 4.5%
- Decreased androgen status may mask prostate cancer
- Is low testosterone a risk for men treated with testosterone substitution?

Morgentaler A et al. *JAMA*. 1996;276(23):1904-1906.

Low T Increases Prostate Cancer Risk

References	Number of Pts	Study Type	Endogenous TTh Level	CaP Outcomes
Morgentaler et al.[29]	77	Retrospective	T <300 ng/dl or free T <1.6 ng/dl	CaP incidence of 14% (11/77)
Mearini et al.[31]	206	Prospective	≤2.4ng/ml ≤0.5ng/ml	14.2% of patients had clinically locally advanced or metastatic CAP, and 57.1% have a pathological locally advanced CaP
Shin et al.[32]	568	Prospective	<3.85ng/ml	CaP incidence 38.0% (vs. 29.5% high testosterone
Karamanolakis et al. [39]	718	Prospective	<3.0 ng/ml	CaP incidence 30% (29/97)
Morgantaler et al. [30]	345	Retrospective	<250ng/dl	CaP incidence 21% (vs. 12% in men with T>250ng/dl)
Hoffman et al.[33]	117	Retrospective	T<300ng/dl or free T<1.5ng/dl	CaP incidence 43% (vs. 22%)
Garcia-Cruz et al.[34]	137	Prospective	<346 ng/dl	Tumor burden 53% (vs. 32% in men with T >346 ng/dl); tumor bilaterality 50% (vs. 25.5% in men with T >346
Isom-Batz et al.[35]	326	Retrospective	<385ng/dl	Associated with advanced pathological stage (OR 2.3, 95% CI 1.1-5.0; p = 0.03)
Lane et al.[36]	455	Prospective	<220ng/dl	Higher frequency of Gleason 4-5 disease (OR 2.4, 95% CI 1.01-5.7; p = 0.48)
Botto et al.[40]	431	Prospective	<3ng/ml	Higher frequency of Gleason 4 disease (47% vs. 28%)
Salonia et al.[37]	673	Prospective	Total T <1ng	Higher incidence of seminal vesicle invasion (OR 3.11)
Teloken et al.[38]	64	Retrospective	<2.7ng/ml	Increased positive surgical margins (p = 0.026)

Pastuszak AW, Rodriguez KM, Nguyen TM, Khera M. Transl Androl Urol 2016 (in press)

Hypogonadism

A Marker for More Aggressive Prostate Cancer?

- Patients with a biopsy Gleason score of 8 or greater had low testosterone.[1,2]

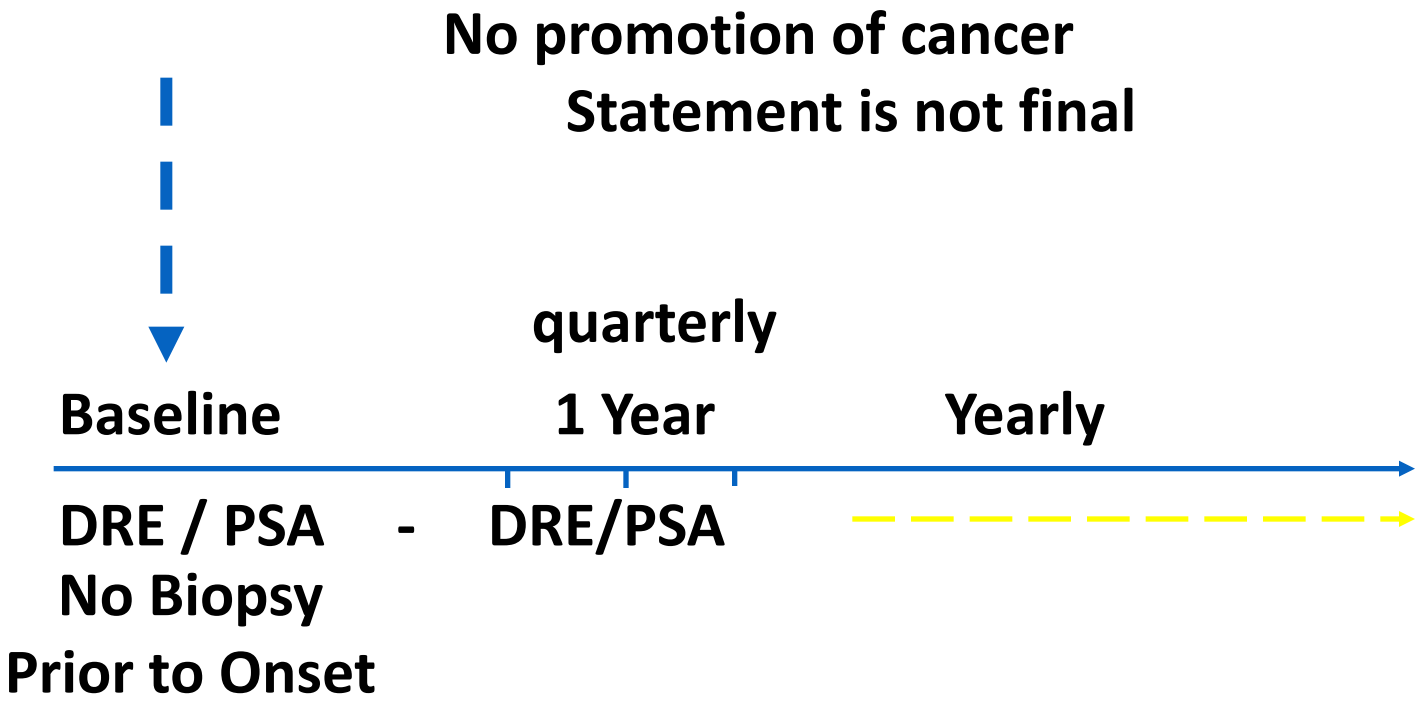
- Pretreatment testosterone level is an independent predictor of extraprostatic disease in patients with localized prostate cancer.[3]

1. Hoffman MA et al. *J Urol*. 2022;163(3):824-827.
2. Schatzl G et al. *Prostate*. 2001;47(1):52-58.
3. Massengill JC et al. *J Urol*. 2003;169(5):1670-1675.

Final Thought…..

- After a radical prostatectomy, if you do not replace testosterone levels in hypogonadal men to make them eugonadal, then how can you justify not lowering testosterone levels in eugonadal men to make them hypogonadal?

T- Replacement and
PCa – Risk Follow-up



Testosterone Treatment

Summary

- **Testosterone treatment: beneficial effects for multiple systems**
- **Safe, with appropriate medical monitoring**
- **Need for more evidenced-based studies**

The great enemy of the truth is very often not the lie . . . but the myth, persistent, persuasive and unrealistic

John F. Kennedy

IT TAKES A LONG TIME

TO BECOME YOUNG

Pablo PICASSO