# 12-year-old boy with 47,XXY Klinefelter Syndrome

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# Chief Complaint

- 12 year and 9 month-old boy with 47,XXY Klinefelter Syndrome presents to re-establish care in our endocrinology clinic and discuss management of his potential infertility

# History of Present Illness

- Diagnosed with 47,XXY by karyotype in-utero via amniocentesis
- Karyotype repeated at 9 mo: No mosaicism
- Microphallus identified at birth
- Penile length “2-2.5 cm” at 10 months of age

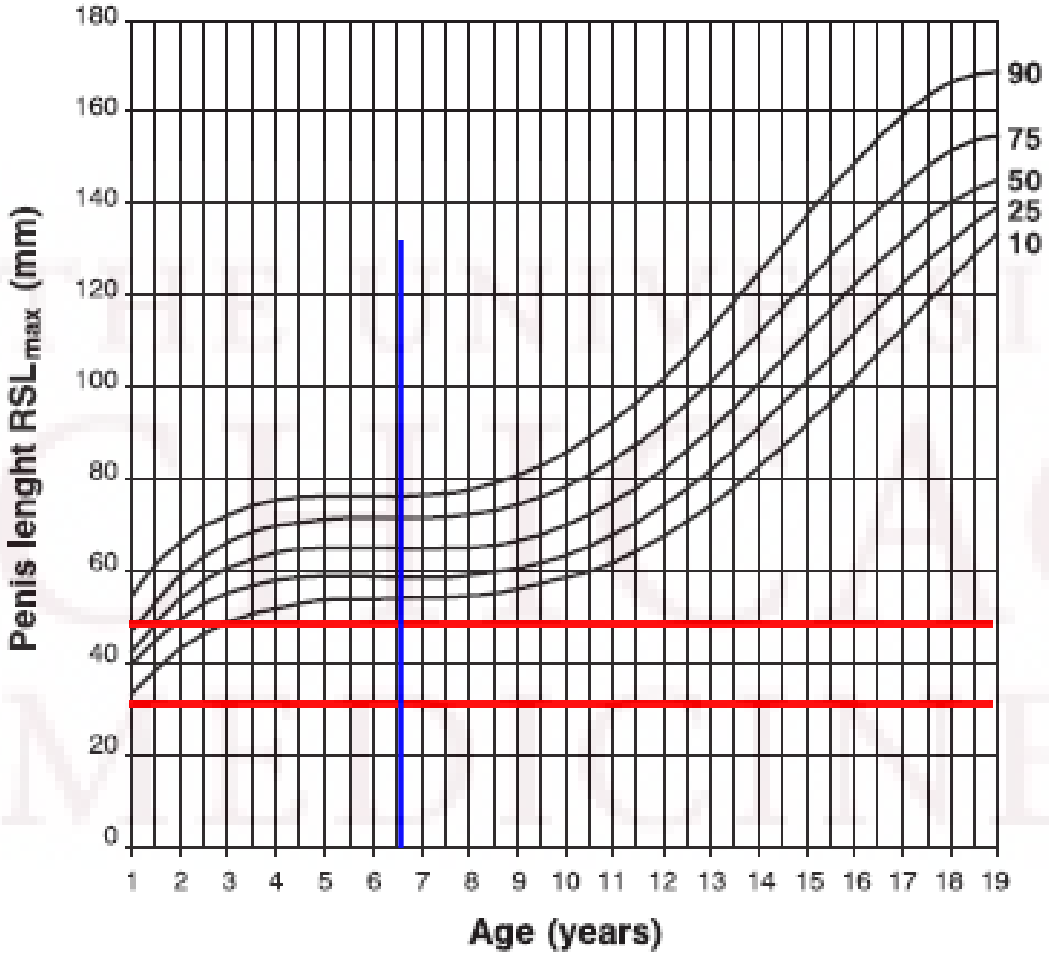



**Figure 1** - Distribution of penis size values, assessed as real fully-stretched length ($RSL_{max}$), expressed as the 10th, 25th, 50th, 75th and 90th percentiles

# 8 yrs 2mo: Enrolls in Clinical Trial

- "Androgen Effects on Cognition in Klinefelter Syndrome."
- Dr. Judith Ross, Thomas Jefferson University
  - Goal of Study: "Address questions regarding the relationship of early androgen deficiency to learning and social-behavioral functions."
  - Enrolled boys age 4-12 years old
  - Randomized to either Oxandrolone 0.06 mg/kg/day or Placebo control for 2 years
  - Bone age/Labs: baseline, 3 mo and every 6 mo
  - Cognitive testing: baseline, 12 mo and 24 mo

# History During Trial Course

- Prior to trial at 8 yrs 2 mo:
  - Denies testicular growth, penile growth, growth spurt and all secondary sex characteristics
- 1st year of trial:
  - Develops axillary hair, acne, and body odor
  - Dose of trial medication “changed”
- 2-year follow-up at 10yrs 2mo:
  - Develops mustache hair, Tanner IV pubic hair, and testes measuring 6mls
  - Bone Age: Advanced at 13 years skeletal age

# Rest of History Following Trial

- Continues to grow taller, develop more pubic hair and axillary hair
- Continues to have acne requiring topical prescription treatment
- Shaves infrequently
- 1 year prior to presentation develops breast buds, no galactorrhea

# More History…

- **Birth History:**
  - Uncomplicated pregnancy and delivery
  - Full-term
  - Birth Weight 8 lbs, 1 oz (AGA)
- **Past Medical History:**
  - ADHD
  - Oppositional Defiant Disorder
  - Nocturnal enuresis
  - Allergic Rhinitis
  - Insomnia
- **Allergies:** None
- **Immunizations:** Up-To-Date
- **Medications:**
  - Clonidine 0.1 mg daily
  - Methylphenidate 54 mg daily PRN
  - Trazodone 50 mg qhs
  - Desmopressin 0.2 mg PRN

- **Social History**
  - Lives with mother, father, and brother in Southwest Chicago
  - 7th grade student with “good” grades
  - Enjoys participating as middle school mascot, the “Cardinal”

- **Family History**
  - No family history of precocious puberty
    - Mother with menses at 14 yo; 5’5.5’’
    - Father with growth spurt during “high school”; 6’3’’

# Review of Systems

- Constitutional: Negative for fever, diaphoresis, weight change or appetite change
- HENT: Negative for congestion, rhinorrhea, sore throat, neck swelling or difficulty swallowing.
- Eyes: Negative for visual disturbance.
- Respiratory: Negative for cough or shortness of breath.
- Cardiovascular: Negative for palpitations or chest pain.
- Gastrointestinal: Negative for abdominal pain, nausea, vomiting, diarrhea. +intermittent constipation.

# Review of Systems Continued

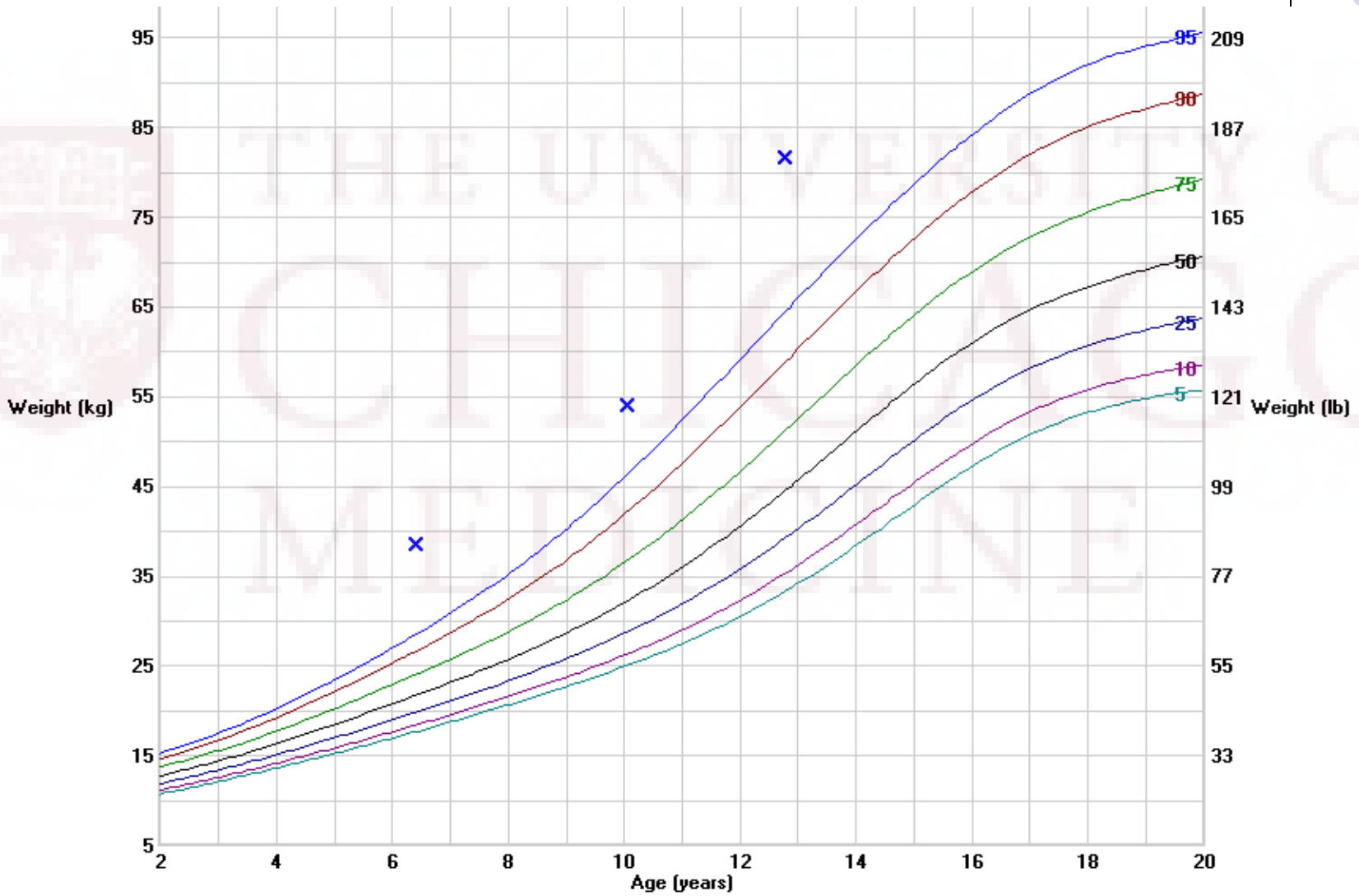
- Genitourinary: +Nocturnal enuresis. +enlarged phallus. +pubic hair.
- Musculoskeletal: Negative for arthralgias, edema. +low muscle tone.
- Skin: Negative for dry skin, rash. +acne.
- Neurological: Negative for weakness, light-headedness, seizure, fainting. +intermittent headache.
- Psychiatric/Behavioral: Negative for depression. +some nervousness, +insomnia, +ODD, +ADHD

# Physical Exam

- Vital Signs:
  - T 36.1C, P 63, BP 107/64
- Weight:
  - 81.67 kg (99.4%)
- Height:
  - 178.8 cm (99.8%)
- BMI:
  - 25.54 kg/$m^2$ (95.8%)

# Growth Chart: Height for Age

# Growth Chart: Weight for Age




Source: Centers for Disease Control ar

- Constitutional: Appears well-developed and well-nourished. Active. Appears older than stated age and very tall.
- Head/Face: No dysmorphic features.
- Eyes/Mouth/Throat: Conjunctivae and EOM are normal. Pupils are equal, round, and reactive to light. Mucous membranes are moist. Dentition is normal. Oropharynx is clear.
- Neck: Neck supple. No adenopathy. No thyromegaly.
- Cardiovascular: Normal rate and regular rhythm. Radial pulse is 2+ bilaterally. No murmur heard.
- Pulmonary: Effort normal. There is normal air entry. No wheezes.
- Chest: +Glandular breast tissue palpable bilaterally (Tanner stage 3). Left breast larger than right breast. Areola is not raised. No galactorrhea expressed.

- Axilla: Abundant pigmented, coarse axillary hair.
- Abdominal: Soft, no distension. No hepatosplenomegaly. No masses. No tenderness. Normal bowel sounds.
- Genitourinary: Tanner 5 pubic hair. Adult-appearing phallus, pigmented scrotum, testes descended bilaterally, left 3.1 cm and right 3 cm in long diameter. No testicular masses.
- Musculoskeletal: Normal range of motion. There is no edema and no tenderness.
- Neurological: Exhibits normal muscle tone. No motor weakness. 2+ Patellar DTRs. Balance and gait in tact.
- Skin: Skin is warm. +Fine mustache hair. +Sparse acne on forehead. No acne on chest.

# Bone Age Study

Male 12-yr and 6mo


Our Patient

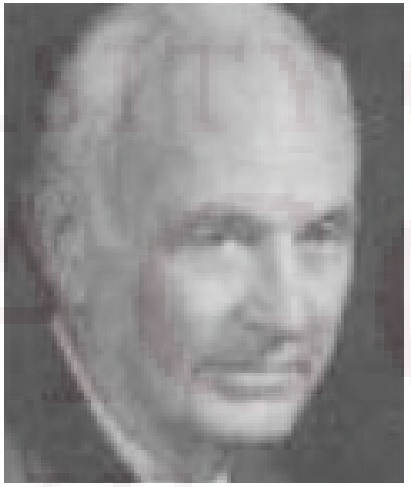
Male 16-year-old

# Laboratory Studies

| | Value | Range |
|---|---|---|
| **LH** | 20.5 IU/L | Prepubertal: <0.3 IU/L<br>Adult: 2-6.8 IU/L |
| **FSH** | 35.2 IU/L | Prepubertal: <1 IU/L<br>Adult: 1.2-8 IU/L |
| **Total Testosterone** | 332 ng/dL | Tanner 4: 200-620 ng/dL<br>Tanner 5: 350-970 ng/dL<br>Adult: 350-1030 ng/dL |
| **SHBG** | 37 nmol/L | Pubertal Males: 72-220 nmol/L |
| **Free Testosterone** | 95 pg/mL | Adult Males: 52-280 pg/mL |
| **Estradiol** | 23 pg/mL | Adult Males: 8-35 pg/mL |

# Klinefelter Syndrome

- 47,XXY or 46,XX/47,XXY mosaic
- Prevalence: 1 in every 600 males
- Only ¼ of males are diagnosed
- Phenotype is result of extra inactivated X-chromosome



Harry Klinefelter, M.D

Groth et al. JCEM. 2013. 98(1):20-30.
http://www.britannica.com/EBchecked/topic/320066/Klinefelter-syndrome

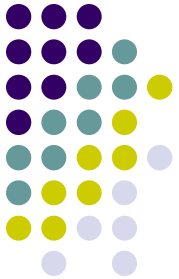
**Table 1**
Clinical features (%) of adult patients with Klinefelter syndrome.[3,38,81]

| | |
|---|---|
| Small testes (<4–6 mL) | >95 |
| Infertility | >99 |
| Azoospermia | >95 |
| Decreased facial hair | 60–80 |
| Decreased pubic hair | 30–60 |
| Abdominal adiposity | 50 |
| Gynecomastia | 38–75 |
| Varicose veins | 40 |
| Decreased libido and potency | 70 |
| Decreased muscle strength | 70 |
| The metabolic syndrome | 46 |
| Type 2 diabetes | 10–39 |
| Osteopenia and osteoporosis | 40 + 10 |
| Mitral valve prolapse | ≤55 |



Wikstrom, AM and Dunkel, L. Best Practice & Research Clinical Endocrinology & Metabolism. 2011. 25(2):239-250.

# Clinical Questions



- What is the pathophysiology of hypergonadotropic hypogonadism and infertility in 47,XXY males?
- What is the most effective means of preserving fertility in 47,XXY patients?
- What is the effect of pre-pubertal androgen therapy on the neurocognitive development of 47,XXY patients?

# 47, XXY and Hypergonadotropic Hypogonadism

- Pathophysiology is still poorly understood

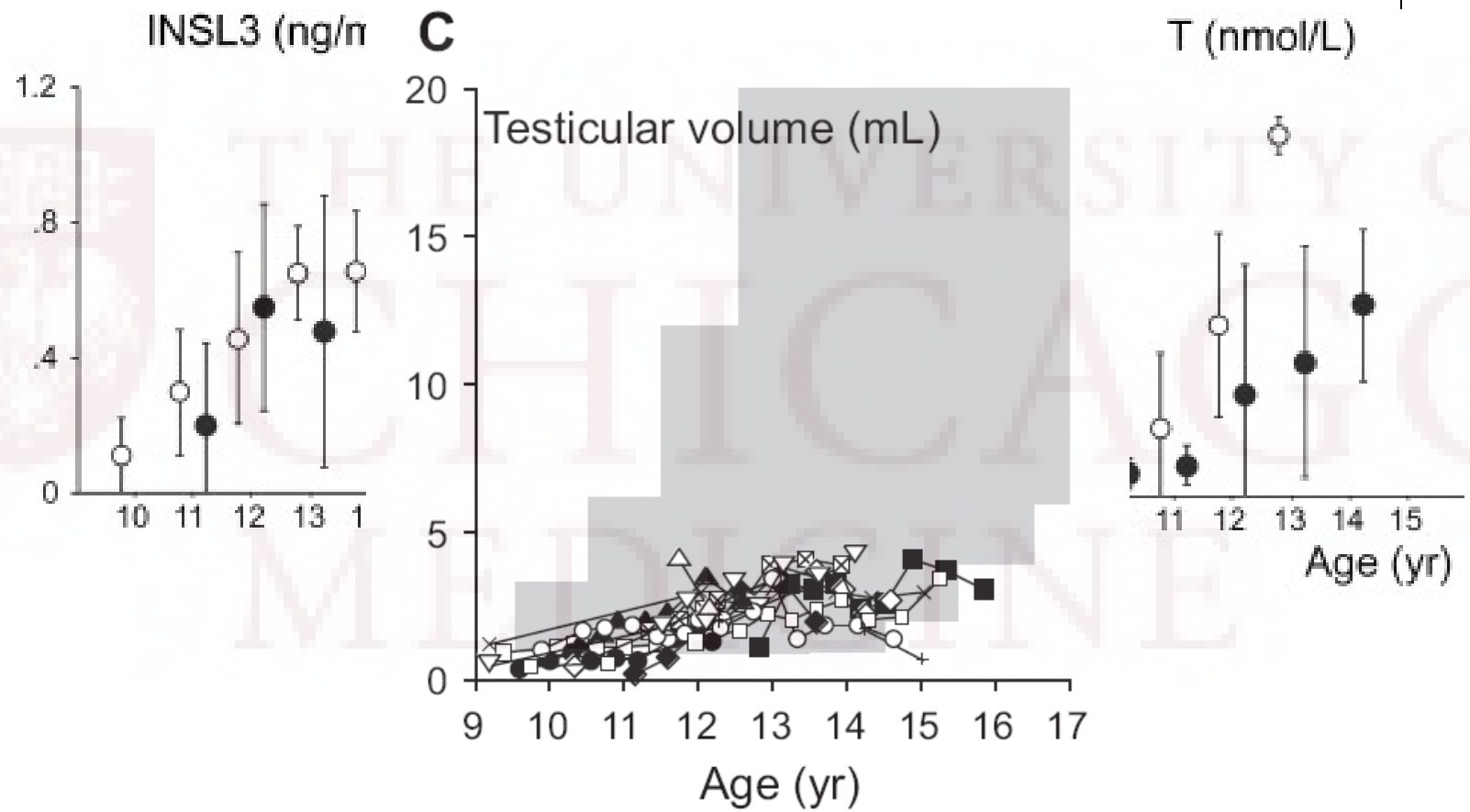
- Histology in KS:
  - Hyalinization of seminiferous tubules
  - Loss of germ cells
  - Leydig cell hyperplasia

Groth et al. JCEM. 2013. 98(1):20-30.

| | HP-T Axis | Testis |
|---|---|---|
| Infancy | Impairment Leydig cell function | Spermatogonia decline |
| Childhood | Normal FSH/LH, T | Spermatogonia do not enter meiosis |
| Puberty | T increase then plateau at low/nl<br>FSH/LH rise | Accelerated:<br>-Sertoli cell degeneration<br>-Leydig cell hypertrophy |
| Adult | FSH > LH, both high<br>T low (65-85%)<br>E2 high | - Extensive fibrosis and hyalinization of the seminiferous tubules<br>- Azospermia (90-95%) |

Wikstrom, AM and Dunkel, L. Best Practice & Research Clinical Endocrinology & Metabolism. 2011. 25(2):239-250.

# Pubertal Changes in 47, XXY Boys




Wikstrom, AM and Dunkel, L. Best Practice & Research Clinical Endocrinology & Metabolism. 2011. 25(2):239-250.

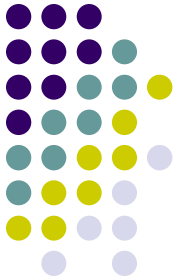
# Fertility and 47, XXY

- Only 8.5% of adults with spermatozoa
  - Still risk of genetically-imbalanced sperm
- Fertility Treatments:
  - Boys:
    - Cryopreservation
  - Adults:
    - Testicular Sperm Extraction (TESE)
    - Intracytoplasmic Sperm Injection (ICSI)



Groth et al. JCEM. 2013. 98(1):20-30.

# Clinical Questions



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# Neurodevelopment in 47,XXY

- Neuropsychological phenotype is variable
- Adults have low-normal IQ
- Typical areas of Cognitive impairment[1]:
  - Speech delay and language-based learning disabilities
  - Impairments in attention
  - Motor difficulties

Groth et al. JCEM. 2013. 98(1):20-30.
1. Ross et al. American Journal of Medical Genetics Part A. 2008. 146A:708-719.
Ross et al. Pediatrics. 2012. 129(4):769-778.

# Effect of Testosterone Therapy on Neurocognitive Function

TABLE III. Neurodevelopmental Results at 36 Months

| | Group 1 | | Group 2 | | | |
|---|---|---|---|---|---|---|
| **Test type** | **Mean** | **STD** | **Mean** | **STD** | **Tests** | ***P*-value** |
| PLS-4 | 109 | 14 | 102 | 17 | Auditory comprehension | 0.03 |
| WPPSI | 109 | 18 | 94 | 7 | FSIQ | 0.02 |
| WPPSI | 12 | 4 | 8 | 3 | Vocabulary | 0.0006 |
| WPPSI | 10 | 2 | 8 | 2 | Comprehension | 0.01 |

STD, standard deviation; PLS-4, Preschool Language Scale-4; WPPSI-III, The Wechsler Preschool and Primary Scale of Intelligence-third edition; FSIQ, Full Scale IQ; N, number.

TABLE IV. Neurodevelopmental Results at 36 and 72 Months

| | | Group 1 | | Group 2 | | |
|---|---|---|---|---|---|---|
| **Test type** | **Sub-test** | **Mean** | **Std** | **Mean** | **STD** | ***P*-value** |
| 36 Months | | | | | | |
| PLS-4 | Auditory comp | 109 | 14 | 102 | 17 | 0.03 |
| PLS-4 | Verbal ability | 101 | 14 | 97 | 16 | 0.09 |
| WPPSI | FSIQ | 109 | 18 | 94 | 7 | 0.02 |
| WPPSI | VIQ | 109 | 19 | 95 | 8 | 0.02 |
| 72 Months | | | | | | |
| PLS-4 | Auditory comp | 111 | 9 | 101 | 15 | 0.02 |
| PLS-4 | Verbal ability | 106 | 14 | 95 | 16 | 0.01 |
| WPPSI | FSIQ | 111 | 16 | 102 | 18 | 0.02 |
| WPPSI | VIQ | 109 | 14 | 99 | 16 | 0.01 |

STD, standard deviation; PLS-4, Preschool Language Scale-4; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence-III; FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient.

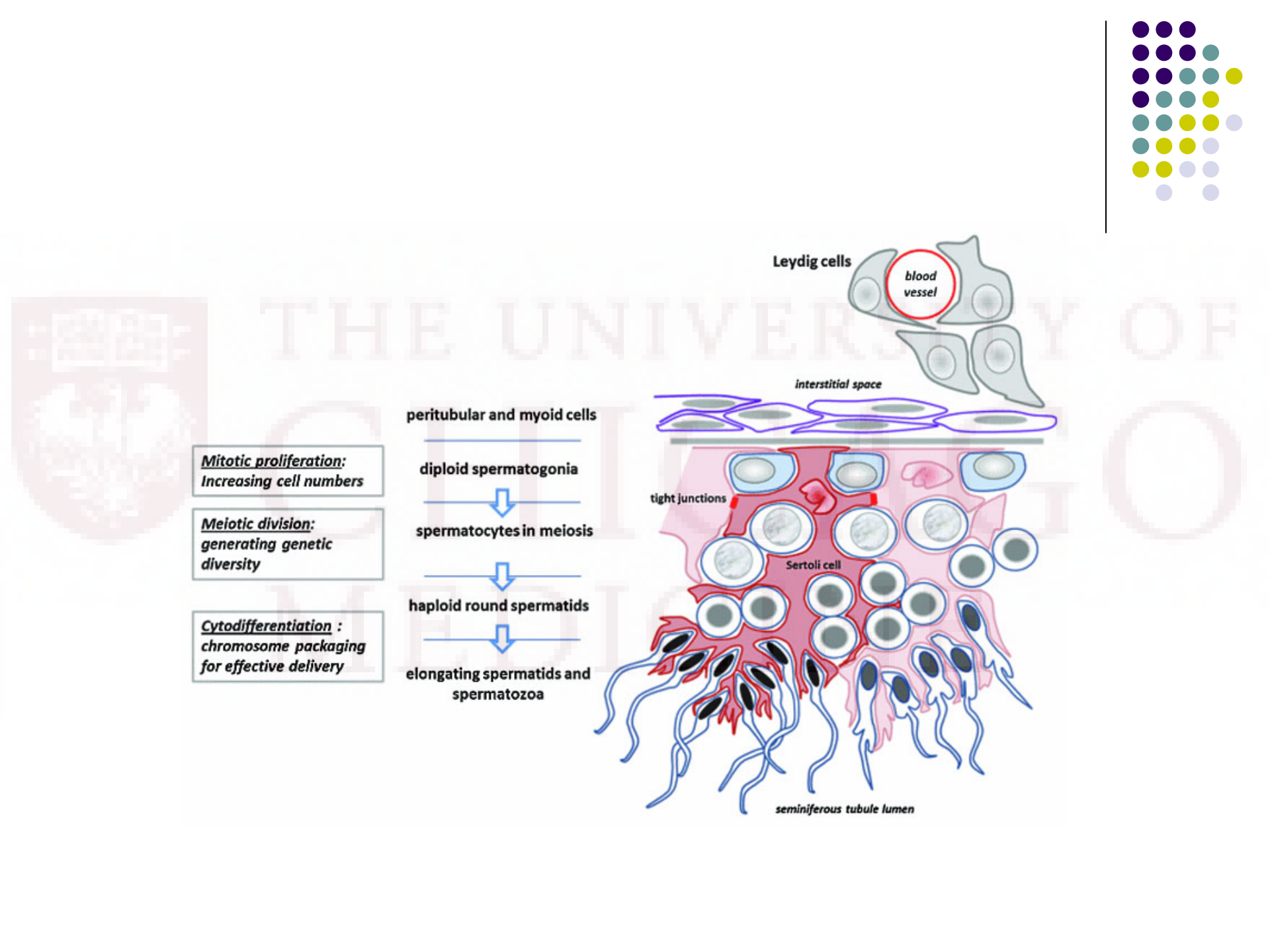
Samango-Sprouse et al. American Journal of Medical Genetics Part A. 2013. 161A:501-508.

# Summary

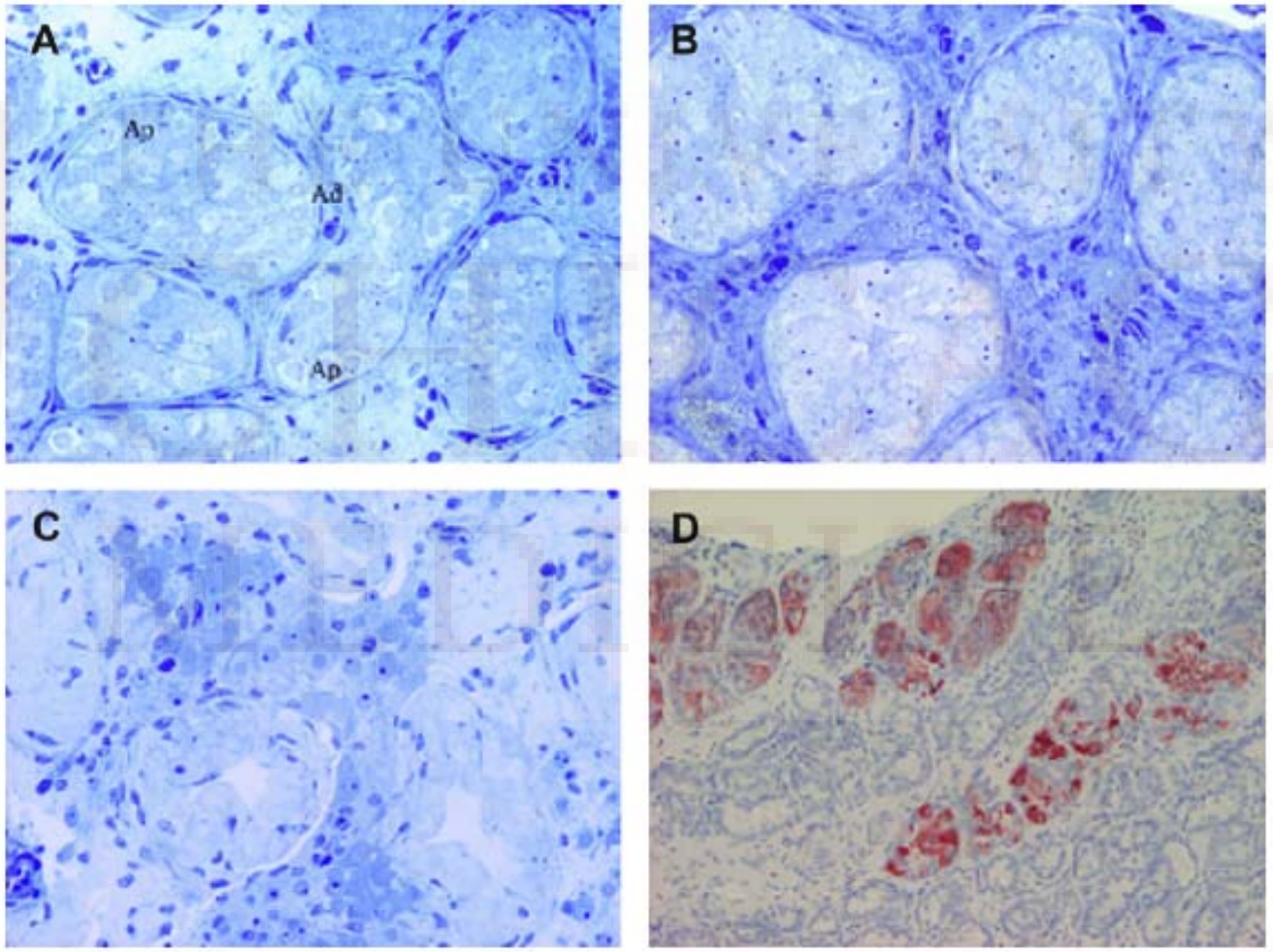
- 47,XXY Klinefelter Syndrome is a common disorder resulting in hypergonadotropic hypogonadism and infertility
- Modern techniques do allow for preservation of fertility especially if implemented prior to mid-puberty
- Neurodevelopmental outcomes in patients with 47,XXY can potentially improve with short course androgen therapy

# Works Cited


- Groth et al. “Klinefelter Syndrome – A Clinical Update.” JCEM. 2013. 98(1):20-30.
- Ross et al. “Behavioral and Social Phenotypes in Boys with 47,XYY Syndrome or 47,XXY Klinefelter Syndrome.” Pediatrics. 2012. 129(4):769-778.
- Ross et al. “Cognitive and Motor Development During Childhood in Boys with Klinefelter Syndrome.” American Journal of Medical Genetics Part A. 2008. 146A:708-719.
- Samango-Sprouse et al. “Positive Effects of Short Course Androgen Therapy on the Neurodevelopmental Outcome in Boys with 47,XXY Syndrome at 36 and 72 Months of Age.” American Journal of Medical Genetics Part A. 2013. 161A:501-508.
- Wikstrom, AM and Dunkel, L. “Klinefelter Syndrome.” Best Practice & Research Clinical Endocrinology & Metabolism. 2011. 25(2):239-250.


Mitotic proliferation: Increasing cell numbers
Meiotic division: generating genetic diversity
Cytodifferentiation : chromosome packaging for effective delivery
peritubular and myoid cells
diploid spermatogonia
spermatocytes in meiosis
haploid round spermatids
elongating spermatids and spermatozoa
Leydig cells
blood vessel
interstitial space
tight junctions
Sertoli cell
seminiferous tubule lumen

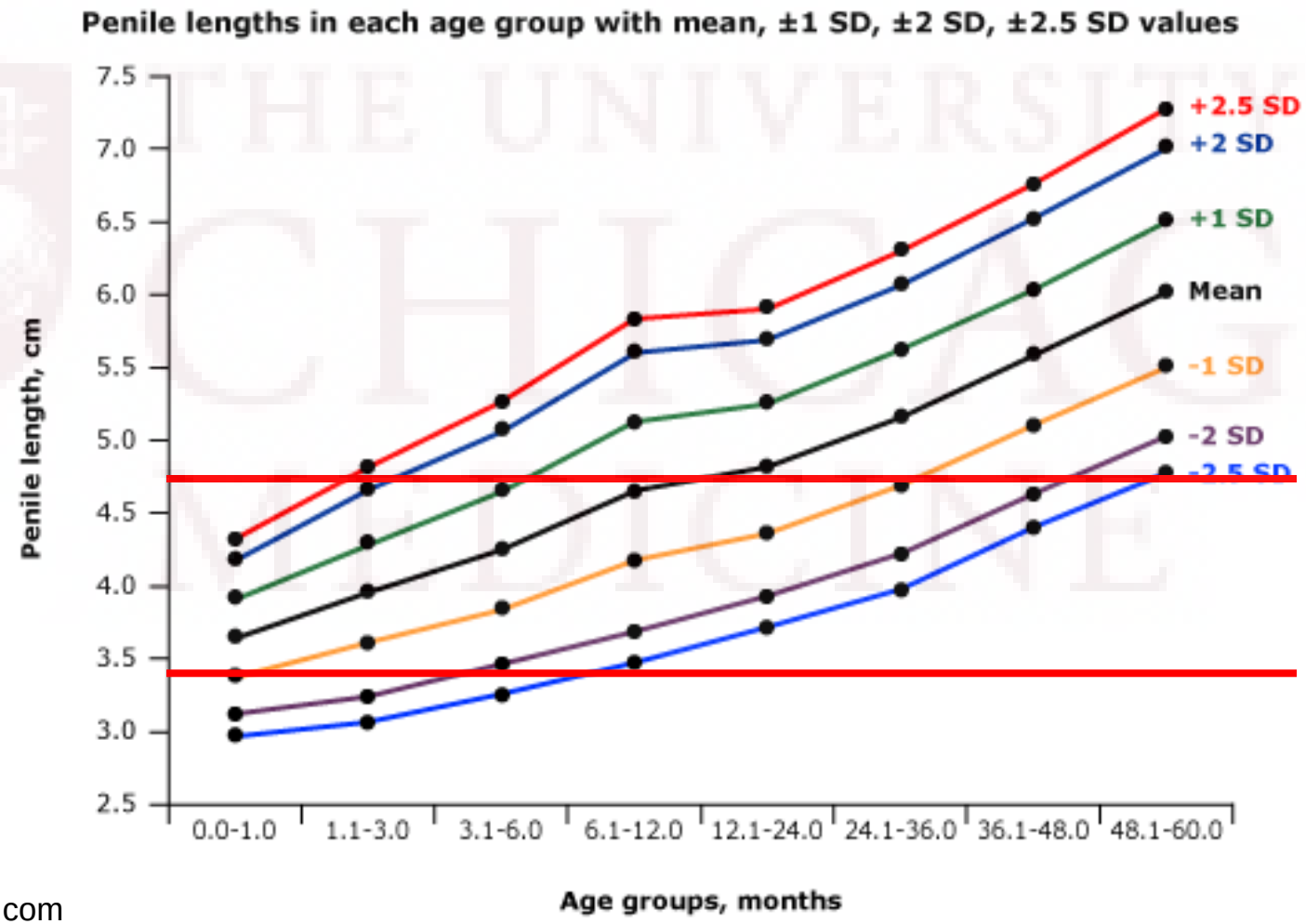
# Testicular Biopsies of Adolescents with 47, XXY



- http://www.youtube.com/watch?v=6351uZSwDps

# 6 yrs 6 mo: Endocrine Consult

## Penile length of boys aged 0 to 5 years




UptoDate.com

# Bone Age Study


**Our Patient**

**Male 16-year-old Standard**