TRT Overview

It is important to take into account the ***signs & symptoms in addition to the lab values*** when making TRT decisions. Evaluation of the blood analysis should not be the only consideration in the TRT treatment pathway. When testosterone levels are not obviously abnormal, clinicians can choose to treat patients based on their symptoms (see empiric therapy below). A trial of treatment is easily warranted for such potential significant life changing improvements with a low risk profile. The goal should be to get patients at least to the average testosterone level of their age group or better.

Indications for TRT

There are two primary indications for testosterone replacement in adult men with low circulating testosterone levels. One indication is for the treatment of men with substantially decreased serum T concentrations as a consequence of a significant disruption of the hypothalamus-pituitary-gonadal (HPG) axis, such as in men with certain brain surgeries, absent / atrophic testes, or due to the use of certain prescribed medications (opiates and corticosteroids are usually the main 'culprits').

A second more common indication is for the treatment of men exhibiting signs or symptoms of testosterone deficiency associated with low circulating testosterone values irrespective of age (assuming no other possible cause of their symptoms). Sleep apnea, depression, thyroid conditions, anemia, elevated prolactin levels and other issues can have similar symptoms to low testosterone.

Empiric (based on experience and expectation) treatment with TRT

The Journal of Sexual Medicine published an article "Diagnosis and Treatment Guidelines for Testosterone Deficiency: Recommendations for the Fourth International Consultation for Sexual Medicine ICSM 2015" : J Sex Med 2016; 13:1787-1804

This article states ***"A 3-6 month trial of empiric TRT can be considered in men with suggestive symptoms but without definitive diagnostic blood test results, because there is no absolute T concentration that reliably distinguishes who will or who will not respond to treatment and because of substantial interindividual variation in T physiology".***

A good comparison of this process is reflected in amphetamine medications for kids and adults who potentially have ADHD or ADD - it is hard to 'know' if a patient actually needs treatment medications (there is no blood test for ADD/ADHD, just recognized symptoms that suggest the diagnosis), but the benefit can be dramatic, so we try the patient on medications - if the medication makes a difference in their concerning behaviors or focus ability, then they clearly need continued treatment. If it doesn't, the provider stops the use of medication. The same clinical decision making process (as above) can apply for providers when considering treatment with TRT. If it works, great! Treatment should continue. If it doesn't work (assuming appropriate treatment levels are reached without improvement in symptoms), treatment should stop.

All this means is that some ***SYMPTOMATIC*** men even with completely 'normal' testosterone levels may benefit from testosterone treatment. Men without possible low testosterone symptoms should not be treated.

Evaluation and treatment for low T is not a simple blood test decision

A. *Mean (Average)* - measured levels by age of multiple studies since 2015: (n = >5,000)

{ *n = # of men studied* }

18 - 25	692	
25 - 29	669	
30 - 34	521	(theory that life complexity/stress/increased cortisol which diminishes T for this group)
35 - 39	597	
40 - 44	597	
45 - 49	546	
50 - 54	554	
55 - 59	552	

B. Overall average in other studies (n = > 3,000) Patients ages were between 21 - 50… **total average was 619.** This is a reasonable number to aim for as a goal level by providers, right?

C. Another study (A Validated Age-Related Normative Model for Male Total Testosterone Shows Increasing Variance but No Decline after Age 40 Years by Kelsey, et al - 2014) **included over 15,000 men**, and resulted in average T levels broken down by ages. For simplicity the following table is broken down in 5 year age increments and results percentiles. The values in the study were in nmol/L. Each value multiplied x 28.85 to get ng/dL (seen here).

- - - - - - - percentiles % - - - - - - - - -

Age	**30th**	**50th**	**70th**	**90th**	**95th**
20	380	444	562	733	849
25	358	413	516	664	765
30	340	392	488	626	720
35	332	381	476	612	708
40	326	375	470	609	702
45	323	375	470	612	708
50	323	375	473	617	718
55	320	375	479	629	731
60	320	375	482	638	744
65	320	375	488	649	760
70	320	378	493	658	773

D. An article in Journal of Clinical Endocrinology & Metabolism from 2017 (Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe J Clin Endocrinol Metab. 2017 Apr 1; 102(4): 1161-1173) ***(400 healthy, non-obese young men aged 19-39) yielded this***: (ng/dL)

2.5th percentile	5th percentile	50th percentile	95th percentile	**97.5th percentile**
264	303	531	852	**916**

* This is the research LabCorp uses to establish its 'normal range' of 264 - 916.
Leaves one wondering what about men older than 39 and any man of any age who isn't perfectly 'healthy'. It is reasonable to assume the results are lower than these.

E. Lastly, The Journal of Urology recently published a study in December 2022 **What is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old** (volume 28, pages 1295-1302)

Age	Mean morning T (ng/dL)	2.5th%	5th%	10th%	25th%	33rd%	50th%	66th%	75th%	90th%
20-24	501	189	225	283	376	409	484	558	604	757
25-29	514	177	217	273	372	413	491	575	643	771
30-34	456	178	222	266	326	359	421	498	559	678
35-39	438	169	193	259	323	352	423	478	533	632
40-44	430	184	220	247	311	350	418	473	504	640
All Men	466	177	216	261	337	374	444	511	563	712

{in the study, the 33rd percentile was used to determine age-specific cut-off levels for each 5-year age grouping}

It is obvious that the absolute middle of the pack, ***the 50% men, were all WELL-ABOVE the 300 ng/dl levels)***

Clinical Decision Making Considerations

LabCorp's current range is 264 - 915 and Quest is 250 - 1100 (The 2 largest testing labs in the country) — These are **extremely** wide ranges compared to almost all other narrow normal medical testing ranges. This range makes facilitating a definitive clinical pathway more difficult. Each patient's case is a unique combination of symptoms and lab test values. ***A lab result "bright line rule" does not exist; clinicians should consider the individual patient presentation each time.*** Low testosterone is very much a 'symptom disease' rather than a hard line 'lab-diagnosed' one. Low T is not a number; it is a presentation of symptoms that need to be evaluated and addressed. Often TRT is the answer and should be explored more liberally rather than excused as a potential cause based solely on a numerical value. Men who do not have symptoms should not be considered for treatment, regardless of lab values.

ADAM scale scores are currently the most utilized symptomatic screening tool for potential androgen deficient men. ADAM is extremely sensitive (catches most men that need TRT). It is relatively poor at ruling out men who don't have the disease (specificity). Therefore, a 'normal' questionnaire result doesn't mean the patient would or wouldn't benefit from TRT treatment. The best way to know if someone needs TRT is to treat them and see if they improve symptomatically.

A positive ADAM score is answering either YES to question #1 or #7 or any three YES answers out of the 10 questions - overwhelmingly patients with a positive ADAM score (mostly regardless of T level) symptomatically improve with the initiation of TRT, assuming there is not another primary cause of symptoms (thyroid issues, depression, sleep apnea, anemia, etc. can all mimic similar symptomatology).

An excellent research article in The Aging Male (2022, Vol.25, No.1, 29-40) discussed certain life conditions that affect testosterone levels in men. Obesity is associated with lower than expected T levels. Married men tend to have lower levels than single men, especially among younger males. Smokers tend to have higher levels (not even close to a good reason to start smoking). Patients with elevated HbA1C and with Type II diabetes have lower levels. And men with metabolic syndrome (high blood pressure, high blood sugar, too much body fat, and irregular cholesterol levels) are also at higher risk for low T.

BASIC TRT GAME PLAN for discussing with a potential TRT provider

Discuss parameters and expectations of treatment with provider

Do they evaluate only on blood levels? Symptomatic presentation? What?
What level of T are they comfortable getting you to during treatment?
Different treatment options - weekly injections > biweekly injections > cream/gel > pellet implants
How often will labs be obtained to track progress and potential biological side effects?
If injections are used, do they allow at home dosing or are you required to be at the office every time?
What do they do if a patient develops symptomatic estrogen elevations or elevated blood volumes?
Etc.

Evaluate for low testosterone

Questionnaire(s) to help determine severity of symptoms (also to check for improvements along the way by comparing to the original)
Laboratory evaluation to check T levels and rule in/rule out other biological causes
Reasonable labs to obtain for all men with any aspect of ED issues and/or low T symptoms: CBC, total T/free T, PSA, TSH, FSH/LH, Estradiol, Prolactin, Lipids (chol, TG), LFTs, and glucose
Show your provider the ***research contained here*** and the ***discussion of average testosterone levels*** provided in this section so an appropriate ballpark treatment T level goal can be decided on

Treatment

Create a diary of complaints/presenting symptoms that had you seek TRT in the first place (so you can compare to future symptoms review to demonstrate improvement or not)
Report any adverse physical side effects or injection site problems, rashes from creams/gels, or any other potential issue with treatment
Follow provider instructions regarding dose amounts, frequency, timing, etc and be CONSISTENT in following those instructions
Consider keeping copies of your lab results organized (physical folder or digital collection, etc) for later review and comparisons
Make sure when it is time to draw blood tests you are consistently having them drawn on the same days post injection - this allows your provider to always be comparing apple to apples to apples to more effectively track changes for dosing

Possible Side Effects of TRT

The two relatively common side effects are increased estrogen levels (due to a process called aromatization (breaking testosterone down into estrogen) and increased blood volume (polycythemia). If they develop, they are typically pretty easy to manage clinically.
Other, less common, possible side effects of TRT include acne, gynecomastia, breast/nipple tenderness or sensitivity, new-onset sleep apnea, fluid retention, and edema, among other less likely issues. These are infrequently encountered.

Crude Numerical Data to Share with Providers

If we just list the rough 50% numbers from the research contained within this information collection, it looks like this:

A. 591 (obtained by simply adding the different mean values and dividing by 8)
B. 619 (from a retrospective study that simply combined all the results from > 3,000 men)
C. 411 (obtained by simply adding up all the 50% values and dividing by 11)
D. 531 (remember, this result is only from 400 healthy, non-obese men between 19-39)
E. 444 (last result listed is "All Men" and 444 is the value listed under 50%)

These 'ballpark' numbers represent quite a variety of studies and research results. **The one thing they all absolutely have in common is - - - - they are all well above the commonly used cut-off values of either 264, 300, or 350 that so many clinician quote patients need to be lower than before they will considerTRT for them.**

Short and Sweet Conclusion

Good protocols should be followed for initiation, maintenance, and side effect surveillance of TRT. TRT is quite safe when managed appropriately, and it can significantly improve men's lives that need it. The available research is pretty clear, both for younger and older men; the clinical presentation is the most important aspect of treatment decision making for men who might need TRT. Basically, regardless of T level (within reason), if the man is symptomatic (based on low T questionnaires), a trial of TRT should strongly be considered. If the patient improves, keep treatment going. If he does not, obviously stop. Clinicians who don't provide TRT often are sometimes unaware of this data regarding TRT. Sharing this information may help their clinical awareness and potentially get patients more access to positively life-altering treatment they otherwise might not receive.

Print this information out or share it with your provider digitally. They are probably completely unaware of the existence of this data. Perhaps once they have reviewed this information or even reviewed the actual research articles listed (from highly reputable sources), they might have a different approach to the evaluation and treatment of low testosterone possibilities.

The days of "your number is in the normal range, so you don't need TRT" should give way to this more obvious approach of symptomatic treatment decisions. Empiric treatment is widely accepted throughout all of medicine; why not for this basic physiologic deficiency?