Common objections to the use of TTh

1. Testosterone therapy increases the risk of cardiovascular events such as MI and stroke.
2. Testosterone therapy leads to the development of new prostate cancer (PCa) or rapid growth of aggressive PCa
3. PDE5 inhibitors work fine for erectile dysfunction I don't need to consider further diagnoses in those patients
4. Testosterone Deficiency doesn't exist, it's just part of the aging process

Objection 1

"Testosterone replacement therapy increases the risk of cardiovascular events such as MI and stroke."

What has caused this concern?

A number of reasons could be the cause:

1. Limited RCT data to either prove or disprove the objection.
2. A petition of the FDA in the US in 2014 from a consumer rights group to add a black box warning about the increased risks of heart attacks and other cardiovascular dangers to the product labels of all testosterone-containing drugs presently on the market in the U.S.

The petition used evidence from the four following studies;

a. Basaria, S et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2): 109-22

https://www.nejm.org/doi/10.1056/NEJMoa1000485?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0www.ncbi.nlm.nih.gov

b. Xu, L et al. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled trials. *BMC Medicine* 2013;11:108

https://bmcmedicine.biomedcentral.com/track/pdf/10.1186/1741-7015-11-108.pdf

c. Vigen, R et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310: 1829-1836

https://jamanetwork.com/journals/jama/fullarticle/1764051

d. Finkle, WD et al. Increased risks of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE* 9(1): e85805. January 2014, Vol 9, Issue 1

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0085805

Each of these studies was flawed either in design, follow up, population or statistical analysis used to determine the outcomes.

OUTCOME: The FDA denied the petition.

What evidence and/or guidelines exist to challenge the concern around CVD?

1. **Evidence**

Shores, M et al, 2012, Testosterone treatment and mortality in men with low testosterone levels, *J Clinical Endocrinol Metab, 97 (6): 2050-2058* - https://pubmed.ncbi.nlm.nih.gov/22496507/

- Conclusion: In an observational cohort of men with low testosterone levels, testosterone treatment was associated with decreased mortality compared with no testosterone treatment.

Muraleedharan, V et al. 2013, Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes, *Eur J Endocrinol, 169: 725-733* - *https://pubmed.ncbi.nlm.nih.gov/23999642/*

- Conclusion: Low testosterone levels predict an increase in all-cause mortality during long-term follow-up. Testosterone replacement may improve survival in hypogonadal men with type 2 diabetes.

Fernández-Balsells et al. 2010, Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis, J Clin Endocrinol Metab. 2010 Jun;95(6):2560-75. doi: 10.1210/jc.2009-2575. - https://pubmed.ncbi.nlm.nih.gov/20525906/

- Conclusion: The adverse effects of testosterone therapy include an increase in haemoglobin and haematocrit and a small decrease in high-density lipoprotein cholesterol. These findings are of unknown clinical significance. Current evidence about the safety of testosterone treatment in men in terms of patient-important outcomes is of low quality and is hampered by the brief study follow-up

Sharma et al. 2015, Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men, Eur Heart J. 2015 Oct 21;36(40):2706-15. doi: 10.1093/eurheartj/ehv346. Epub 2015 Aug 6. **-** https://pubmed.ncbi.nlm.nih.gov/26248567/

- Conclusion: In this large observational cohort with extended follow-up, normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.

Oni et al. 2019, Relation of Testosterone Normalization to Mortality and Myocardial Infarction in Men With Previous Myocardial Infarction, Am J Cardiol. 2019 Oct 15;124(8):1171-1178. doi: 10.1016/j.amjcard.2019.07.019. Epub 2019 Jul 25. - https://pubmed.ncbi.nlm.nih.gov/31409450/

- Conclusion: In a large observational cohort of male veterans with previous MI, normalization of TT levels with TRT was associated with decreased all-cause mortality compared with those with non-normalized TT levels and the untreated group. Furthermore, in this high-risk population, TRT was not associated with an increased risk of recurrent MI.

Ongoing Clinical Trials

The TRAVERSE Study – Study to Evaluate the Effect of Testosterone Replacement Therapy (TRT) on the incidence of Major Adverse Cardiovascular Events (MACE) and Efficacy Measure in Hypogonadal Men - https://www.clinicaltrials.gov/ct2/show/NCT03518034

2. Guidelines

EMA PRAC (European Medicines Agency Pharmacovigilance Risk Assessment Committee) - https://www.ema.europa.eu/en/news/prac-review-does-not-confirm-increase-heart-problems-testosterone-medicines

Conclusion: committee recommends medicines can continue to be given for their authorised uses

European Association of Urology (EAU) - https://uroweb.org/guideline/male-hypogonadism/

There is no substantive evidence that TTh, when replaced to the normal physiological range, is related to the development of MACE. In hypogonadal men, TTh has been demonstrated to have a positive impact on CV risks

4th International Consultation on Sexual Medicine (ICSM) - Khera M et al. J Sex Med 2016;13:1787–804.

https://pubmed.ncbi.nlm.nih.gov/27914560/

The weight of evidence indicates that TTh is not associated with increased CV risk. Preliminary evidence suggests the possibility of beneficial effects of TTh on CV function

Objection 2

"Testosterone replacement therapy leads to the development of new prostate cancer (PCa) or rapid growth of aggressive PCa."

What has caused this concern?

1. Initial publication in 1941 (and Nobel Prize in 1966) by Charles Huggins and Clarence V. Hodges showed that, in a single patient, withdrawal of testosterone by castration and subsequent replacement of testosterone caused the prostate cancer to first involute then regrow.

- Huggins C, Hodges CV. Studies on prostatic cancer. The effect of castration, estrogen and androgen injection on serum phosphatases in metastatic carcinoma. Cancer Res 1941;1:293–7. https://cancerres.aacrjournals.org/content/canres/1/4/293.full.pdf

2. Two small subsequent trials (1967 and 1981) studying exogenous testosterone on prostate cancer patients and demonstrating variable responses by patient type.

- Fowler JR Jr, Whitmore WF Jr. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. *J Urol* 1981;126:372–5. https://pubmed.ncbi.nlm.nih.gov/7277602/
- Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. Cancer 1967;20:1871–8. https://pubmed.ncbi.nlm.nih.gov/4168724/

3. Ongoing general medical training that continues to perpetuate these beliefs such that an International survey in 2007 showed that as many as 70% of healthcare providers were concerned about the association of TRT and prostate cancer.

- (Gooren LJ, Behre HM, Saad F, *et al*. Diagnosing and treating testosterone deficiency in different parts of the world. Results from global market research. *Aging Male* 2007;10:173–81.) https://pubmed.ncbi.nlm.nih.gov/18033626/

What evidence and/or guidelines exist to challenge the concern around PCa?

1. Evidence

Roddam et al, Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 2008;100:170–83 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6126902/pdf/nihms985220.pdf

- Conclusion: In this collaborative analysis of the worldwide data on endogenous hormones and prostate cancer risk, serum concentrations of sex hormones were not associated with the risk of prostate cancer

Morgentaler et al, Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol* 2009;55:310–20. - https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.457.9902&rep=rep1&type=pdf

- Conclusion: The evidence clearly indicates that there is a limit to the ability of androgens to stimulate PCa growth. A Saturation Model based on androgen-AR binding provides a satisfactory conceptual framework to account for the dramatic effects seen with castration as well as the minor impact of T administration in non-castrated men.

Baillargeon et al, (The SEER Study) Long-term exposure to testosterone therapy and the risk of high-grade prostate cancer. *J Urol* 2015:194:1612–6. - https://pubmed.ncbi.nlm.nih.gov/26066403/

- Conclusion: Our finding that testosterone therapy was not associated with an increased risk of high grade prostate cancer may provide important information regarding the risk-benefit assessment for men with testosterone deficiency considering treatment.

Sarkar RR et al. Prostate Cancer Prostatic Dis 2020. https://pubmed.ncbi.nlm.nih.gov/32513967/

- Conclusion: A retrospective study of a large, multi-ethnic, nationwide cohort of men in the US VINCI database with localised PCa who had undergone radical prostatectomy (n=28,651) or radiotherapy (n=41,333) demonstrated that TTh does not increase the risk of prostate cancer recurrence or death after definitive treatment for localised disease

Debruyne FMJ et al. BMJ 2017;119:216–24. (The RHYME Study)
https://pubmed.ncbi.nlm.nih.gov/27409523/

- Large, multinational registry of TTh-treated and -untreated men with newly diagnosed hypogonadism (N=999)
- Conclusion: No increased risk of prostate cancer with TTh use among men in a large, multinational registry (RHYME). Overall, the proportion of PCa-positive biopsies was similar in men using or not using TTh over the course of the study (37.5% vs 37.0%, respectively)

Cui Y et al. Prostate Cancer Prostatic Dis 2014;17:132–43. https://pubmed.ncbi.nlm.nih.gov/24445948/

- Conclusion: Meta-analysis of 22 randomised controlled trials in men without evidence of PCa, receiving TTh or placebo (N=2351). No significant effect of TTh on the likelihood of PCa or need for prostate biopsy vs placebo, irrespective of TTh formulation or duration of use.

2. Guidelines

- **European Association of Urology (EAU)** - Randomised controlled trials support the hypothesis that TTh does not result in changes in prostatic histology. Recent studies indicate that TTh does not increase the risk of PCa, but long-term follow-up data are not yet available. https://uroweb.org/guideline/male-hypogonadism/
- **ISA, ISSAM, EAU, EAA, ASA joint recommendations** - At the present time, there is no conclusive evidence that TTh increases the risk of PCa. There is also no evidence that TTh will convert subclinical PCa to clinically detectable PCa https://pubmed.ncbi.nlm.nih.gov/18772485/
- **American Urology Association (AUA)** - Clinicians should inform patients of the absence of evidence linking TTh to the development of PCa. https://pubmed.ncbi.nlm.nih.gov/29601923/
- **Endocrine Society of Australia (ESA)** - There is no convincing evidence that men with pathological hypogonadism treated with TTh have any increased risk of benign or malignant prostate disease. https://pubmed.ncbi.nlm.nih.gov/27581270/

Objection 3

"Testosterone replacement therapy has not been shown to improve erectile dysfunction and PDE5i treatments are adequate monotherapy."

Where has this objection come from?

The majority of clinical guidelines for male erectile dysfunction globally direct clinicians toward a first line treatment of PDE5 inhibitors.

These treatments are cheap, have a wealth of evidence demonstrating their effectiveness and are relatively safe to prescribe.

The clinical evidence associating endocrinological factors with male sexual health is established, however the data supporting the effectiveness of TRT in sexual symptom improvement is variable based on the severity and idiopathy of a patient's hypogonadism.

What evidence and/or guidelines exist to challenge the objection regarding erectile dysfunction?

1. **Evidence**

Wu FC, Tajar A, Beynon JM, et al; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123-135.

https://pubmed.ncbi.nlm.nih.gov/20554979/

- **Conclusion:** Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol per litre (3.2 ng per millilitre) and a free testosterone level of less than 220 pmol per litre (64 pg per millilitre).

Snyder PJ, Bhasin S, Cunningham GR, et al; Testosterone Trials Investigators. Effects of testosterone treatment in older men. N Engl J Med. 2016;374(7):611-624.

https://www.nejm.org/doi/full/10.1056/nejmoa1506119

- **Results:** Testosterone treatment was also associated with increased sexual desire according to the DISF-M-II (treatment effect, 2.93; P<0.001) and increased erectile function according to the IIEF (treatment effect, 2.64; P<0.001).

Saad F, Aversa A, Isidori A et al: Onset of effects of testosterone treatment and time span until maximum effects are achieved. *Eur J Endocrinol.* 2011;165(5):675−685.

https://eje.bioscientifica.com/view/journals/eje/165/5/675.xml?body=contentSummary-10419

- **Results:** Effects on sexual interest appear after 3 weeks plateauing at 6 weeks, with no further increments expected beyond. Changes in erections/ejaculations may require up to 6 months.

Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med. 2014;11(6):1577-1592.

https://pubmed.ncbi.nlm.nih.gov/24697970/

- **Conclusions:** TS (testosterone supplementation) plays positive effects on male sexual function in hypogonadal subjects. The role of TS is uncertain in men who are not clearly hypogonadal. The apparent difference between industry-supported and independent studies could depend on trial design more than on publication bias. New RCTs exploring the effect of TS in selected cases of PDE5i failure that persistently retain low testosterone levels are advisable.

Corona G, Rastreli G, Morgentaler A et al. Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores.

European Urology Volume 72, Issue 6, 2017; 1000-1011

- **Conclusions:** TTh significantly improves erectile function and other sexual parameters as measured by IIEF in hypogonadal men. These results argue that sexual dysfunction should be considered a hallmark manifestation of T deficiency, since those symptoms can be significantly improved with normalization of serum T. In addition, these results suggest that TTh alone may be considered a reasonable treatment for hypogonadal men with milder degrees of erectile dysfunction, whereas the addition of other treatments, such as phosphodiesterase type 5 inhibitors, may be more appropriate for men with more severe erectile dysfunction.

Aversa A, Duca Y, Condorelli R et al. Androgen Deficiency and Phosphodiesterase Type 5 Expression Changes in Aging Male: Therapeutic Implications. Front. Endocrinol., 11 April 2019

https://doi.org/10.3389/fendo.2019.00225

https://www.frontiersin.org/articles/10.3389/fendo.2019.00225/full

- **Introduction excerpt**: TRT itself is able to decrease endothelial dysfunction, oxidative stress and inflammation, thus lowering the cardiovascular risk. Furthermore, untreated hypogonadism could be the cause of PDE5i ineffectiveness especially in the elderly. For these reasons, aging men complaining of ED who have LOH should undergo TRT before or at the moment when PDE5i treatment is started.
- **Conclusion**: PDE5 gene lower expression is associated to aging and hypogonadism at the corpus cavernosum level. TRT is able to restore the expression of PDE5 gene and this effect is initially attributed to a direct regulation of the gene expression by T. Subsequently, this hypothesis was not confirmed, and the authors hypothesized that the lower expression of PDE5 in hypogonadism was due to the decreased smooth muscle cell content in corpora cavernosa. Therefore, T could be able to increase PDE5 content by reversing these anatomical changes. Anyway, the increased PDE5 gene expression explains the reason for the possible failure of PDE5i administration in hypogonadal patients with ED.

2. Guidelines

NICE CKS (National Institute for Health and Care Excellence – Clinical Knowledge Summaries)
https://cks.nice.org.uk/topics/erectile-dysfunction/diagnosis/assessment/

- Guidance: Arrange appropriate investigations to identify reversible/modifiable risk factor of erectile dysfunction.
- In all men: Measure a morning sample of total testosterone. If indicated, measure bioavailable or calculated-free testosterone to confirm total testosterone measurements.

BSSM Guidelines on Management of Erectile Dysfunction –

http://www.bssm.org.uk/wp-content/uploads/2018/09/BSSM-ED-guidelines-2018-1.pdf

- **Suggested investigation:** Hypogonadism is a treatable cause of ED that may also make men less responsive, or even non-responsive to phosphodiesterase type 5 (PDE5) inhibitors (PDE5Is),15,24 therefore all men with ED should have serum testosterone measured on a blood fasting sample taken in the morning between 8 and 11 AM.
- **Recommended management:** Low testosterone is a frequent reason for failure to respond to PDE5I and correction of low testosterone has been shown in multiple studies to restore the response to PDE5Is. In one study this was significant for total testosterone levels below 10.4 nmol/L and below 8nmol/L in men with T2DM, but improvement in sexual desire was seen up to 12 nmol/L in men with T2DM. Because sexual desire is important in motivating men to take both PDE5Is on demand, we recommend a cut-off of 12 nmol/L for initiating testosterone therapy for PDE5I failures. We also recommend that a trial of testosterone therapy is required for a minimum of 6 months, based on several trials and meta-analyses.

Objection 4

"Testosterone deficiency does not exist or if it does is a rare and insignificant medical condition that has limited impact on male health."

Where has this objection come from?

With indisputable medical evidence from the 1940's of hypogonadism and the impact the condition can have across multiple systems within the human body, it is unclear what still seems to drive this still widely held viewpoint within the healthcare community.

There are examples of consumer groups suggesting the condition is being overplayed by pharmaceutical companies in an attempt to make a profit but these claims have not to date and cannot be substantiated.

What evidence and/or guidelines exist to challenge the objection regarding erectile dysfunction?

Evidence

Channa N. Jayasena, Richard Quinton: Male hypogonadism and general practitioners in the UK. How to increase case recognition, without compromising diagnostic accuracy?

Clinical Endocrinology. 2021;00:1–2. https://onlinelibrary.wiley.com/doi/abs/10.1111/cen.14432?af=R

Male Hypogonadism (MH) results in sexual dysfunction, sarcopenia, anaemia, glandular gynaecomastia and loss of bone mass and secondary sexual characteristics in affected men. It is also associated with mental health issues, along with a tendency to insulin resistance that arises from disordered body composition. Testosterone is a highly effective therapy licenced for male hypogonadism.

Wu FC, Tajar A, Beynon JM, et al; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123-135.

https://pubmed.ncbi.nlm.nih.gov/20554979/

- **Conclusion:** Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol per litre (3.2 ng per millilitre) and a free testosterone level of less than 220 pmol per litre (64 pg per millilitre).

Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care. 2004;27(5):1036-1041.

https://pubmed.ncbi.nlm.nih.gov/15111517/

- **Conclusions**: Low total testosterone and SHBG levels independently predict development of the metabolic syndrome and diabetes in middle-aged men. Thus, hypoandrogenism is an early marker for disturbances in insulin and glucose metabolism that may progress to the metabolic syndrome or frank diabetes and may contribute to their pathogenesis.

Antonio L, Wu FC, O'Neill TW, et al; EMAS Study Group. Associations between sex steroids and the development of metabolic syndrome: a longitudinal study in European men. J Clin Endocrinol Metab. 2015;100(4):1396-1404.

https://pubmed.ncbi.nlm.nih.gov/25636052/

- **Conclusions:** In men, lower T levels, but not E2, are linked with an increased risk of developing MetS, independent of SHBG, BMI or insulin resistance. A lower E2/T ratio may be protective against developing MetS.

Ohlsson C, Barrett-Connor E, Bhasin S, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men: the MrOS (Osteoporotic Fractures in Men) study in Sweden. J Am Coll Cardiol. 2011;58(16):1674-1681.

https://pubmed.ncbi.nlm.nih.gov/21982312/

- **Conclusions:** High serum testosterone predicted a reduced 5-year risk of CV events in elderly men.

Behre HM, Tammela TL, Arver S, et al; European Testogel Study Team. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. Aging Male. 2012;15(4):198-207.

https://pubmed.ncbi.nlm.nih.gov/22834649/

- **Conclusions:** Six months 1% T gel improved body composition and HRQoL in symptomatic men with low to low-normal T, with further improvements over the following 12 months.

Moskovic DJ, Araujo AB, Lipshultz LI, Khera M. The 20-year public health impact and direct cost of testosterone deficiency in U.S. men. J Sex Med. 013;10(2):562-569.

https://pubmed.ncbi.nlm.nih.gov/23035926/

- **Conclusion:** TD may be a significant contributor to adverse public health. Further study is needed to definitively describe whether TD is a modifiable risk factor for CVD, DM, and ORFs. This may represent an opportunity for nationwide public health initiatives aimed at preventive care.

Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med. 2014;11(6):1577-1592.

https://pubmed.ncbi.nlm.nih.gov/24697970/

- **Conclusions:** TS (testosterone supplementation) plays positive effects on male sexual function in hypogonadal subjects. The role of TS is uncertain in men who are not clearly hypogonadal. The apparent difference between industry-supported and independent studies could depend on trial design more than on publication bias. New RCTs exploring the effect of TS in selected cases of PDE5i failure that persistently retain low testosterone levels are advisable.

Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol. 2016;174(3):R99-R116.

https://pubmed.ncbi.nlm.nih.gov/27241317/

- **Conclusions:** Present data support the view of a positive effect of TS on body composition and on glucose and lipid metabolism. In addition, a significant effect on body weight loss was observed, which should be confirmed by a specifically designed RCT.

Isidori AM, Balercia G, Calogero AE, et al. Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian Society of Endocrinology. J Endocrinol Invest. 2015;38(1):103-112.

https://pubmed.ncbi.nlm.nih.gov/25384570/

- **Conclusions:** We recommend T supplementation (TS) for adult men with severely reduced T levels (T < 8 nmol/L) to improve body composition and sexual function. We suggest that TS be offered to subjects with T < 12 nmol/L to improve glycaemic control, lipid profile, sexual function, bone mineral density, muscle mass and depressive symptoms, once major contraindications have been ruled out. We suggest that lifestyle changes and other available interventions (e.g. for erectile dysfunction) be suggested prior to TS. We suggest that TS should be combined with currently available treatments for individuals at high risk for complications, such as those with osteoporosis and/or metabolic disorders. We recommend against using TS to improve cardiac outcome and limited mobility. We recommend against using TS in men with prostate cancer, unstable cardiovascular conditions or elevated haematocrit. The task force places a high value on the timely treatment of younger and middle-aged subjects to prevent the long-term consequences of hypoandrogenism.

Snyder PJ, Bhasin S, Cunningham GR, et al; Testosterone Trials Investigators. Effects of testosterone treatment in older men. N Engl J Med. 2016;374(7):611-624.

https://pubmed.ncbi.nlm.nih.gov/26886521/

- **Conclusions:** In symptomatic men 65 years of age or older, raising testosterone concentrations for 1 year from moderately low to the mid-normal range for men 19 to 40 years of age had a moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms but no benefit with respect to vitality or walking distance. The number of participants was too few to draw conclusions about the risks of testosterone treatment.

Guidelines:

Morgentaler, A; Zitzmann, M; Traish, AM et al. Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions.

Mayo Clin Proc. 2016 Jul;91(7):881-96. https://pubmed.ncbi.nlm.nih.gov/27313122/

Resolution 1: TD is a well-established, significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life. TD may predict increased risk of developing diabetes, metabolic syndrome, contributes to decreased bone mineral density, is associated with increased all-cause and cardiovascular mortality and negatively impacts general health and quality of life.