Testosterone and Male Pubertal Maturation

Presentation to the Pediatric Advisory Committee

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by
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Disclosures

- Presentation prepared for consortium of 5 companies which have INDs for testosterone products
    - Acerus Pharmaceuticals Corp.
    - Clarus Therapeutics, Inc.
    - Ferring Pharmaceuticals, Inc.
    - Lipocine Inc.
    - Viramal Limited

Agenda

- Background
- Physiology of the HPG axis in boys at puberty
- Estimate of number of adolescents who may require testosterone
- Challenges in designing and operationalizing studies of testosterone therapy in adolescents
- Conclusions

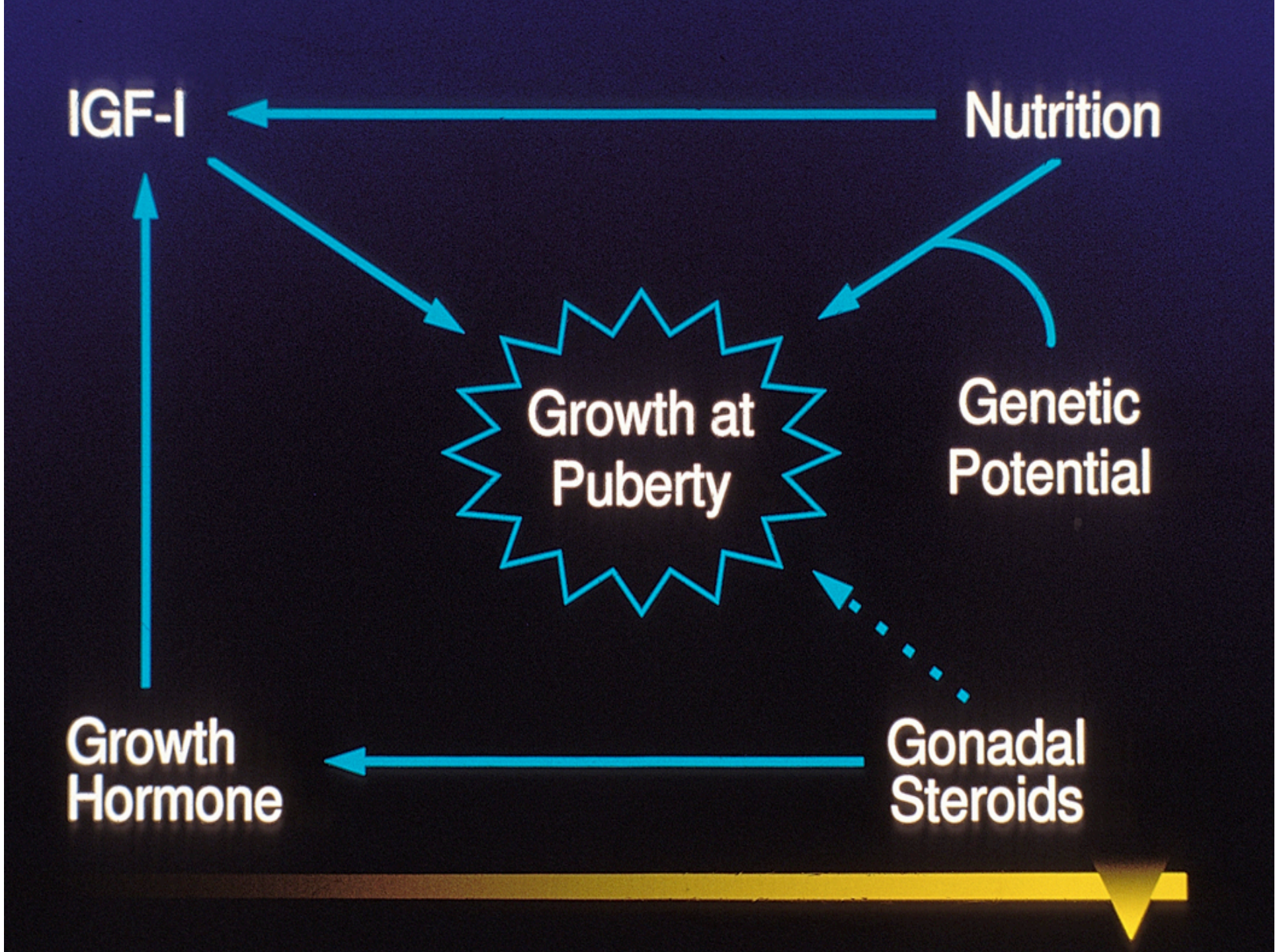
Indication on Package Insert of TRTs

[Product] is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

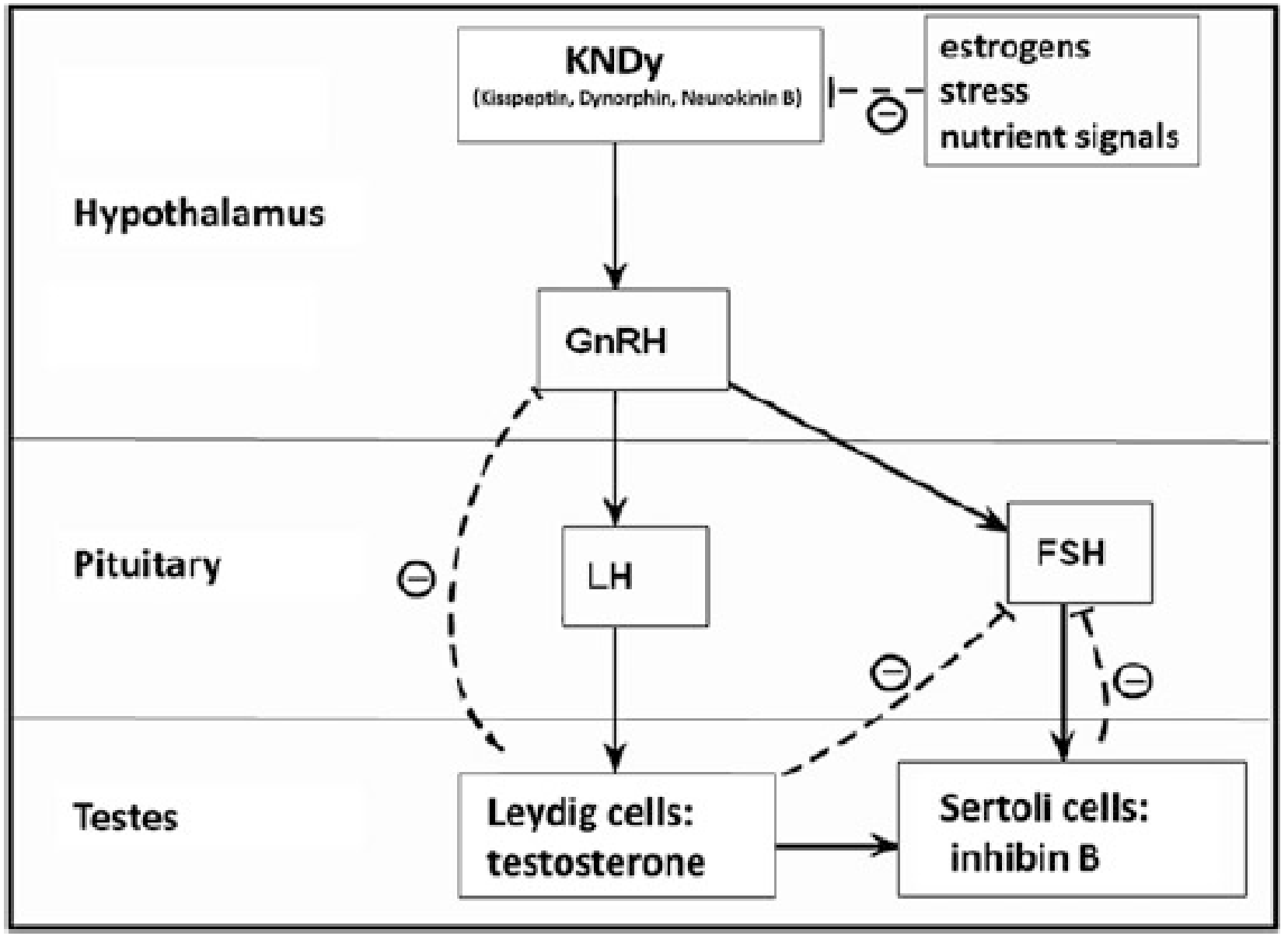
- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Limitations of use:

- Safety and efficacy of [Product] in males less than 18 years old have not been established.


IGF-I
Nutrition
Growth at Puberty
Genetic Potential
Growth Hormone
Gonadal Steroids

Hypothalamic-Pituitary-Gonadal Axis



Effects of Testosterone and its Active Metabolites

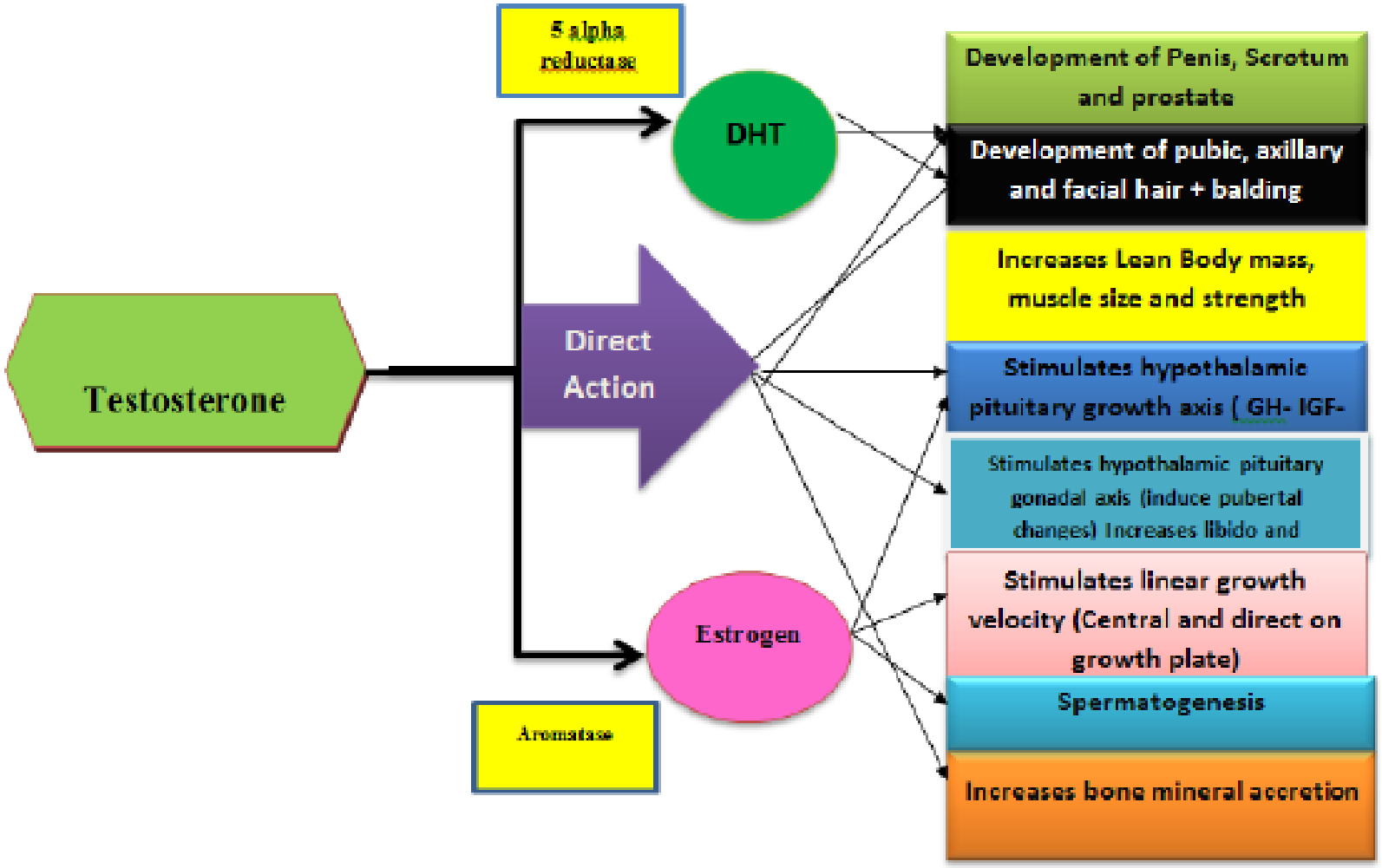
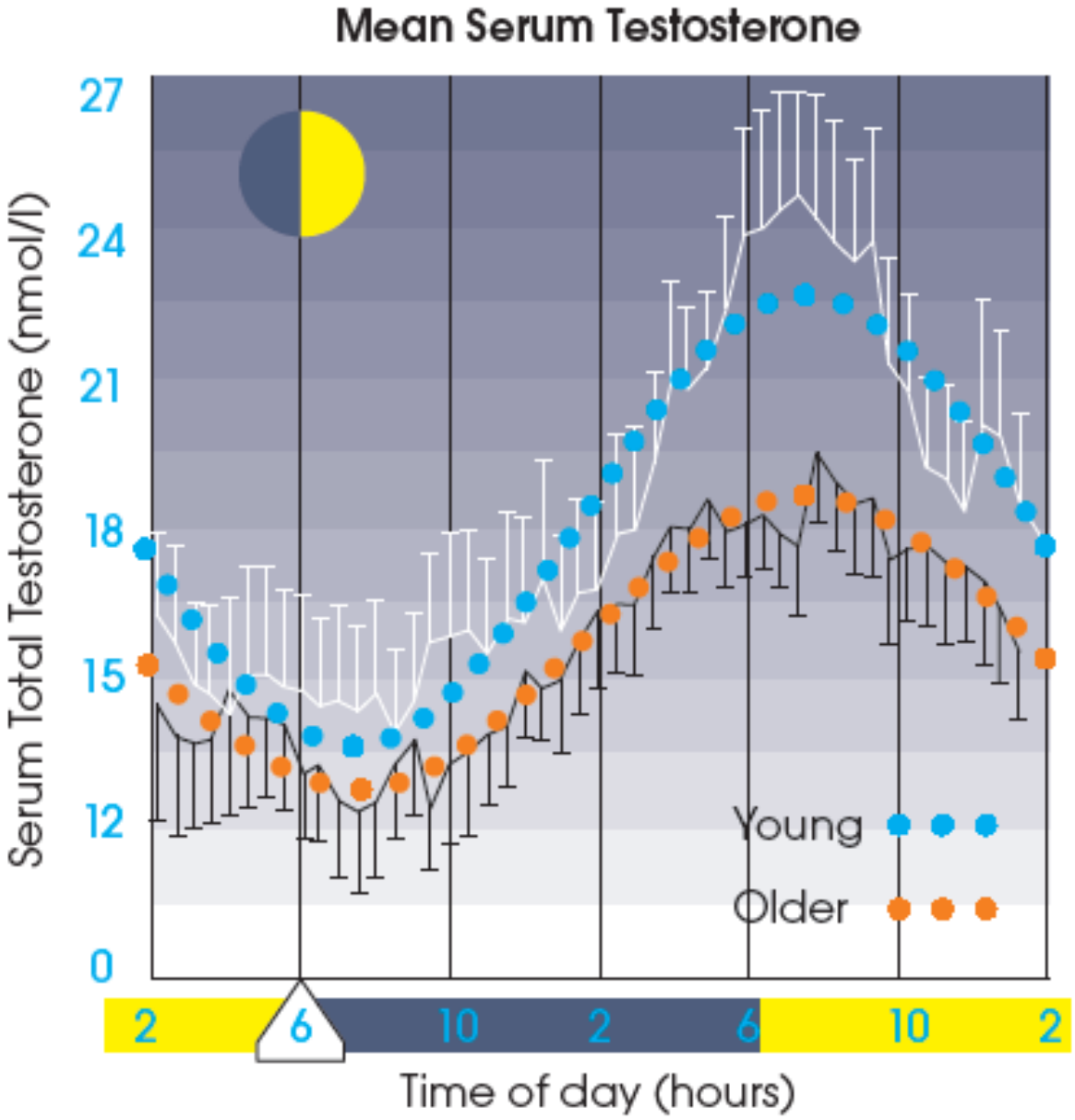


Figure 1: Different effects of testosterone on body organs.

Andrology 2014; 3:124-135

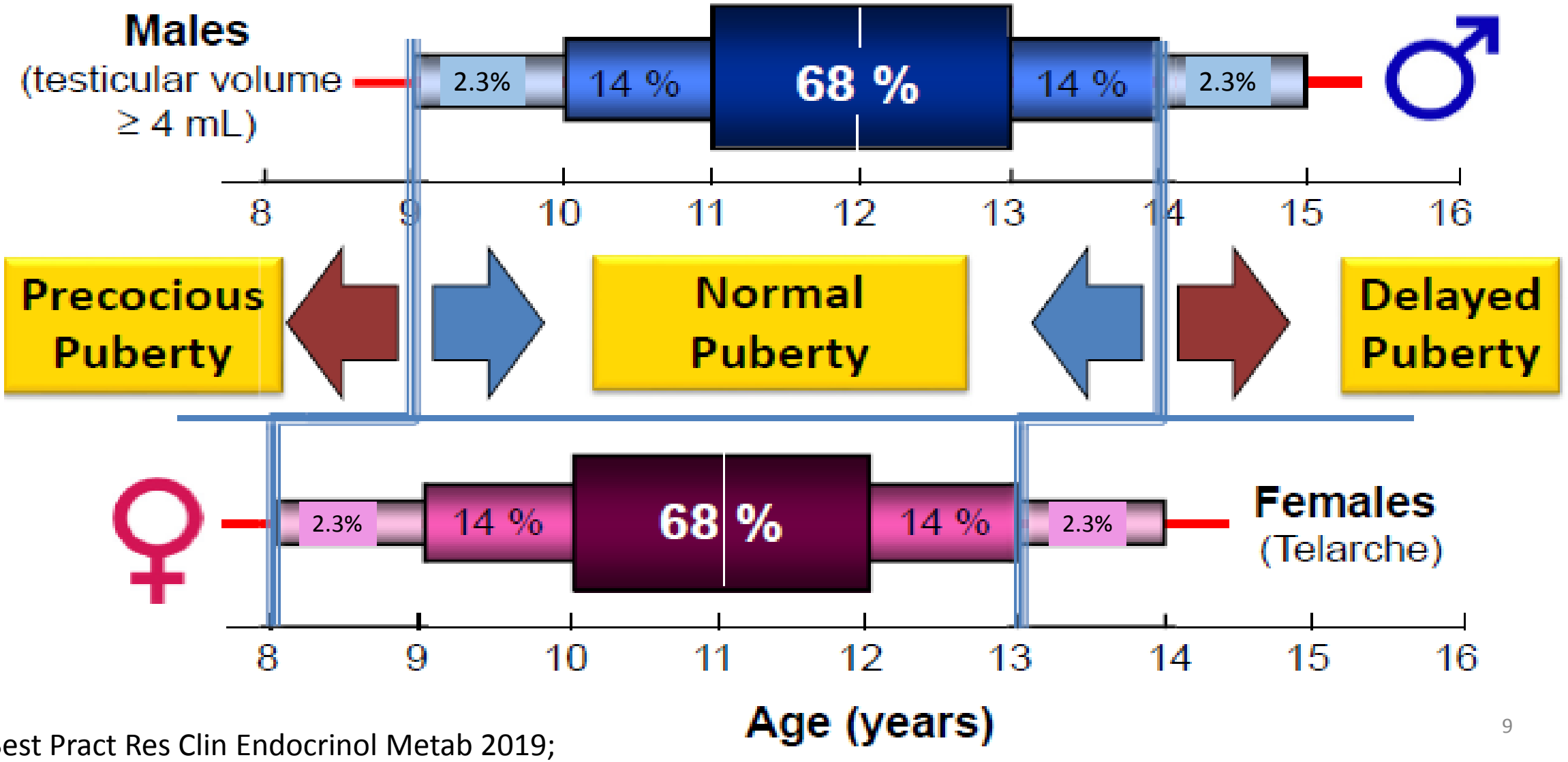
Serum Testosterone Level has Circadian Rhythm



Total T displays both circadian and ultradian rhythms in young and older me.

Andrology 1991; 12:185-190

All Cause Delayed Puberty in 2.3% of Males



Best Pract Res Clin Endocrinol Metab 2019;

Population of boys with delayed puberty

- The ***US census from the year 2017*** notes the following population statistics for boys—[total census at that age divided by 2]:
  - Age 14 = 2.06×10^6
  - Age 15 = 2.06×10^6
  - Age 16 = 2.11×10^6
  - Age 17 = 2.15×10^6

  Total = 8.38×10^6

- The 97th percentile [>2 SD, and thus "abnormal"] for starting puberty in boys is 13.7 years from a well-designed population study of Belgian boys[1].

[1] Roelants M, Hauspie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders, Belgium. Ann Hum Biol, 2009; 36(6): 680–694.

Population size: CDGP (1)

- Thus, for the 14 year old boys, **2.3** % have delayed puberty, of which 65% have CDGP
  - $2.06 X10^6 X\ 0.023 X\ 0.65 = 3.08 X\ 10^4$
  - Clearly those with delayed puberty diminish as the age nears 18 years, especially those with CDGP. Conservatively, diminish that by 50 % each year, yielding 1.54, 0.77 and 0.39 for the ensuing years for a total of ***≈57,800***

Population size: CDGP (2)

- For this calculation will use the least parsimonious number, **2.3** %
- That number relates to the 14 year olds and is clearly less for the older age bands for CDGP.
- I have arbitrarily halved the percentage each additional year, although clinical experience over more than 4 decades would note that number to be high
- Two large single center studies from academic centers noting differing referral patterns show approximately ***65%*** of the boys with delayed puberty have CDGP

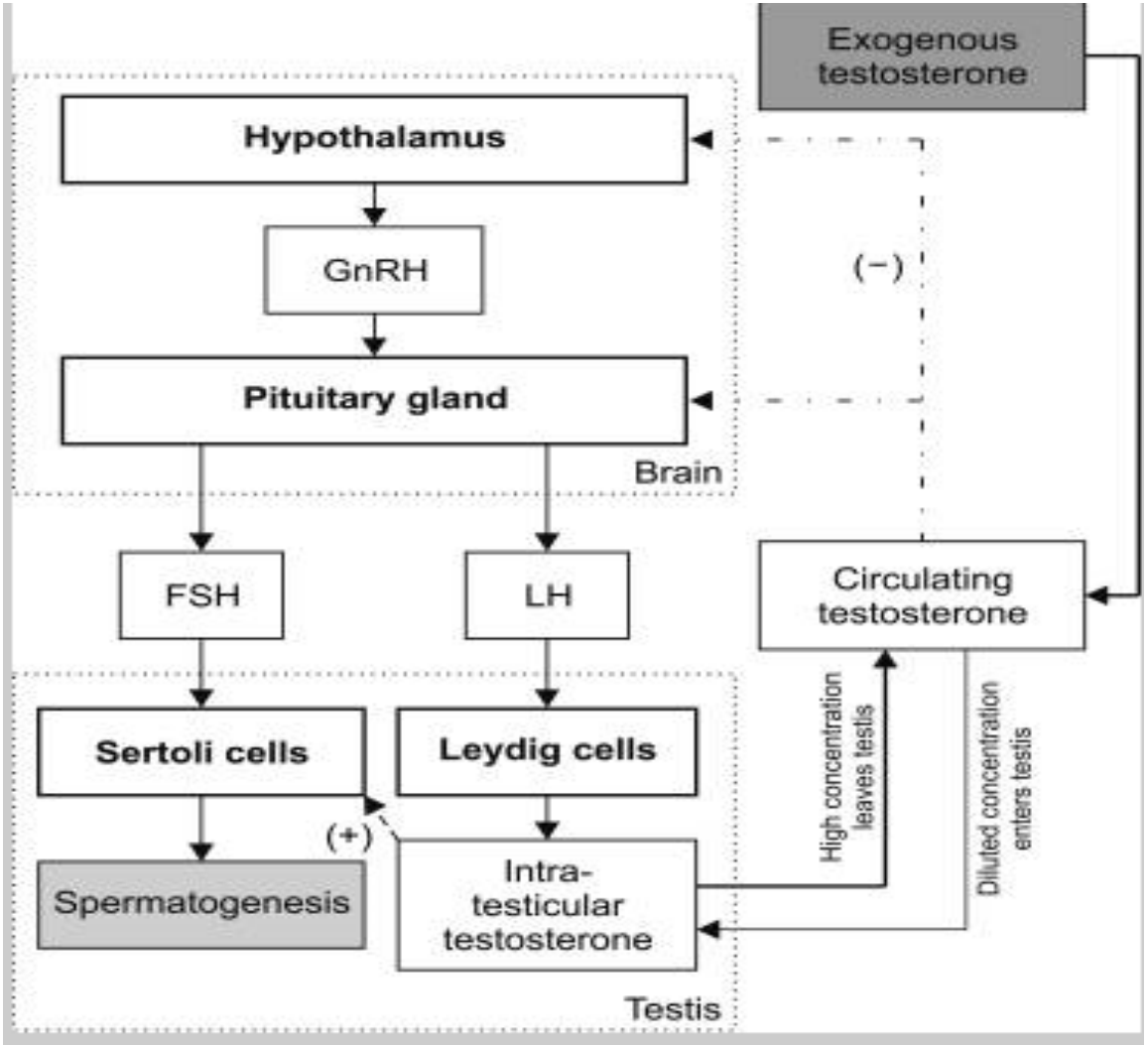
Population size: Klinefelter syndrome (primary hypogonadism)

- Klinefelter syndrome estimated to be ~1:500-600 males and that is the most prevalent form.
- However only about 10% present before age 18.
- Boys 14 to 18 y = $8.38 \times 10^6 / 6 \times 10^2 = 1.4 \times 10^4$ but only ≈10% present before age 18 y, so ***≈1,400*** adolescents diagnosed with Klinefelter syndrome

Population size: Kallmann syndrome and IHH

- Kallmann syndrome estimated to be ~1:10,000 males and that is the most prevalent form of IHH
- Boys 14 to 18 y = $8.38 \text{ X } 10^6 / 1 \text{ X } 10^4$ = **838.**
- Once again, not all will have a diagnosis, but these adolescents will likely not have started any pubertal development and more will be captured earlier than those with the Klinefelter syndrome, where most do start pubertal maturation.

Hypothalamic-Pituitary-Gonadal Axis

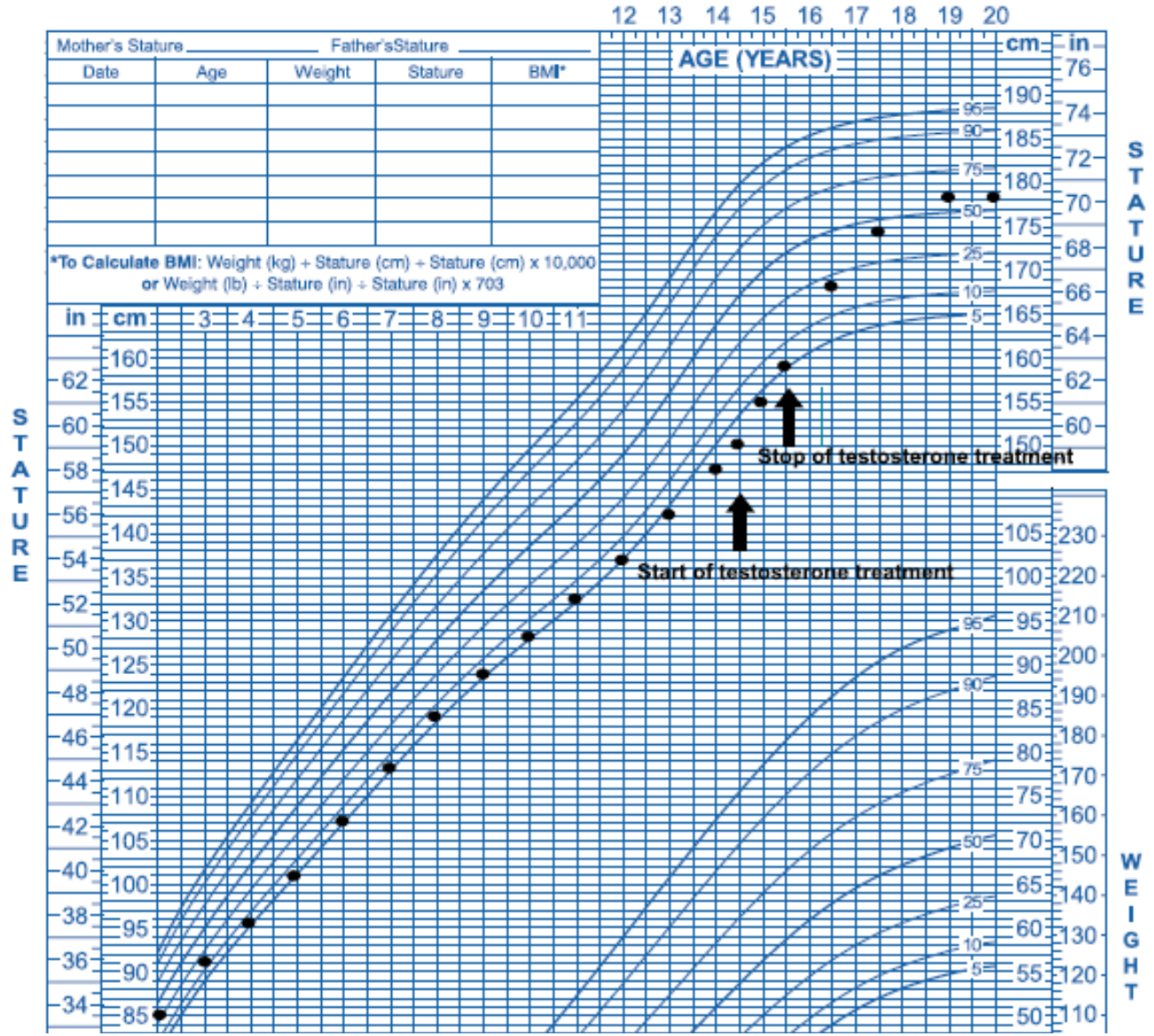


World J Men's Health 2019; 37:45

CDGP *versus* IHH

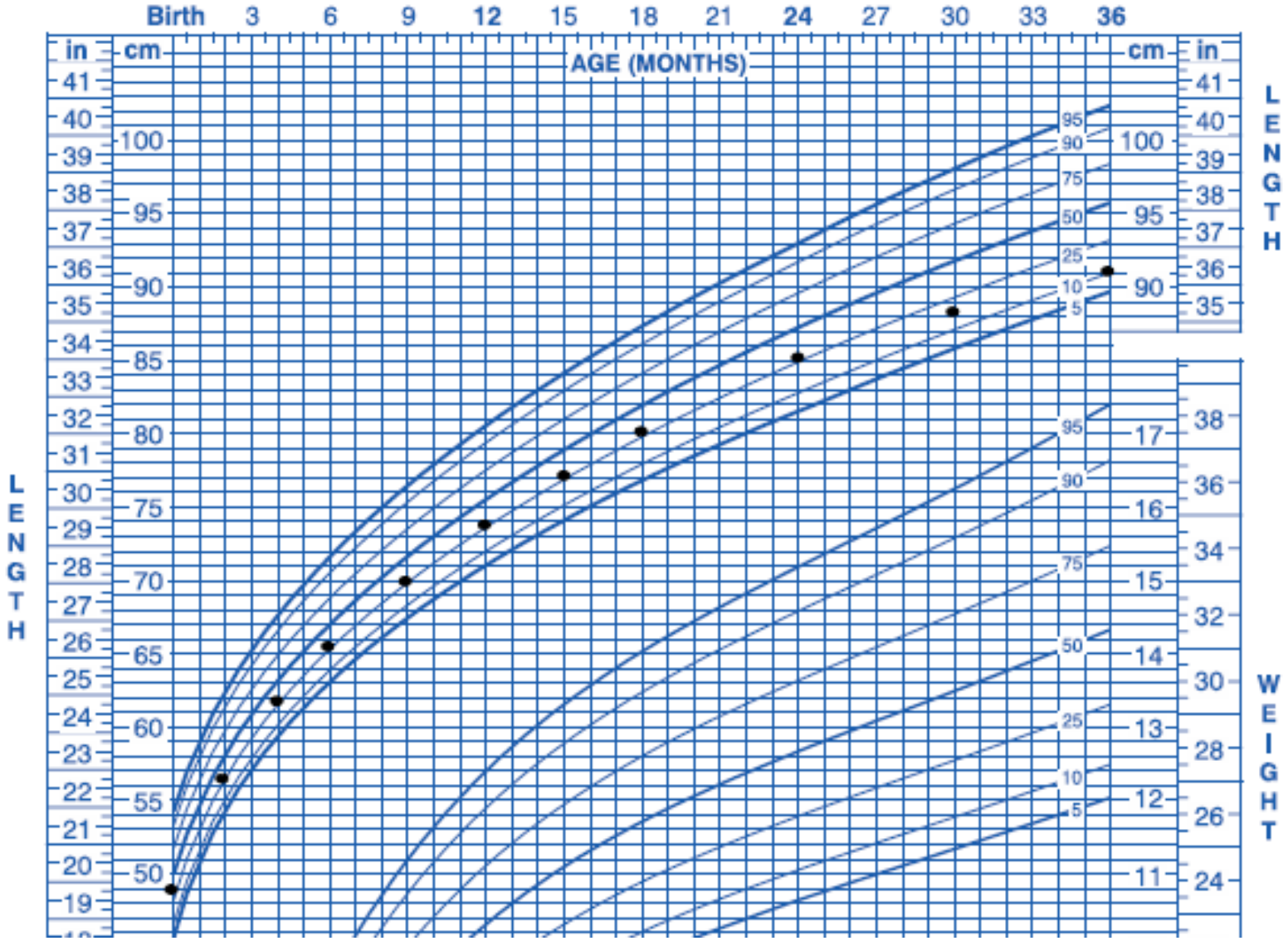
- Differential diagnosis can be difficult, especially in the early adolescent (by age).
- Both may be familial
- Growth curves may help to distinguish
- Very early signs of pubertal maturation may help to distinguish

Growth curve for boy with CDGP treated with T

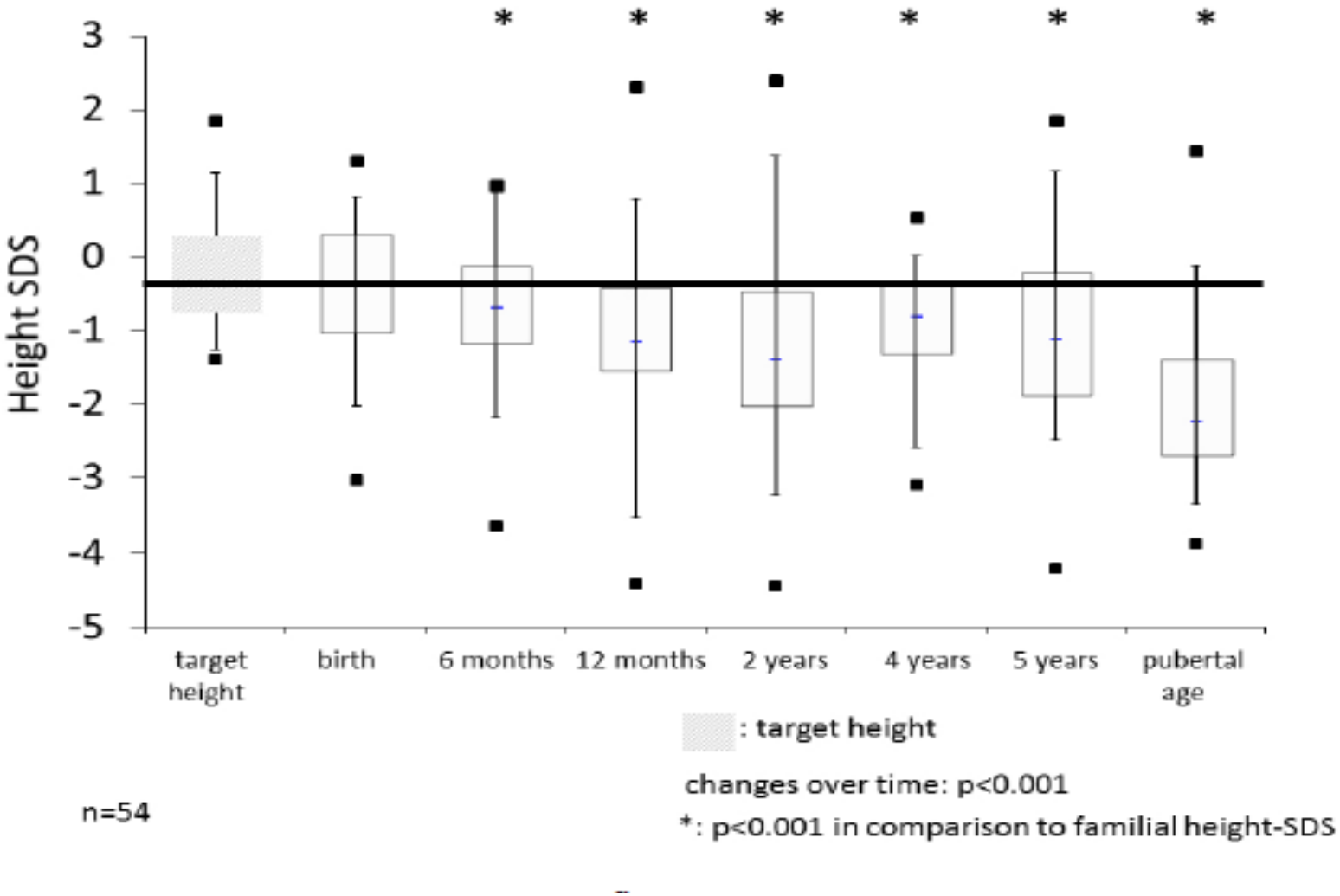


Growth curve for boy with CDGP

Figure 1: Growth chart of patient with CDGP. Birth to 36 months: Boys. Length-for-age and weight-for-age percentiles.

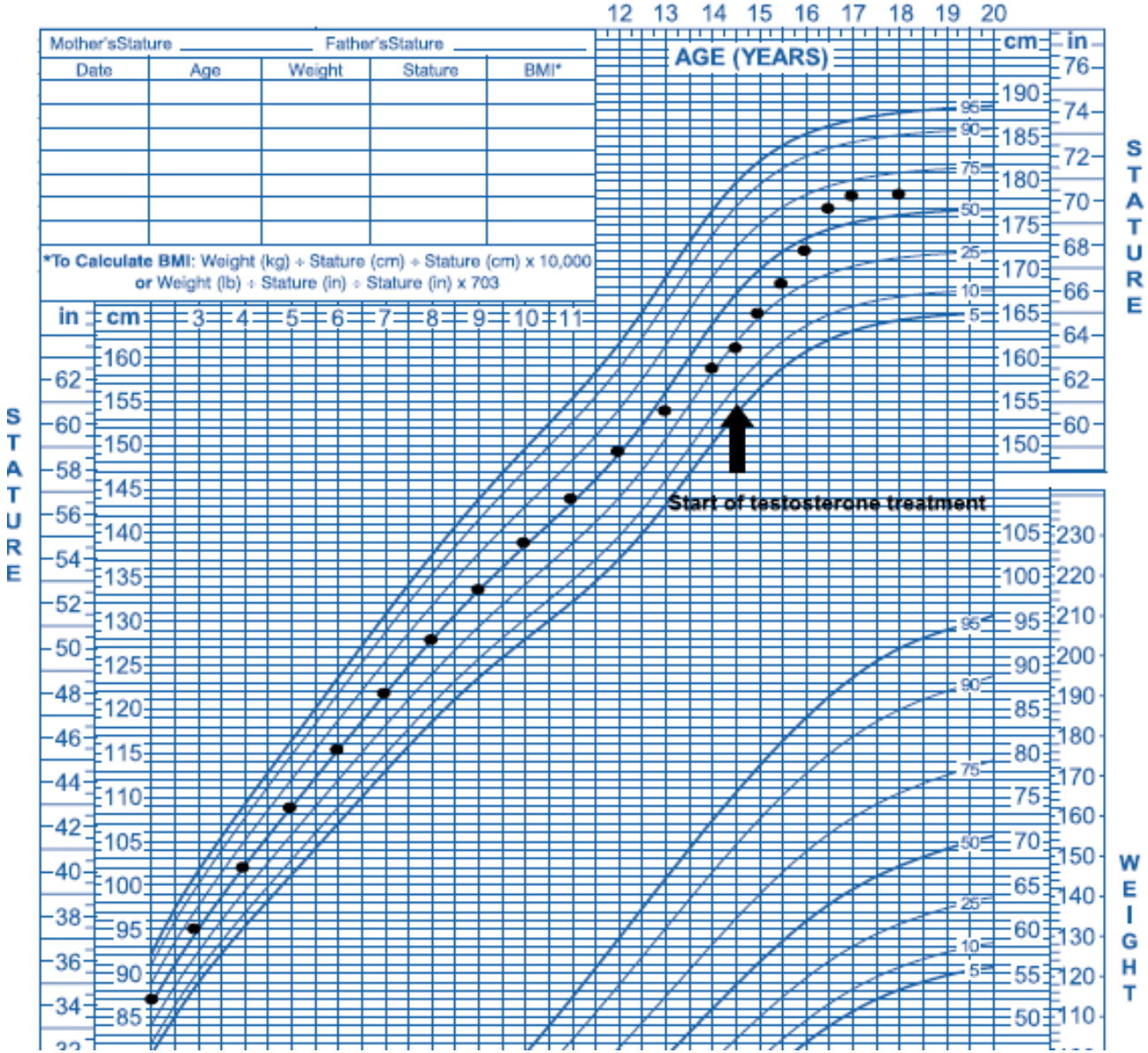


Height SDS in Boys with CDGP



Reinehr T, *et al* Clin Endocrinol 2019 *in press*

Growth curve for a boy with IHH



General Principles of Androgen Therapy

- To lead to or to restore serum T levels within the normal range for age and stage of pubertal maturation
- To administer only to those who are transiently or permanently hypogonadal, whether primary or secondary

Goals of Testosterone Therapy (Adolescent)

- Linear growth (physiological growth spurt)
- Normal progression of secondary sexual characteristics
  - Growth of testes during androgen therapy, even to supraphysiologic levels, indicates gonadotropin secretion is robust and ***not*** inhibited by negative feedback at the attained levels
- Acquisition of pubertal and then adult body composition (muscle mass and regional distribution of body fat)
- Accrual of adequate bone mineral content
- Physiologic psychosocial development

Forms and dose ranges from previous studies

- Mixed testosterone esters
  - 50 to 125 mg monthly for 12 months
- Testosterone enanthate (TE)
  - 200 mg *im* for four months
  - 50-100 mg monthly for 12 months

After one year virtually all had a growth spurt without unduly rapid bone maturation and in the few studies carried out to (near) adult height there was no loss compared to predicted adult height at initiation of therapy nor deviation from familial target height.

Physiologic and Pharmacologic T Concentrations (1)

- Physiology notes pulsatile GnRH and gonadotropin patterns at all ages
- Testosterone concentrations are very low except at “mini-puberty” and at puberty
  - Gonadotropin levels show increased pulse amplitude early morning as pubertal maturation unfolds
  - Testosterone levels follow with an early morning rise and then lower levels during the day
  - Mid-to-late puberty notes increasing gonadotropin levels during a greater part of the day with night greater than day
  - T levels are easily measurable for greater parts of the day and become like the adult in late puberty

Physiologic and Pharmacologic T Concentrations (2)

- T levels following multiple different TRT drugs and doses do not mimic physiology
- Yet multiple forms administered by any of multiple routes are able to mimic pubertal maturation in those with CDGP, IHH, or primary hypogonadism
- Mechanisms for tracking adverse effects of testosterone therapy
  - Height velocity excessive
  - Bone age maturation excessive
  - Adverse behavioral effects
  - Acne
  - T levels (when and what to measure)
    - AUC versus peak (C_{max})

Clinical Trials

- Conditions associated with a deficiency or absence of endogenous testosterone
  - Primary hypogonadism
  - Isolated or combined gonadotropin deficiency—usually GnRH deficiency

PMR on NDA approval letter of recent TRTs

- *A trial of testosterone replacement therapy in pediatric males **ages 14 years and older** for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism.*

Identifying the correct patient: CDGP vs IHH

- Can have nearly identical clinical presentation
- Both will respond to T treatment
- CDGP is not on label while IHH is
- May need to assign final diagnosis after a course of T

Challenges for Clinical Trials: Recruitment (1)

- Small percent of the adolescents get to the specialist early
  - They are the ones that want something done ***RIGHT NOW***
  - Many 14 y.o. patients have already started T treatment
- Physicians prescribing off label
  - Sure to get drug
- Study design
  - In placebo controlled trial there can be perception of patient/ family that there is an inferior arm (e.g., delayed T therapy)
  - However, new formulations, especially without needles, makes the recruitment a bit easier, as well as highly educated families

Challenges for Clinical Trials: Recruitment (2)

- Subset for PK studies
  - Lack of direct benefit to patients
  - Limited capacity for the younger subjects to understand study
  - Inability to properly compensate patients and parents, especially the latter for loss of work
  - Travel/invasive procedures for proper trials
  - Difficulty scheduling because of school (time commitment)

Challenges for Clinical Trials: Patient population

- Study design (cont)
  - Klinefelter syndrome, although easily confirmed, is a problem because only ~10 % are diagnosed by pubertal age. The adolescents have variable T levels, often within normal limits for age, but high gonadotropin levels, especially FSH
  - When to start, what level is appropriate based on T or gonadotropin levels?

Challenges for Clinical Trials: Study design (details)

- Multiple etiologies, even for isolated hypogonadotropic hypogonadism (IHH), inclusion criteria
  - Are all the same?
  - Development *versus* maturation
  - Behavioral aspects are important
  - Controls-required for CDGP (transient) what about others?
    - Precisely who are the controls?
- Exclusion criteria
  - certain genetic conditions
  - Concomitant medications?
    - Endocrine active including nasal and inhaled glucocorticoids
    - CNS active, e.g., mood stabilizers, anti-psychotics, ADHD

Outcomes (1)

- Height velocity or change in height SDS (easy)
- Body composition (not so easy depending on methods)
  - Adult body composition reached mid-third decade
- Metabolic parameters—insulin sensitivity
- Is issue to initiate puberty or to go through the entire sequence
  - First not sure that that is valid and what does *initiate* mean other than in adolescents with CDGP or IHH

Outcomes (2)

- Psychosocial aspects—to ameliorate
  - Low self esteem
  - Distorted body image
  - Impaired psychosocial development
  - Increased anxiety
  - Depression

Conclusions

- Testosterone trials are difficult in adolescent boys
  - Distinguish CDGP from IHH at young ages
  - Many boys seek therapy below the age of 14 and they can get it off label
  - Mechanics of trial participation can be difficult for families especially with pharmacokinetic studies
  - Few patients with IHH
  - Few patients with Klinefelter syndrome diagnosed before emerging adulthood

Unequal battle between early and late maturing athletes

The only sure foundations of medicine are, an intimate knowledge of the human body, and observations on the effects of medicinal substances on that.

Thomas Jefferson, letter to
Dr. Caspar Wistar, 1807

THANK YOU