



HORMONES IN XXY, XXYY AND XXXY

AXYS 2019

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Puberty: a time of change

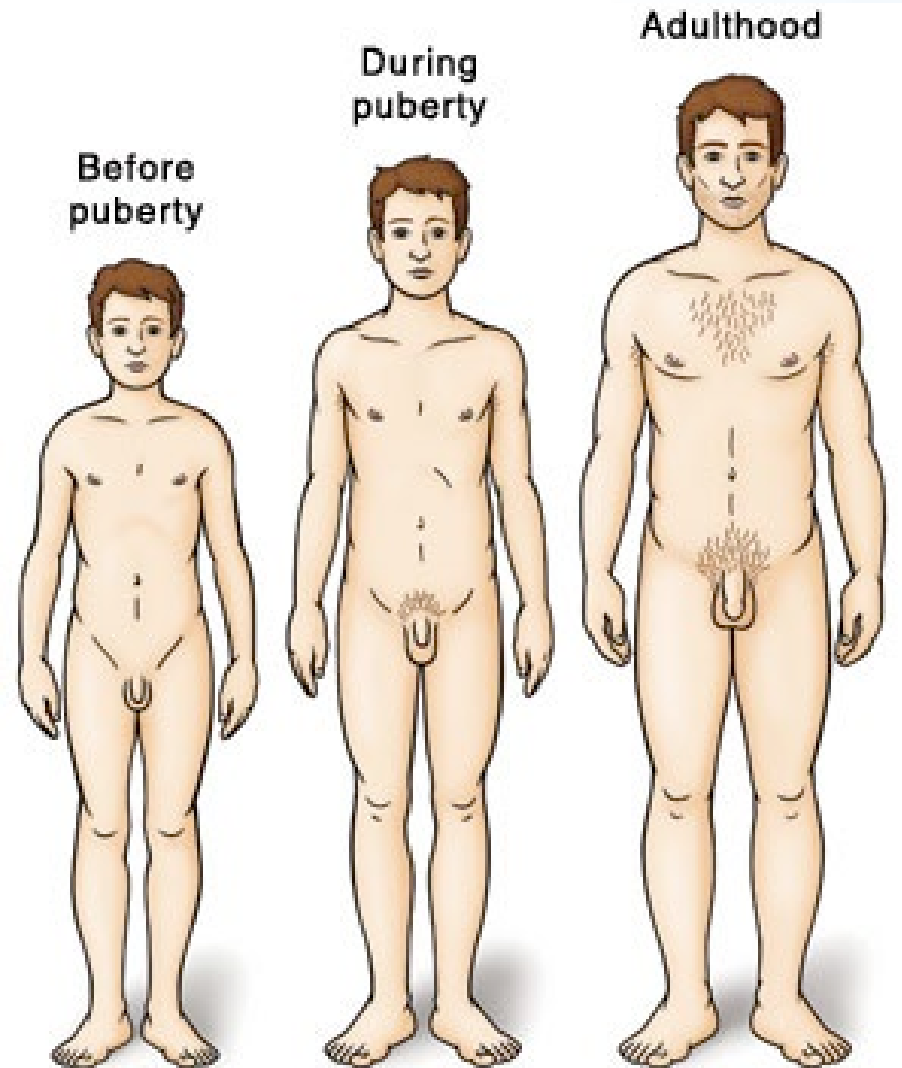
PUBERTY is the process of physical changes involved when a child's body matures into an adult body

First sign? testicular enlargement

When? Starts 11-12 years old
(anywhere 9-14 years is normal)

How long? ~5 years

Why? Hormones



Hormones 101

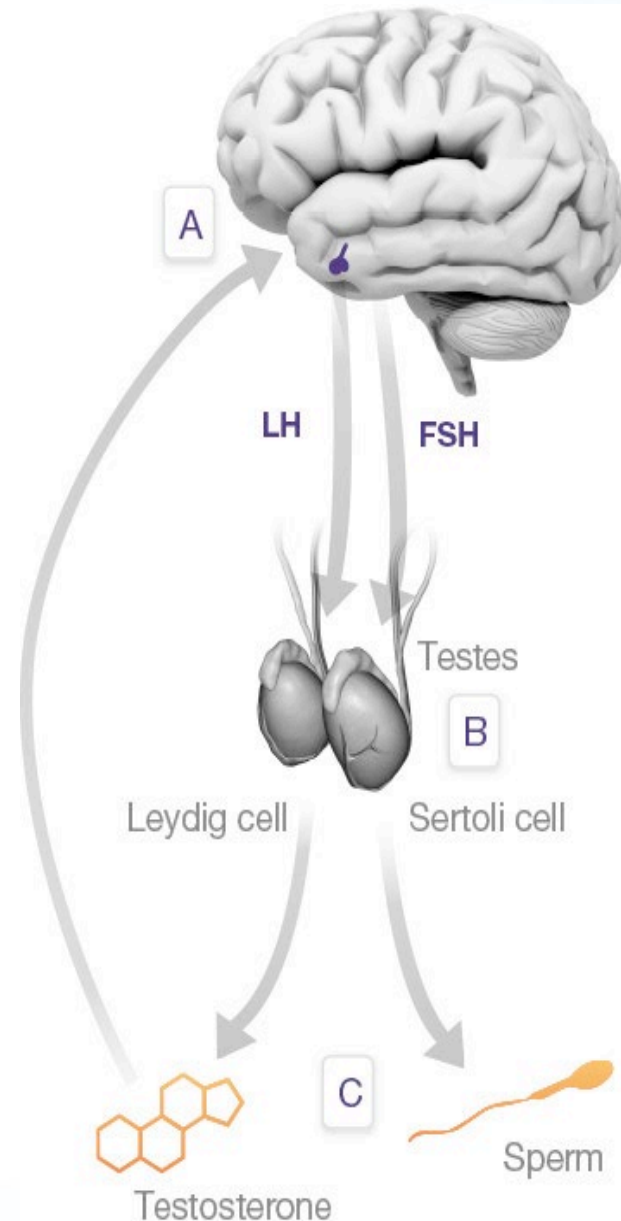
A HORMONE is a message sent from one part of the body to another.

At the start of puberty: the brain “turns on” the system

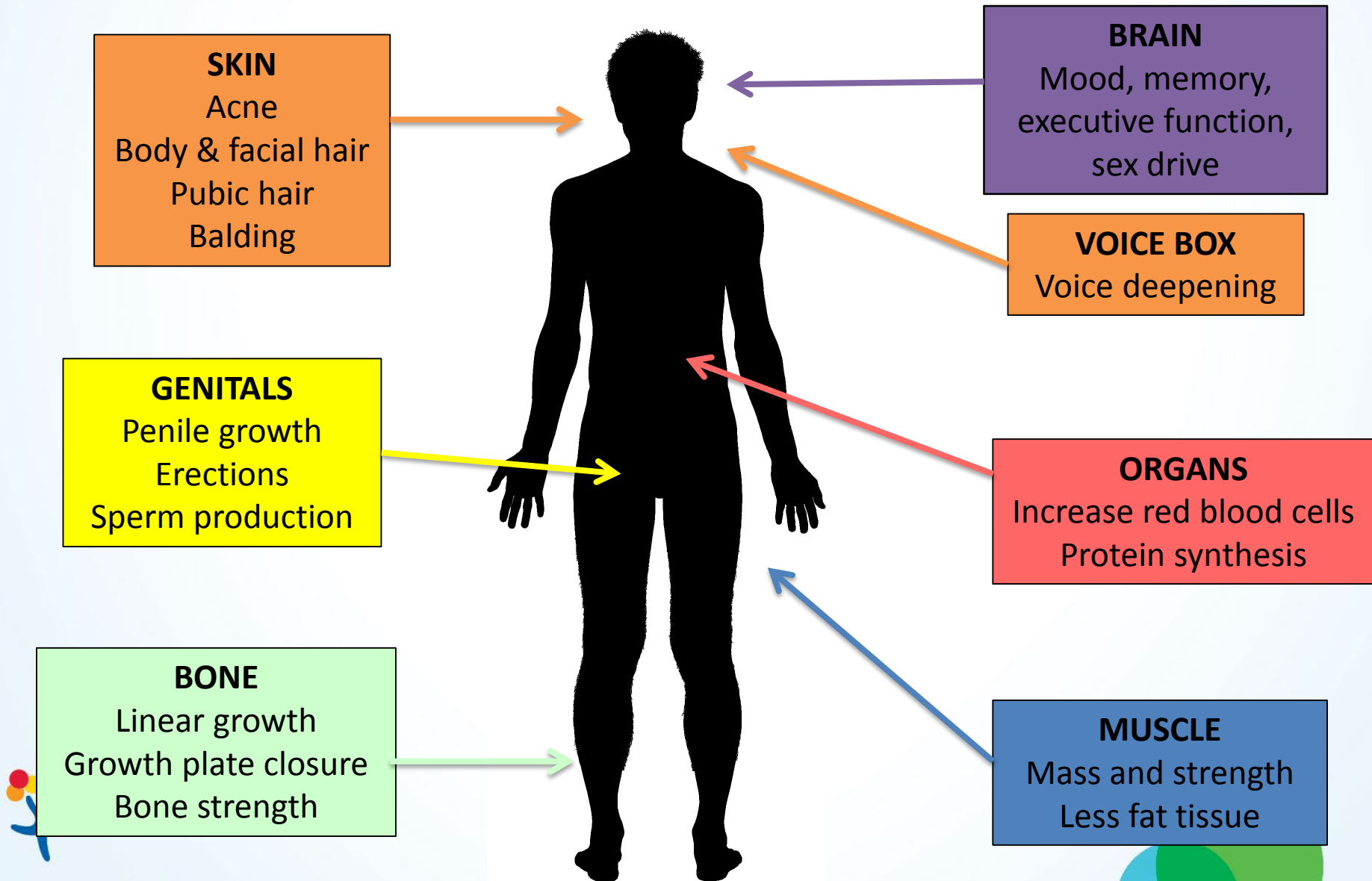
The pituitary gland releases LH and FSH

LH talks to the cells in the testes that produce testosterone

FSH talks to the cells in the testes that make the testes grow and support germ cell (sperm) development

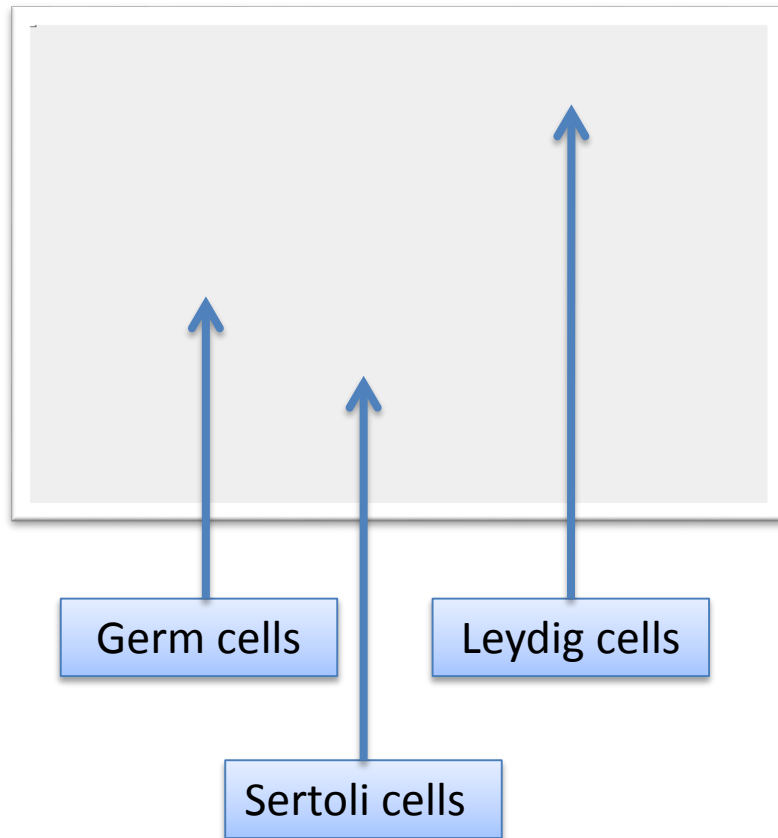


Testosterone Effects

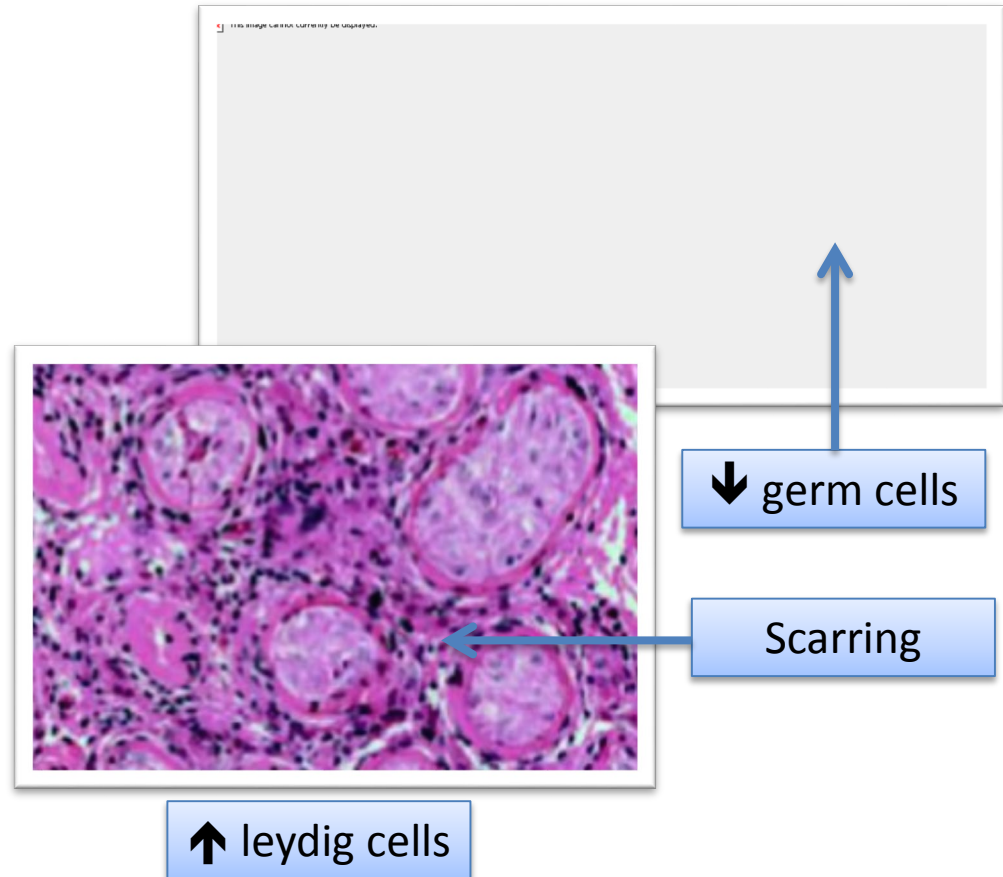


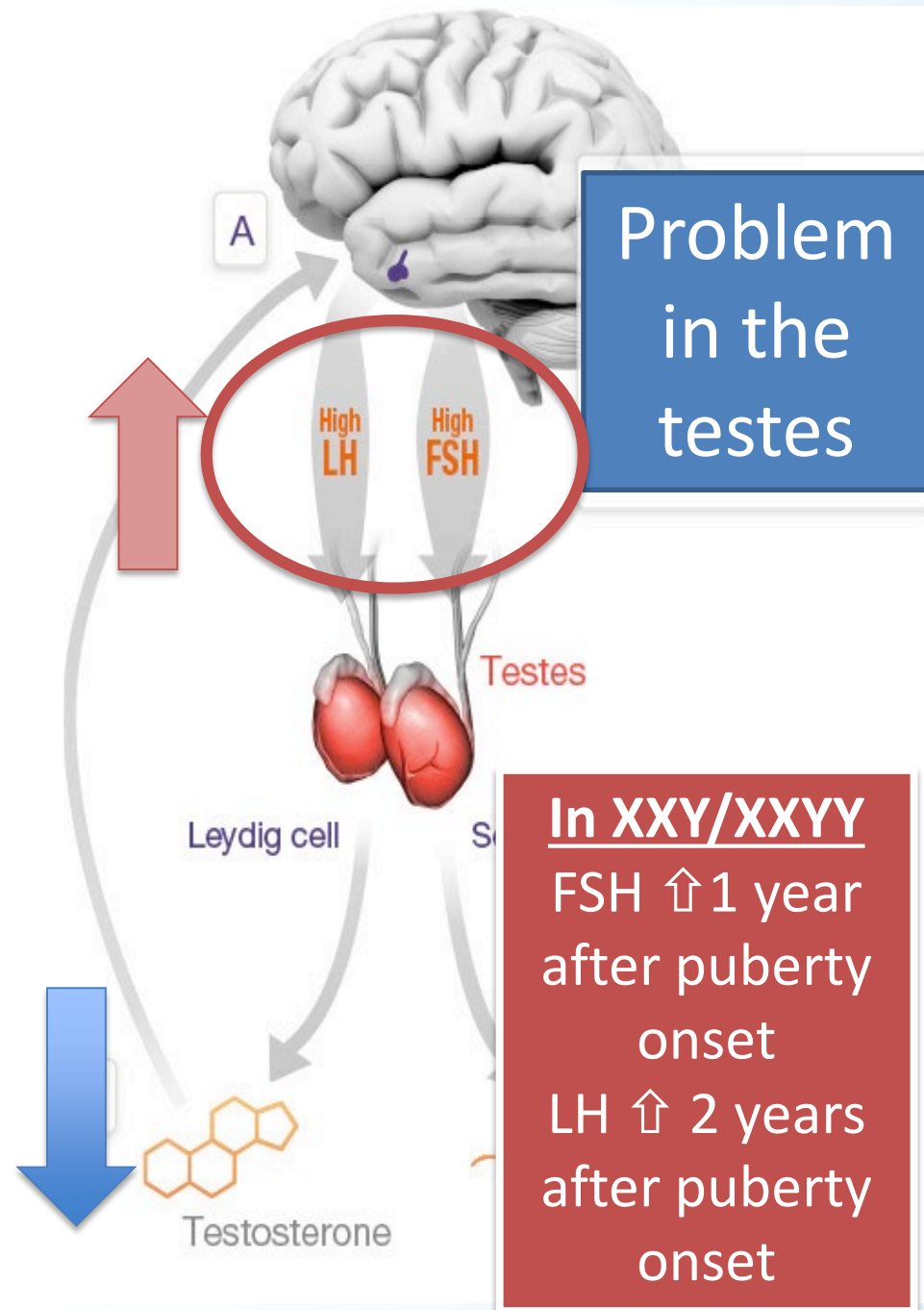
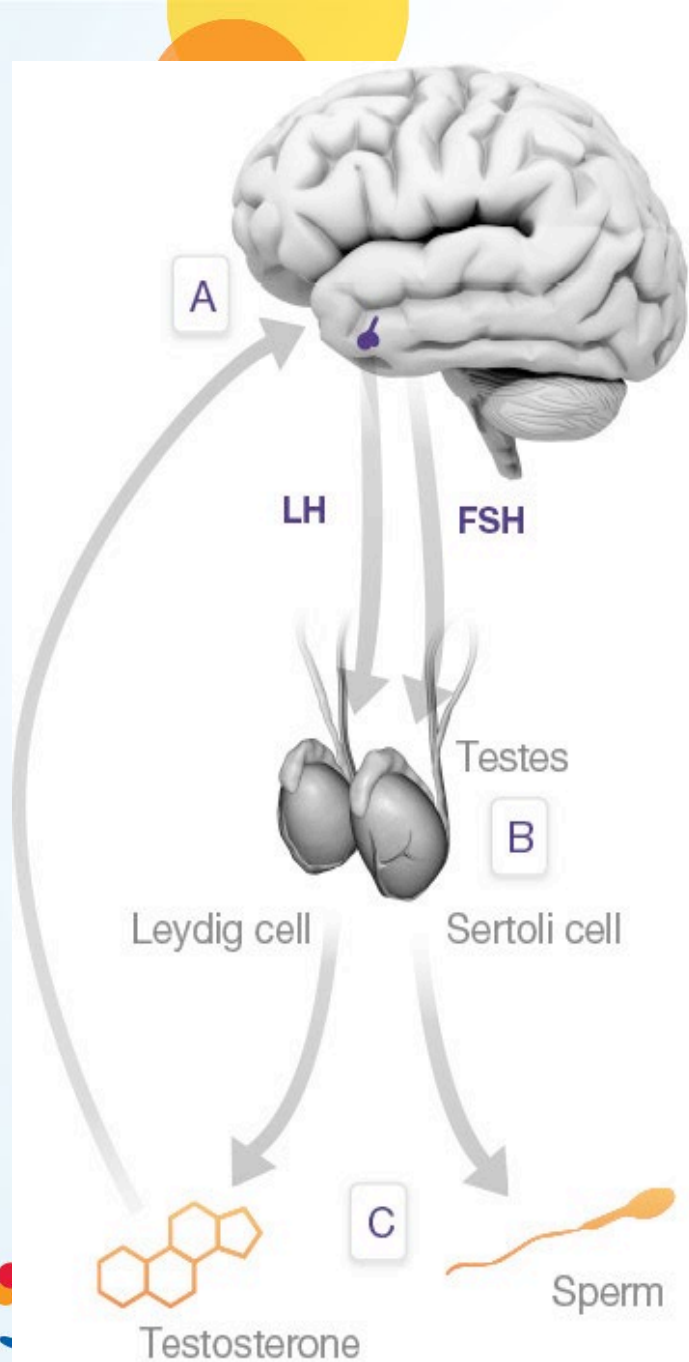
Testicular Development

9 yo XY Male Testis



9 yo XXY Male Testis

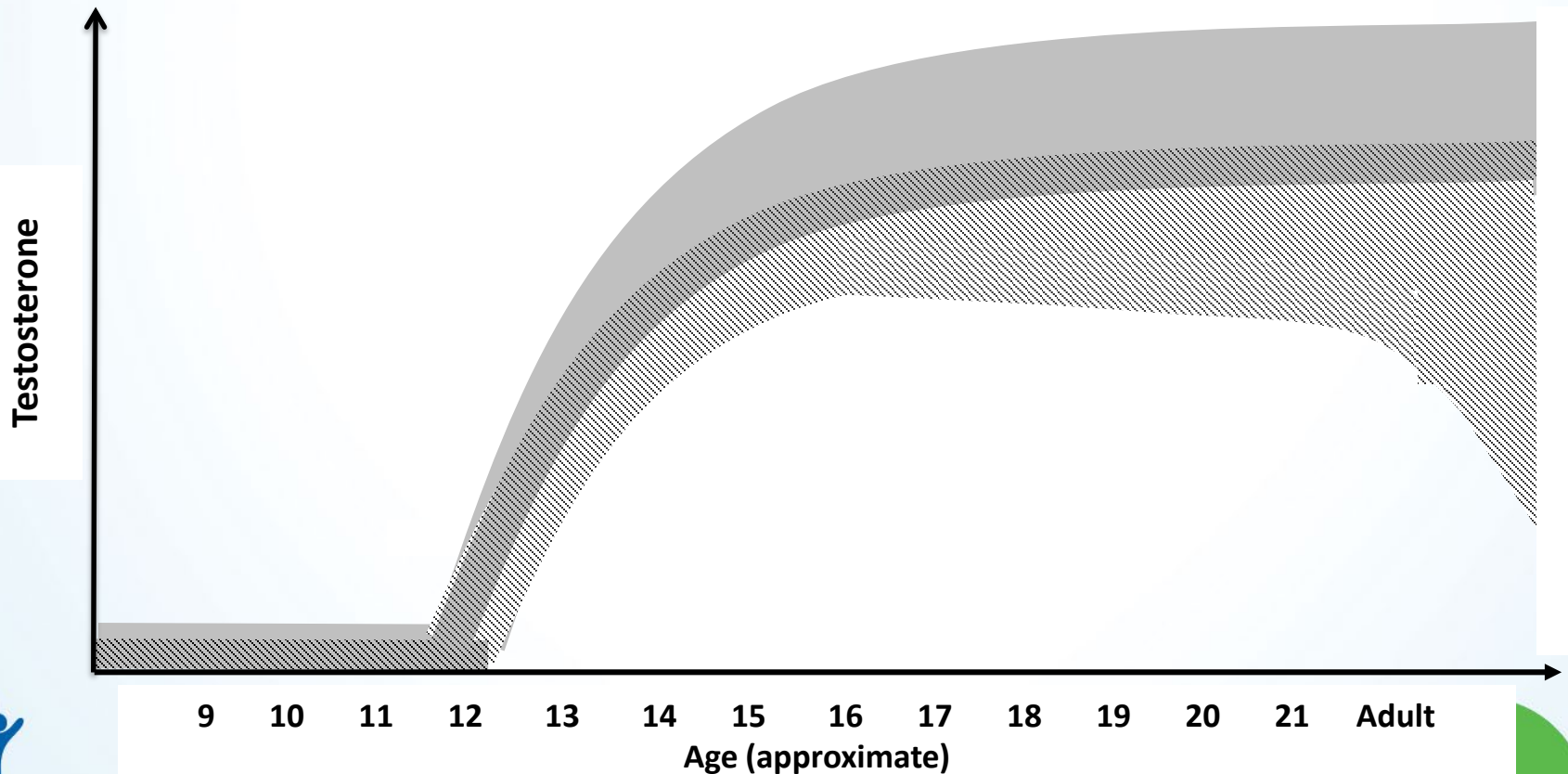




Testosterone Levels

Normal range of testosterone for 46,XY males

Testosterone range in XXY/XXYY/XXXY



Puberty in **XXY/XXYY/XXXY**

- Pubic hair occurs before testicular enlargement in over half (average age 11.5)
- Testicular enlargement is minimal (max 5-8 mL), often decreases later to 2-4 mL
- Less body hair
- Less muscle bulk
- Taller stature
- More gynecomastia?





When to start testosterone?

- Not yet any evidence-based or even consensus guidelines
- Considering the boy's age, pubertal development, mental and physical health, and blood work – not just based on a blood level
- Not cookie-cutter and input from the parents (and ideally the child) is helpful

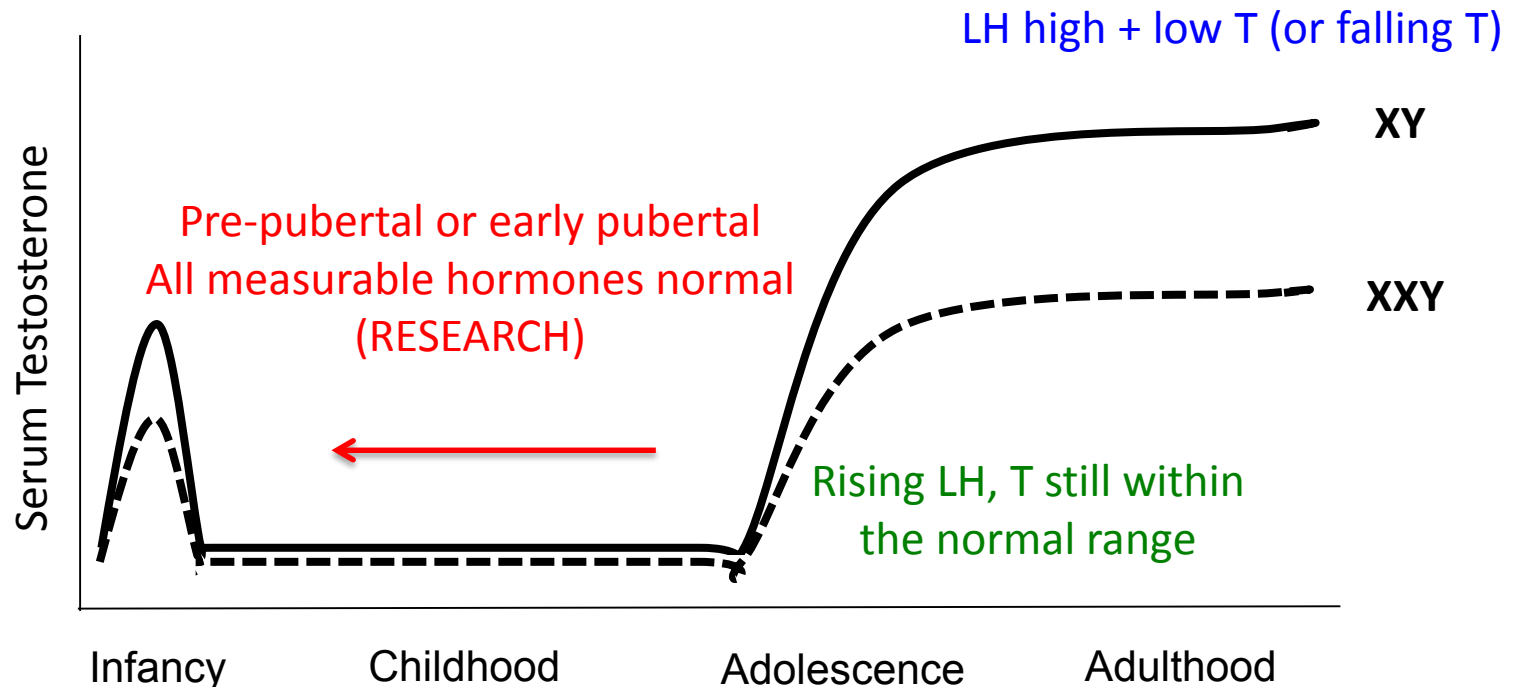


FAQ: When to start testosterone?

No consensus guidelines for XXY

Endocrine Society Hypogonadism Guidelines

Low T + clinical signs of testosterone deficiency



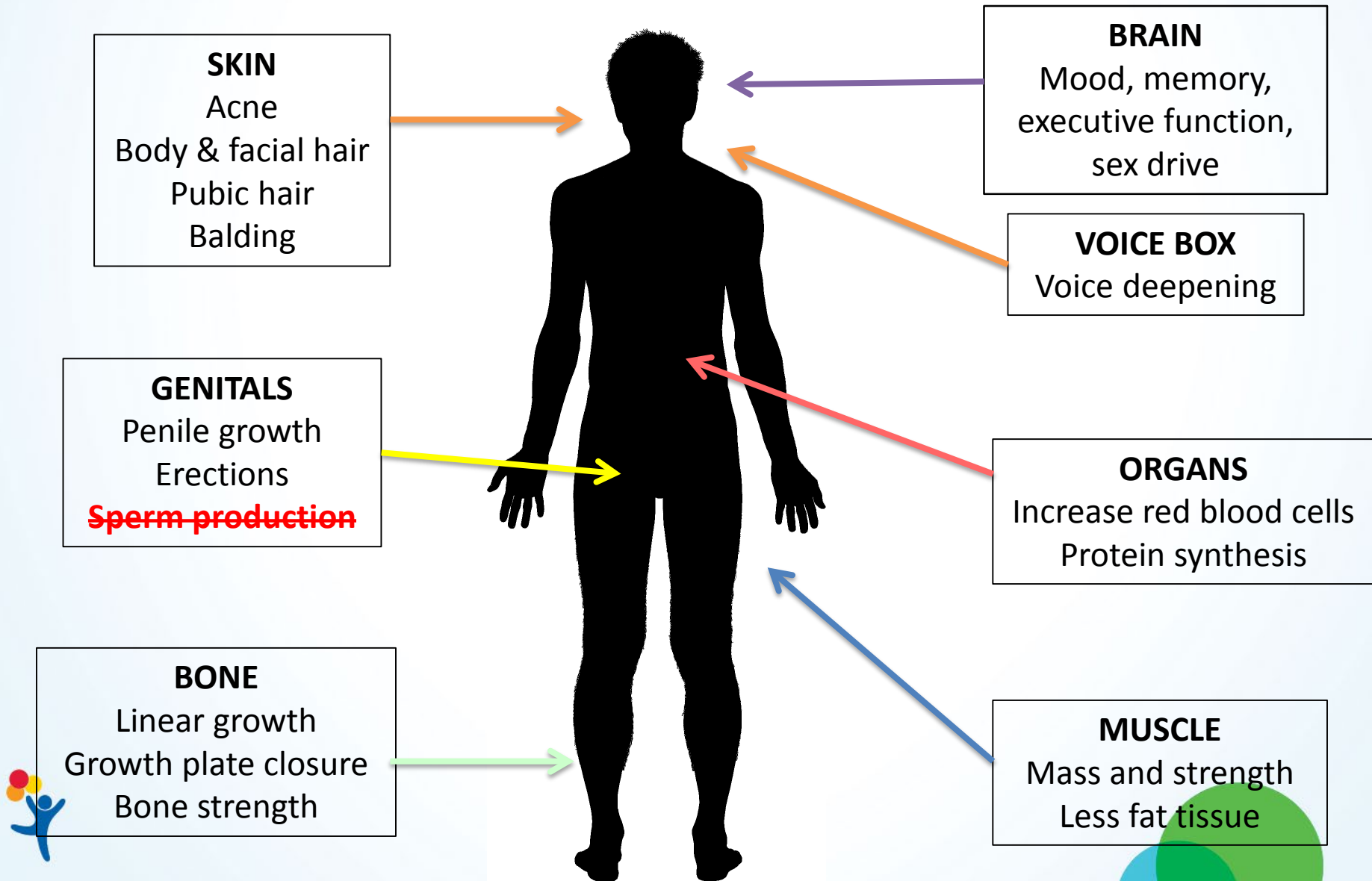
Our Practice

- Endocrinology evaluation at ~10 yrs or first sign of puberty – **build a relationship**
- Physical Examination
- Bone age x-ray
- LH, FSH, T
 - Every ~6 months

LH above the upper limit of normal for pubertal stage or consistently rising we consider testosterone supplementation



Supplemental Testosterone





FAQ: How do we give T?

- There are many formulations of T on the market
- < 18 years, our choices are more limited
 - Testosterone shots (IM or SQ)
 - Testosterone gel
- Pros and cons → individualization



FAQ:What is the best formulation/dose?

- One small study on 1% gel in XXY
 - Start 1 pump daily → sometimes too much
 - Titrate serum levels, exam, symptoms
- Weekly subcutaneous injections
 - Start at 20-30 mg/week
 - Titrate serum levels (trough), exam, symptoms
- Monthly IM injections
 - Start 100-150 mg/month
 - Titrate up based on exam, symptoms (max 200 q2 wks)
- Patches aren't my first choice
- Other formulations too potent

Rogol et al, J Adolesc Health 2014
Davis, Rogol, Ross, EMCNA 2015



FAQ: What are the side-effects?

- Local skin reactions / allergies (preservatives)
- Acne
- Bone age advancement / fusion of growth plates
- Clotting or bleeding issues; increased hematocrit
- Mood changes or aggression
- Preoccupation with sex, frequent erections, priapism
- Testosterone *can* be a drug of abuse
- FDA warning heart attacks/death – *old men*

Our goal is always to NORMALIZE testosterone concentrations NOT to exceed normal levels



FAQ: Does every guy with XXY need T?

- “Need” is hard to define
- Universally, testes do not function normally
- Almost all will have elevated LH levels, but not all will have low testosterone levels
- Most will benefit from supplementary T
 - Bone density
- Encourage trials (can come off)
- Individualize therapy with parents and patient

FAQ: Does T worsen behavior?

- No evidence implicating T treatment to worsened behavior in XXY (if kept in the normal range)
- Adolescence is a time when psychiatric conditions develop and behavior worsens (for all)
- Start low & go slow if concerns



FAQ: Once T is started, can it ever be stopped?

- YES. It does not have to be a permanent decision
- I encourage the patient to be involved in the discussion
- “Trials” are perfectly fine
- May have to stop if considering attempt at sperm preservation



FAQ: Does T reduce fertility outcomes?

Giving T: ↓ LH →

↓ intratesticular testosterone → ↓ spermatogenesis

BUT, this doesn't seem to be permanent...right away

Table 3. Positive TESE Rate According to Age Group and Previous T Treatment

		Previous T Treatment		
		Yes	No	Total
Ages 15-24 years →	Young group	6/10 (60.0)	7/15 (46.2)	13/25 (52.2)
Ages 24-35 years →	Adult group	3/7 (42.9)	7/9 (77.8)	10/16 (62.5)
	Total	9/17 (52.9)	14/24 (59.1)	23/41 (56.4)

Plotton et al, TESE in Young vs Adult Nonmosaic 47,XXY JCEM, 2015

FAQ: Does T reduce fertility outcomes?

ORIGINAL ARTICLE: ANDROLOGY

Successful testicular sperm retrieval in adolescents with Klinefelter syndrome treated with at least 1 year of topical testosterone and aromatase inhibitor

Akanksha Mehta, M.D., Alexander Bolyakov, M.Sc., Jordan Roosma, Peter N. Schlegel, M.D., and Darius A. Paduch, M.D., Ph.D.

Department of Urology, Weill Cornell Medical College, New York, New York

Our approach (right now):

- ~>14 years old (new diagnosis, etc), discuss with family, offer referral to repro team if desired
- ~<14 years old, do not delay testosterone treatment if needed
- Continue fertility discussions

Patient characteristics and success of sperm retrieval.

Patient	Age at TESE (y)	Testis volume (cm ³)	Duration of hormone therapy (mo)	Total T (ng/dL)		LH (mIU/mL)		FSH (mIU/mL)		Sperm retrieved
				Base	Pre-op	Base	Pre-op	Base	Pre-op	
1	14	3	15	161	345	1.8	12.1	17.6	58.6	Yes
2	14	2.5	40	40	253	2.9	17.3	8.3	74.5	No
3	16	10	14	214	990	12	7.4	23	20.2	Yes
4	15	5.5	34	251	895	1.9	8.6	8.1	16.7	Yes
5	15	2.5	22	210	873	20.4	16.5	47.3	40.1	Yes
6	14	6	12	57	126	1.0	6.3	2.4	31.1	No
7	16	2	12	179	746	25.1	24.6	40.7	27.9	Yes
8	22	2.5	>60	350	744	19	46.2	34.6	45.0	Yes
9	14	1	30	226	513	0.6	4.8	1.4	4.7	Yes
10	15	3.4	35	236	513	0.4	4.1	1.2	15.3	No



Limitations & Future Directions

- We have so little evidence-based research on when, why, and how to start testosterone in boys with XXY/XXXY/XXYY
- More research to come to help us!
- THANK YOU to the boys and families who participate in important research!!!





Summary

- The decision of when to start testosterone should involve the patient, parents, and the physician
- It may include all of the following
 - Growth and pubertal exam
 - Laboratory measures (LH, FSH, T)
 - Mental & physical health considerations
 - Patient and family preferences
- Our goal is to replace without causing side effects or exceeding normal values
- Advocate for yourself/child

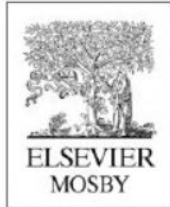


Cardiometabolic Screening in XXY

(My Approach)

Screening	When to get it	What to know
Height & Weight	Every visit (at least annually)	Plot on growth curves including BMI, trend is most important
Blood Pressure	Annually > 3 years old	Blood pressure norms depend on sex, age, and height
LDL, HDL, triglycerides	At 9-11 years old in all, then every 1-3 years	Cholesterol (lipids) screening, best done when fasting
HbA1C	Annually if obese > 10 years old, as needed for symptoms/risk	Diabetes screening; Measures of blood sugar over the last 3 months
AST, ALT	Every 1-3 years starting in puberty	Liver function tests, screening for fatty liver disease
Vitamin D	Depends on diet/history	Low in many people, may or may not have consequences

Resource for Providers



Advances in Pediatrics 63 (2016) 15–46

ADVANCES IN PEDIATRICS

Advances in the Interdisciplinary Care of Children with Klinefelter Syndrome

Shanlee Davis, MD^{a,b}, Susan Howell, MS, CGC, MBA^{a,c},
Rebecca Wilson, PsyD^c, Tanea Tanda, BS^{a,c}, Judy Ross, MD^{d,e},
Philip Zeitler, MD, PhD^{a,b}, Nicole Tartaglia, MD, MS^{a,c,*}



questions