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Children's Health

Pediatric Grand Rounds:
Growth Issues in Children

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Disclosure

- Nothing to disclose

Learning Objects

- Identifying and evaluating growth issues
- Causes of growth issues
- Interesting growth charts
- When to refer
- Treatment Options
- Questions

Why pay attention to children's growth?

- Normal growth is a sign of good health in children.
- Monitoring growth allows early detection of the causes of poor growth.
- Early recognition of poor growth allows early intervention optimizing the possibility of achieving good health and a normal adult height.

Haymond M et al. Early recognition of growth abnormalities permitting early intervention. Acta Paediatr. 2013 Aug; 102(8): 787–796.

Definition

- Short Stature: Below – 2 SDS (2.5 percentile)
- Growth Retardation: A downward deflection of the growth velocity with the resultant growth curve crossing the SD lines or percentiles.

Haymond M et al. Early recognition of growth abnormalities permitting early intervention. Acta Paediatr. 2013 Aug; 102(8): 787–796

Midparental Height

- Genetic Target Height
  - Boys: (father's height + mother's height + 13 cm) / 2
  - Girls: (father's height + mother's height − 13 cm) / 2

- A child whose height SDS falls outside the parental target range is more likely to have a growth disorder.

Haymond M et al. Early recognition of growth abnormalities permitting early intervention. Acta Paediatr. 2013 Aug; 102(8): 787–796

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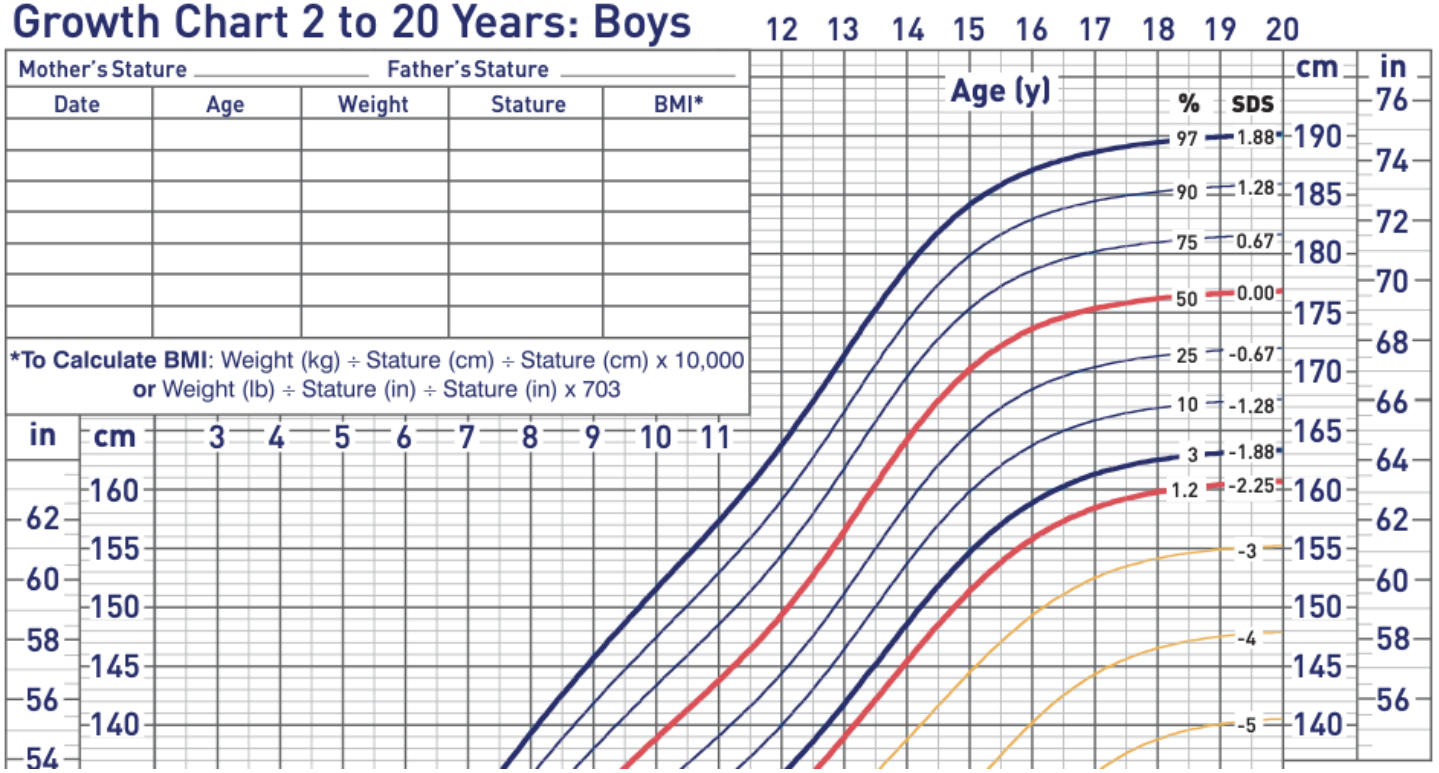
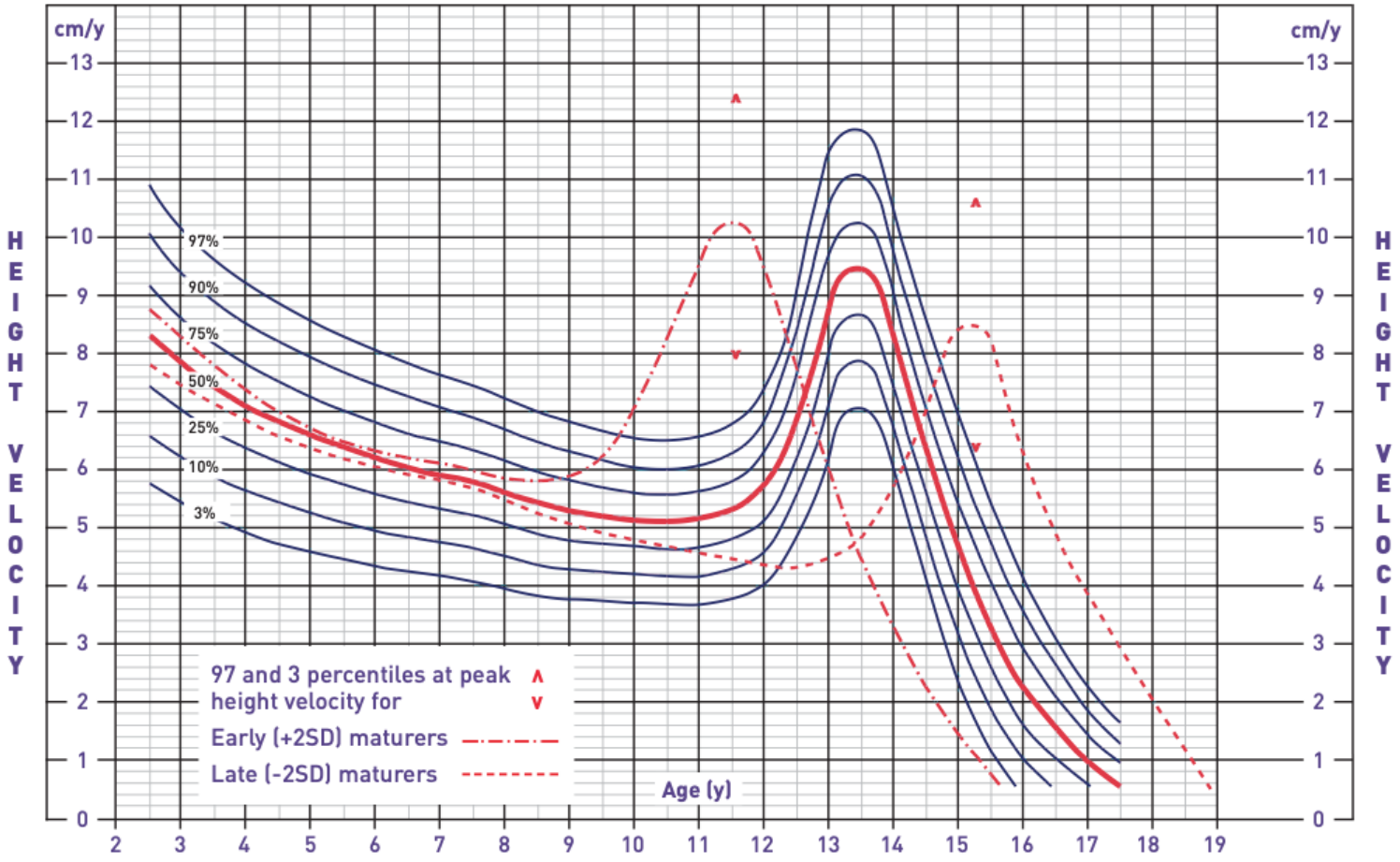


- 1 SDS = 16th percentile
- 2 SDS = 2.5th percentile

http://www.cdc.gov/growthcharts



Tanner JM et al. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr. 1985;107:317-329

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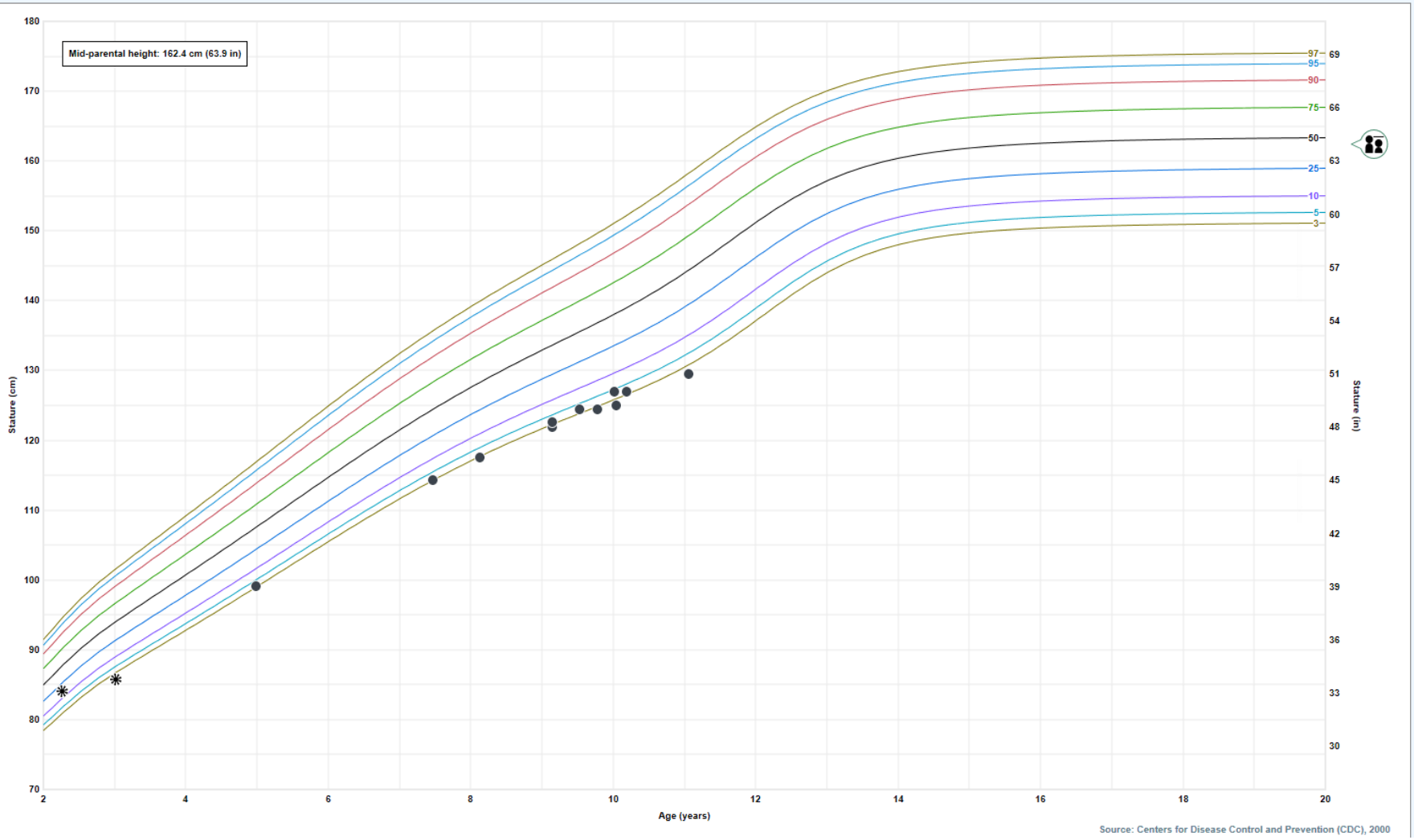
Length | Weight-for-length | Weight | BMI | Parents' Heights

Stature-for-age Percentiles (Girls, 2 to 20 years)

100 % | 100 % | Zoom In | Zoom Out



Source: Centers for Disease Control and Prevention (CDC), 2000

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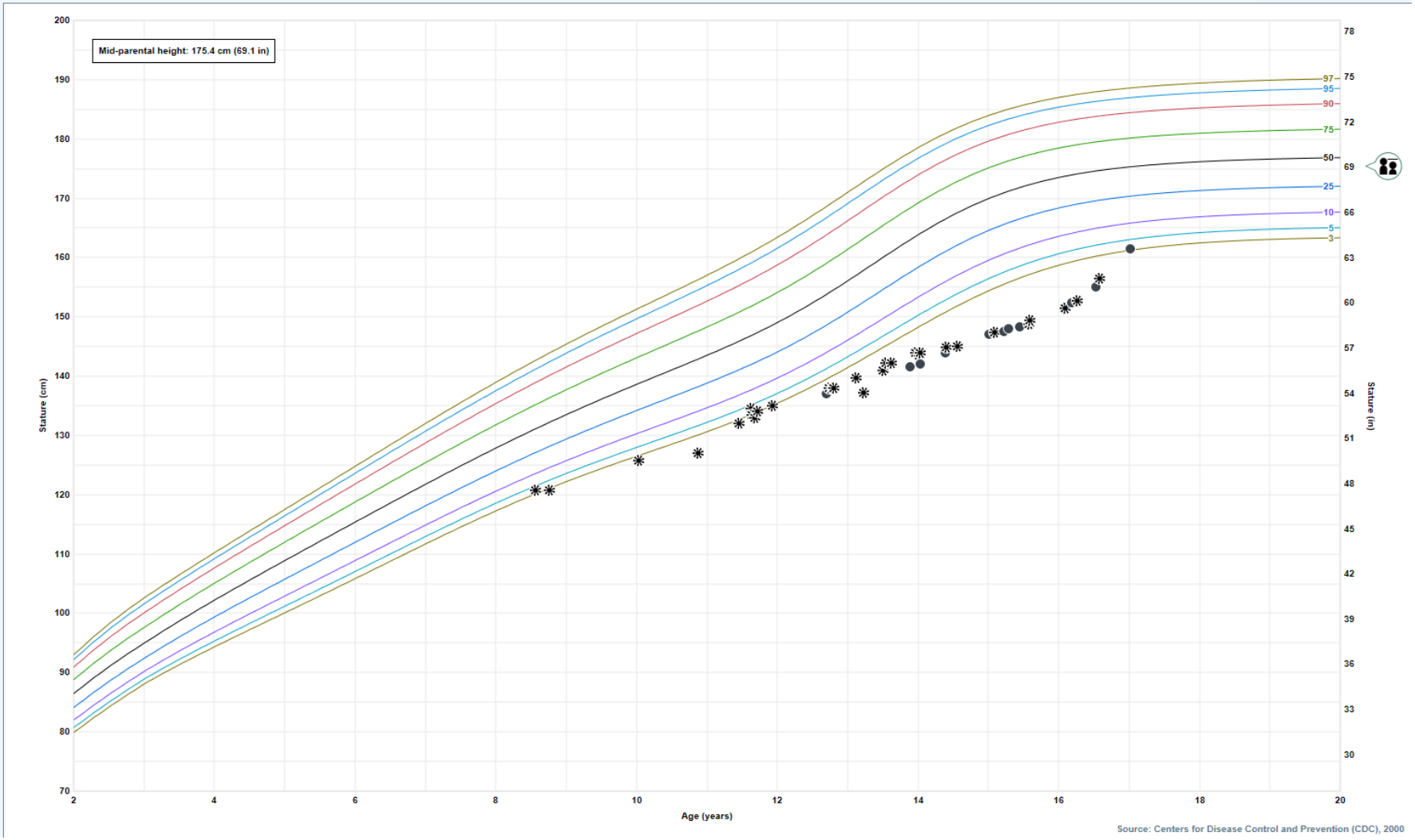
Stature-for-age Percentiles (Boys, 2 to 20 years)



Causes of Growth Disorder

- Many !
- Primary Growth Failure
  - Syndromes: Down, Turner, Noonan, Prader-Willi, Russell-Silver
  - SGA with failure to catch-up
  - Congenital bone dysplasia (achondroplasia, hypochondroplasia)

Ref

Causes

- Secondary Growth Failure – Endocrine system
  - Growth Hormone Deficiency
    - Congenital
    - Acquired (hypothalamic-pituitary lesion such as craniopharyngioma)
  - Hypopituitarism
  - Primary hypothyroidism
  - Consequence of precocious puberty
  - IGF-1 deficiency, ALS-deficiency, IGF-1 resistance

Causes

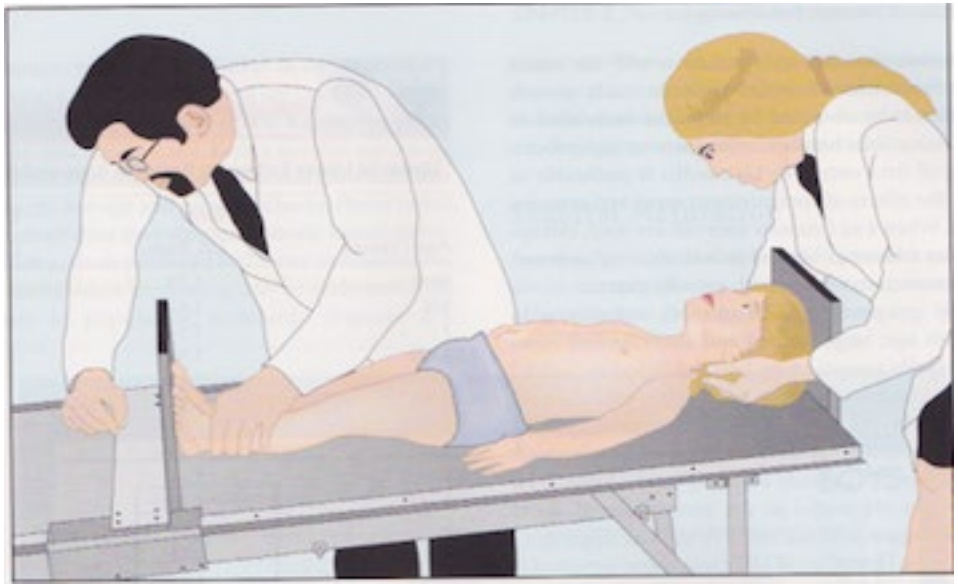
- Secondary Growth Failure
  - Poorly controlled diabetes mellitus
  - Other systems:
    - Renal disease (chronic renal insufficiency)
    - Cardiac (congenital heart disease)
    - Pulmonary disease (cystic fibrosis)
    - GI: Liver disease, short gut syndrome, inflammatory bowel disease, celiac disease
    - Anemia
    - Psychological conditions (anorexia nervosa)

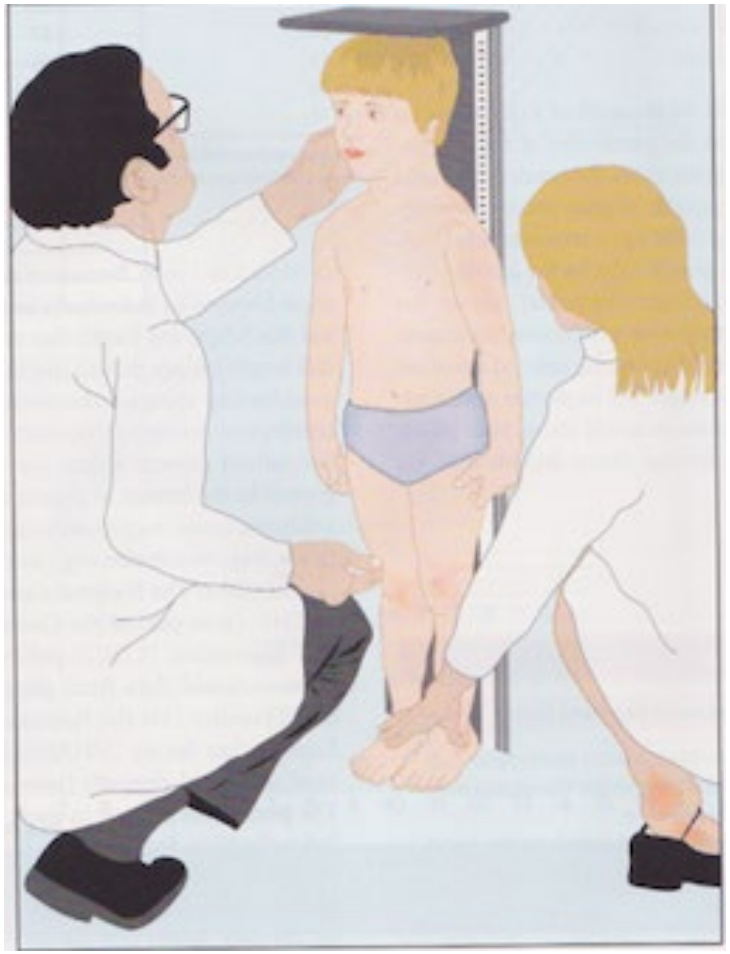
Causes

- Secondary Growth Failure
  - Medications:
    - Glucocorticoid therapy
    - ADHD Medications (methylphenidate)

Causes – Don't forget. Common.

- Human Errors:
  - Measurement Errors
  - Typo (inches vs cm)





Pediatric Practice Endocrinology 2010 Chapter

Physical examination Length or height, weight, head circumference, sitting height (or lower body segment), span, forearm length, weight, weight-for-height, BMI, head circumference are compared with reference charts	A high sitting height/height ratio (or low upper/lower segment ratio) is suggestive of skeletal dysplasia. A low span and short forearm are suggestive of SHOX defect
Underweight	Intestinal disorders, hypocortisolism, metabolic disorders, SGA
Overweight, obese (note: children with nutritional obesity are often relatively tall for chronological age)	Hypothyroidism, Cushing's syndrome, GH deficiency, pseudohypoparathyroidism
Dysmorphic features	Primary growth disorders (syndromes)
Frontal bossing, mid-facial hypoplasia	GH deficiency or resistance, IGF-I deficiency
Moon face, facial plethora	Cushing's syndrome
Inspection of tonsils	Watch for tonsillar hypertrophy
Thyroid size	Enlarged (or decreased) in Hashimoto thyroiditis
Slow pulse rate, slow relaxation of the Achilles tendon reflex	Hypothyroidism
Hypertension	Kidney disease, Cushing's syndrome
Lobulated abdominal fat	GH deficiency
Abdominal distension	Celiac disease
Hepatomegaly, splenomegaly	Hepatic or metabolic disorder
Pubertal stage	Early, normal or late puberty
Micropenis	Hypogonadism, hypopituitarism
Cryptorchidism	Hypogonadism
Virilization	Cushing's syndrome
Muscular hypotonia	Muscular disorder
Fundoscopy, vision, visual field defect	CNS pathology
Signs of neglect or abuse	Emotional deprivation

Oostdiji W et al. Diagnostic Approach in Children with Short Stature. September 2009. Hormone Research 72(4):206-17

Dysmorphic feature	Associated syndrome
Short nose with anteverted nostrils	Smith-Lemli-Opitz
Continuous eyebrows	Cornelia de Lange
Absence of adipose tissue	Leprechaunism
Alopecia	Progeria
Ambiguous genitalia/ abnormal genitalia	Mixed gonadal dysgenesis/ 46,XY/45X chromosomal mosaicism/Smith-Lemli-Opitz/ Aarskog
Asymmetry of the face/ arms/legs	Russell-Silver
Bicuspid aortic valve	Turner
Bird-headed face	Seckel
Broad thumbs and toes	Rubinstein-Taybi
Cataract (congenital)	Hallermann-Streiff
Cleft lip and/or palate	Growth hormone deficiency
Clinodactyly	Russell-Silver
Coarctatio aortae	Turner
Cryptorchism	Noonan, Prader-Willi, Rubinstein-Taybi
Cubiti valgi	Turner

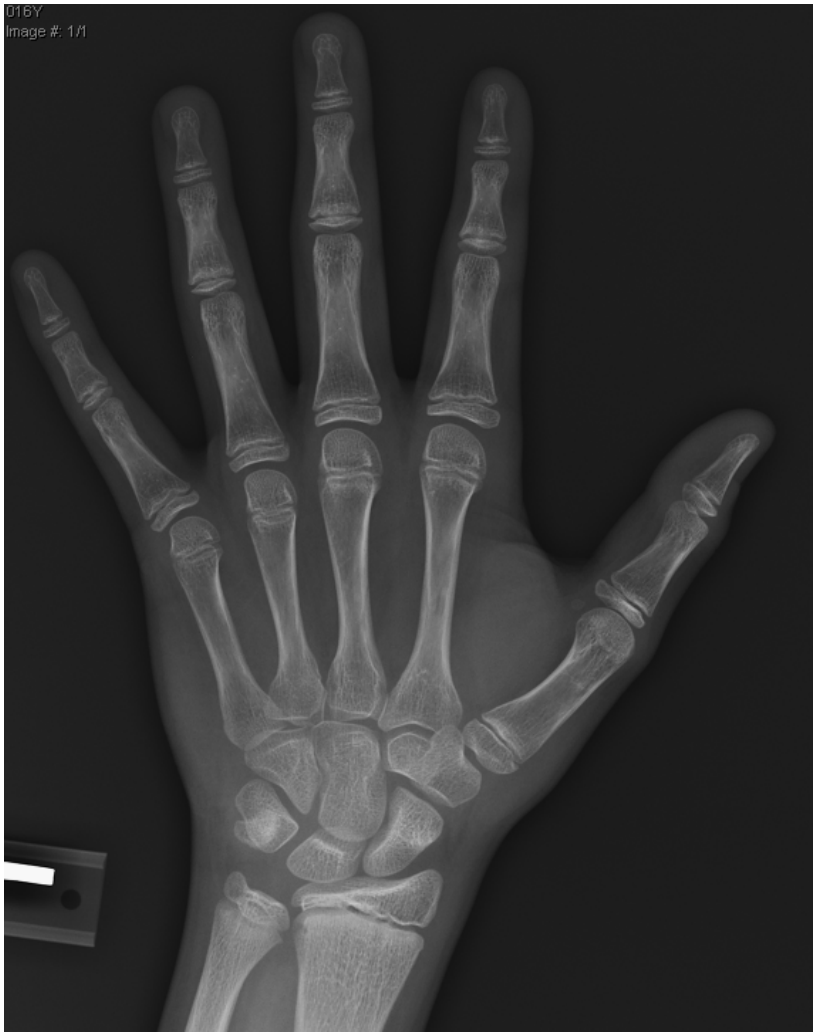
Oostdiji W et al. Diagnostic Approach in Children with Short Stature. September 2009. Hormone Research 72(4):206-17

Dysmorphic feature	Associated syndrome
High arched palate	22q11 deletion syndrome, SHOX
Hirsutism	Coffin-Siris, Cornelia de Lange
Hypogonadism	Robinow, Smith-Lemli-Opitz
Hypoplastic nipples	Turner
Hypospadia	46,XY/45X chromosomal mosaicism
Inverted nipples	Turner
Lymphedema (congenital)	Turner
Madelung deformity	Leri-Weill, SHOX abnormalities
Micropenis	Prader-Willi, growth hormone deficiency
Muscular hypotonia	Down, Prader-Willi
Nail convexity/dysplasia	Turner
Nevi (multiple)	Turner
Ptosis	Aarskog, Dubowitz, Noonan, Turner
Pulmonary valvular stenosis	Noonan
Webbed neck	Noonan, Turner
Short 4th and 5th meta-carpals	Pseudohypoparathyroidism
Single central incisor	Growth hormone deficiency
Small hands/feet	Prader-Willi
Telangiectasia in face	Bloom
Triangular face	Russell-Silver

Oostdiji W et al. Diagnostic Approach in Children with Short Stature. September 2009. Hormone Research 72(4):206-17

Evaluations

Evaluation: Bone Age X-ray

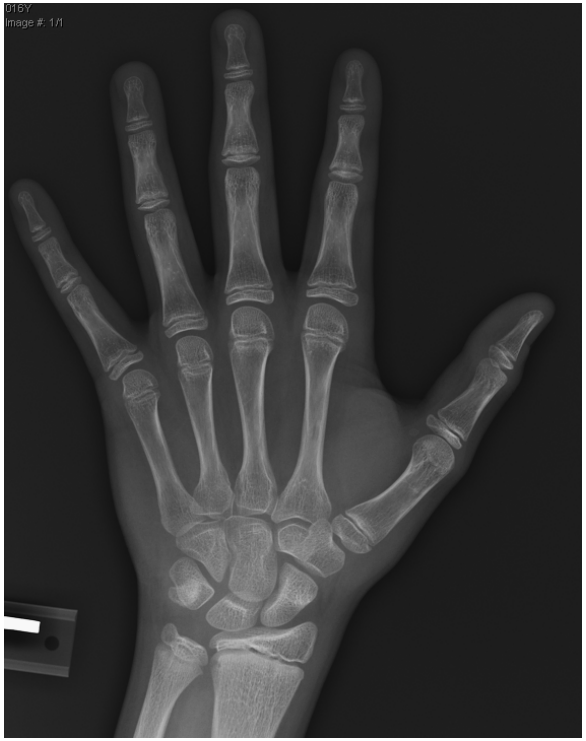


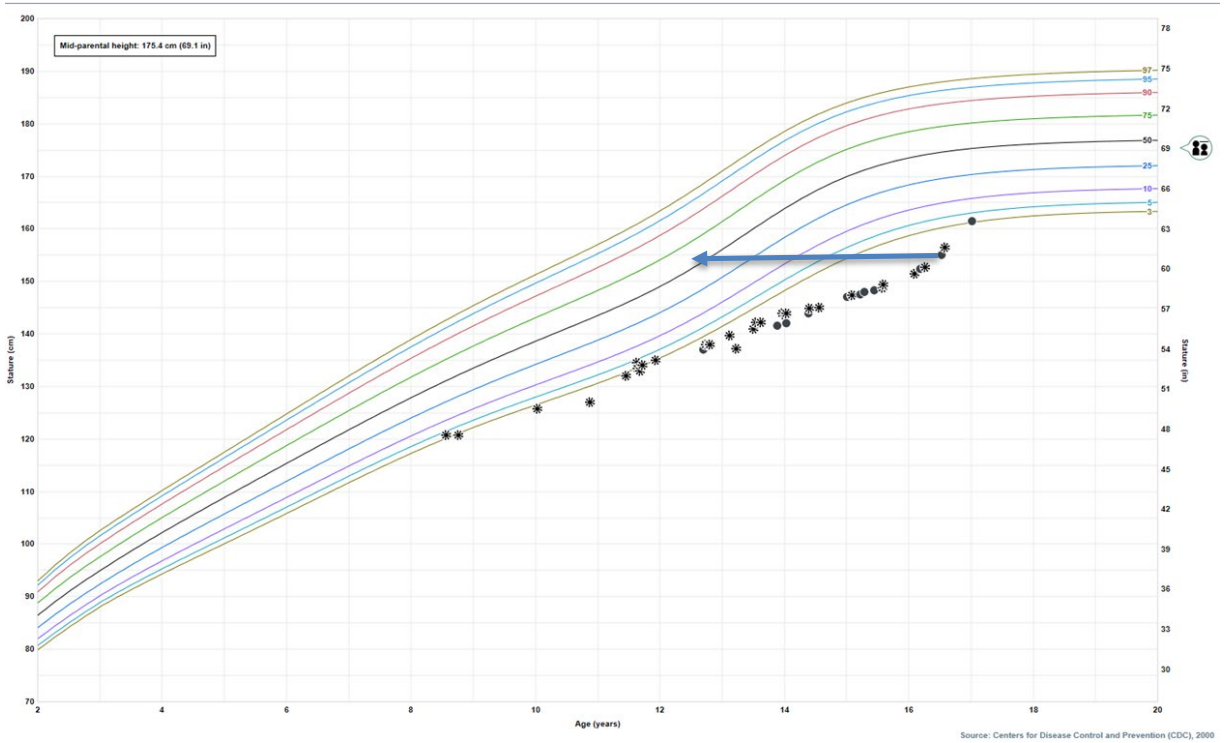
- Extremely Useful!
- Epiphyseal Closures
  - Boys: BA 16 years
  - Girls: BA 14 years

Chronological age 16 y 6 m
Bone age 12 y 6 m

Re

Bone Age X-ray

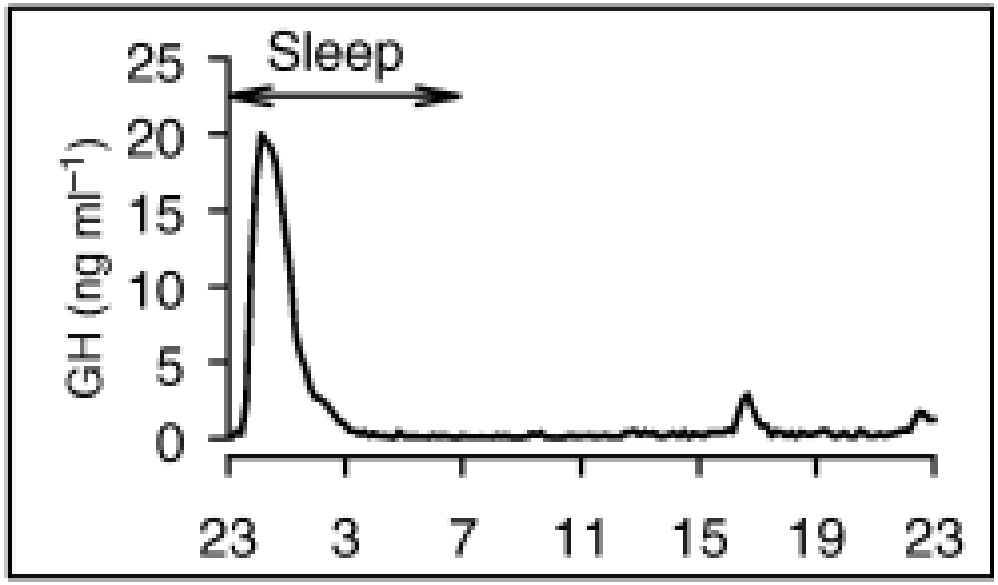




Laboratory Evaluation

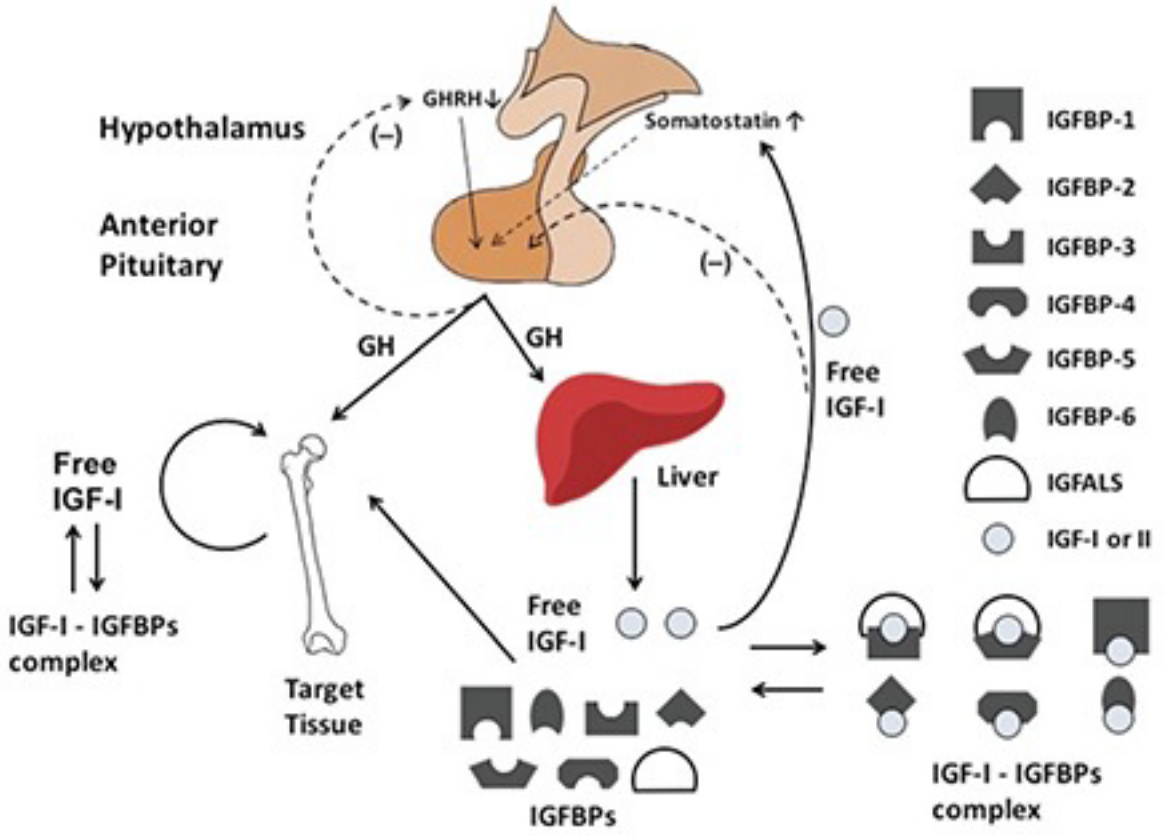
- Thyroid Function Panel (TSH and Free T4)
- Growth Hormone Surrogate Markers IGF-1, IGFBP-3
- IgA, Tissue Transglutaminase IgA
- CBC, Ferritin
- CMP
- 25-hydroxyVitamin D*
- Karyotype for Girls
- Others:
  - PTH, phosphorus
  - CRP, Sed Rate, Stool Calprotectin

Growth hormone



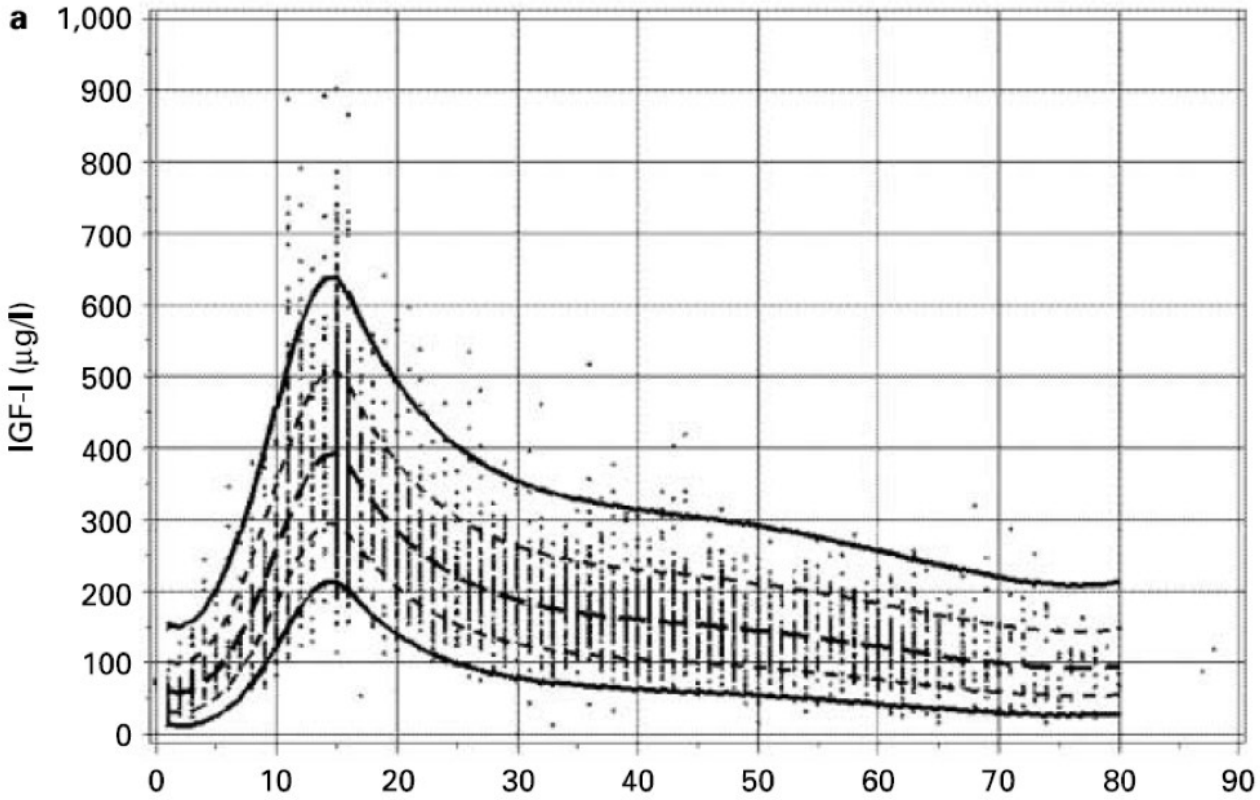
Brandenberger et al. The 24-h growth hormone rhythm in men: sleep and circadian influences questioned. Journal of Sleep Research. September 2004 Pages 251-255

Growth Hormone – IGF axis



Fujimoto M et al. Novel Modulators of the Growth Hormone - Insulin-Like Growth Factor Axis.Journal of Clinical Research in Pediatric Endocrinology, 26 Dec 2017, 9(Suppl 2):1-8

IGF-1



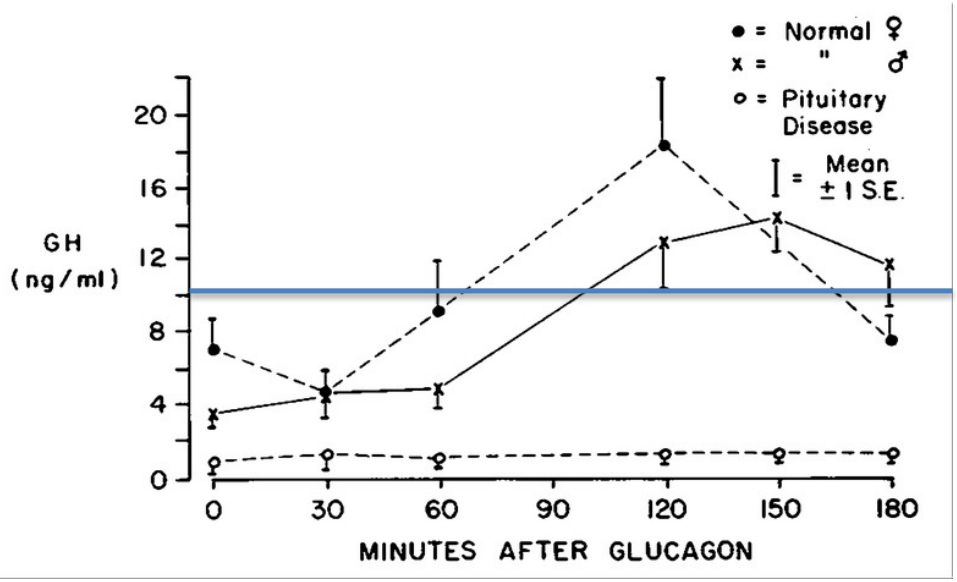
Brabant G et.al. Hormonal Research 2003; 60:53-60

IGF-1

Sex	Age	Range ng/mL	Sex	Age	Range ng/mL
F	0	8-131	M	0	11-100
F	1	9-146	M	1	12-120
F	2	11-165	M	2	13-143
F	3	13-187	M	3	14-169
F	4	15-216	M	4	15-200
F	5	19-251	M	5	16-233
F	6	24-293	M	6	17-269
F	7	30-342	M	7	18-307
F	8	39-396	M	8	20-347
F	9	49-451	M	9	23-386
F	10	62-504	M	10	29-424
F	11	76-549	M	11	37-459
F	12	90-581	M	12	49-487
F	13	104-596	M	13	64-508
F	14	115-591	M	14	83-519
F	15	121-564	M	15	102-520
F	16	122-524	M	16	119-511
F	17	120-479	M	17	131-490
F	18	117-436	M	18	137-461

Growth Hormone Stimulation Test

- Performed to diagnose growth hormone deficiency.
- Insulin-induced hypoglycemia is the most powerful stimulus for GH secretion, but with the greatest potential for harm.
- Arginine & Clonidine
  - Levodopa, glucagon
- Cutoff: 10 ng/mL
- Brain MRI if GH deficient



Mitchell ML et al. Detection of Growth-Hormone Deficiency — The Glucagon Stimulation Test. NEJM 1970; 282:539-541

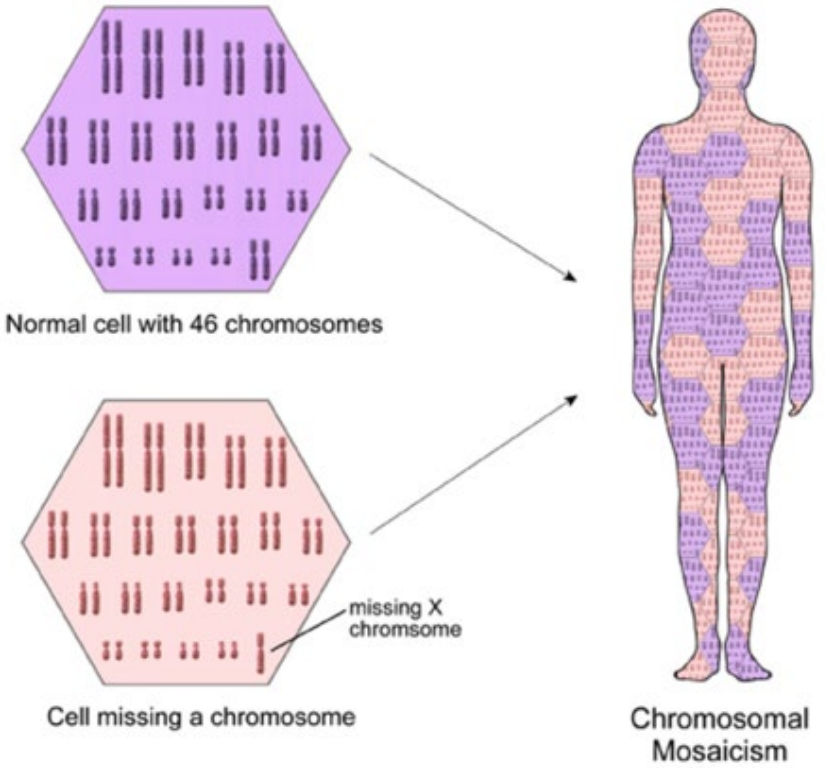
Constitutional Delay of Growth

- Normal birth weight and weight
- Normal growth for the first 4-12 months of life.
- Height is sustained at a lower percentile during childhood.
- Pubertal growth is delayed.
- Often positive family history.
- IGF-1 levels tend to be low for chronological age but within the normal range for bone age.
- Boys with more than 2 years of pubertal delay can benefit from a short course of testosterone therapy to hasten puberty after 14 years of age.

Nelson Textbook of Pediatrics 21st Ed

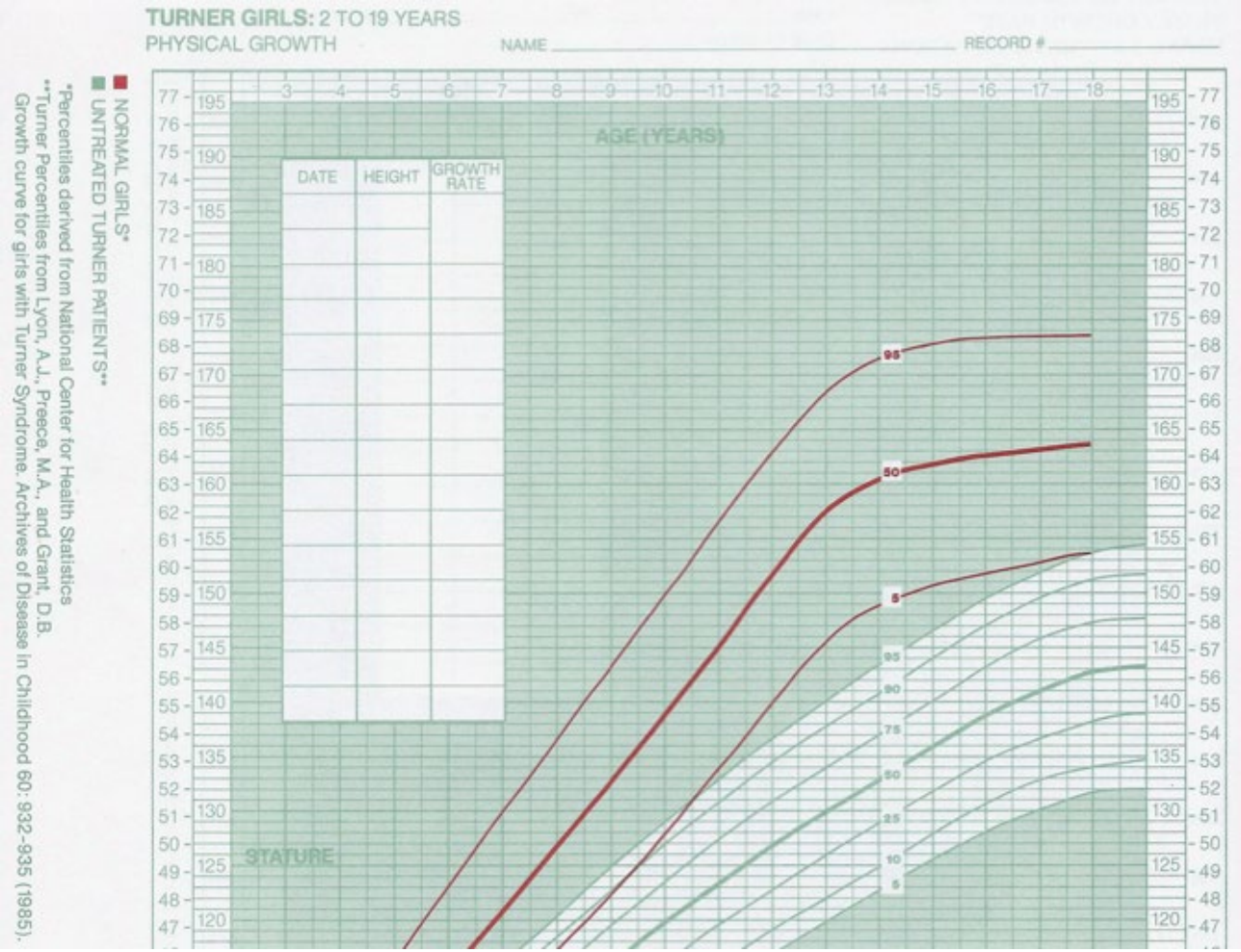
Turner Syndrome

- Frequency: 1 in 2500 newborn girls
- About half of individuals with Turner syndrome have monosomy X
- Some have mosaic Turner syndrome



Medline Plus

Turner Syndrome



Turner Syndrome Society of the United States

When to Refer

- Evidenced-based guideline for referral of children with short stature
  - Height SDS < - 2.5 SDS
  - Height SDS < - 2 SDS AND
    - Born SGA
    - Disproportion and/or dysmorphic features
    - 2 SDS difference from midparental height
    - Height velocity < -1 SDS

Oostdiji W et al. Diagnostic Approach in Children with Short Stature. September 2009. Hormone Research 72(4):206-17

Treatment options

Growth Hormone Therapy (Somatropin)

- Recombinant hGH available since 1982
- 8 brands marketed in the US
- Long-acting growth hormone preparations (q7-14 days) are currently being developed.
- 8 FDA-approved indications
  - Growth Hormone Deficiency
  - Turner syndrome, Noonan syndrome
  - Prader Willi Syndrome
  - SGA with failure to catch up
  - *SHOX* gene abnormality
  - Chronic renal failure before transplantation
  - Idiopathic short stature (less than < -2.25, 1.2 percentile and predicted height below the 5th percentile)

Growth Hormone Therapy (Somatropin)

- FDA approval for a given indication does not ensure that a patient's insurance carrier will approve payment.
- Very expensive ($20000-50000 / year)
- Maximal response to GH occurs in the first year of treatment.
- Adverse effects:
  - A 6-fold increase in the risk for type 2 diabetes
  - An increased risk of second neoplasms in cancer survivors
  - Pseudotumor cerebri
  - Slipped capital femoral epiphysis
  - Gynecomastia
  - Worsening of scoliosis

Growth Hormone Therapy (Somatropin)

- There is no methods that can reliably predict which of children will become taller in adulthood as a result of GH treatment and which will have compromised adult height.

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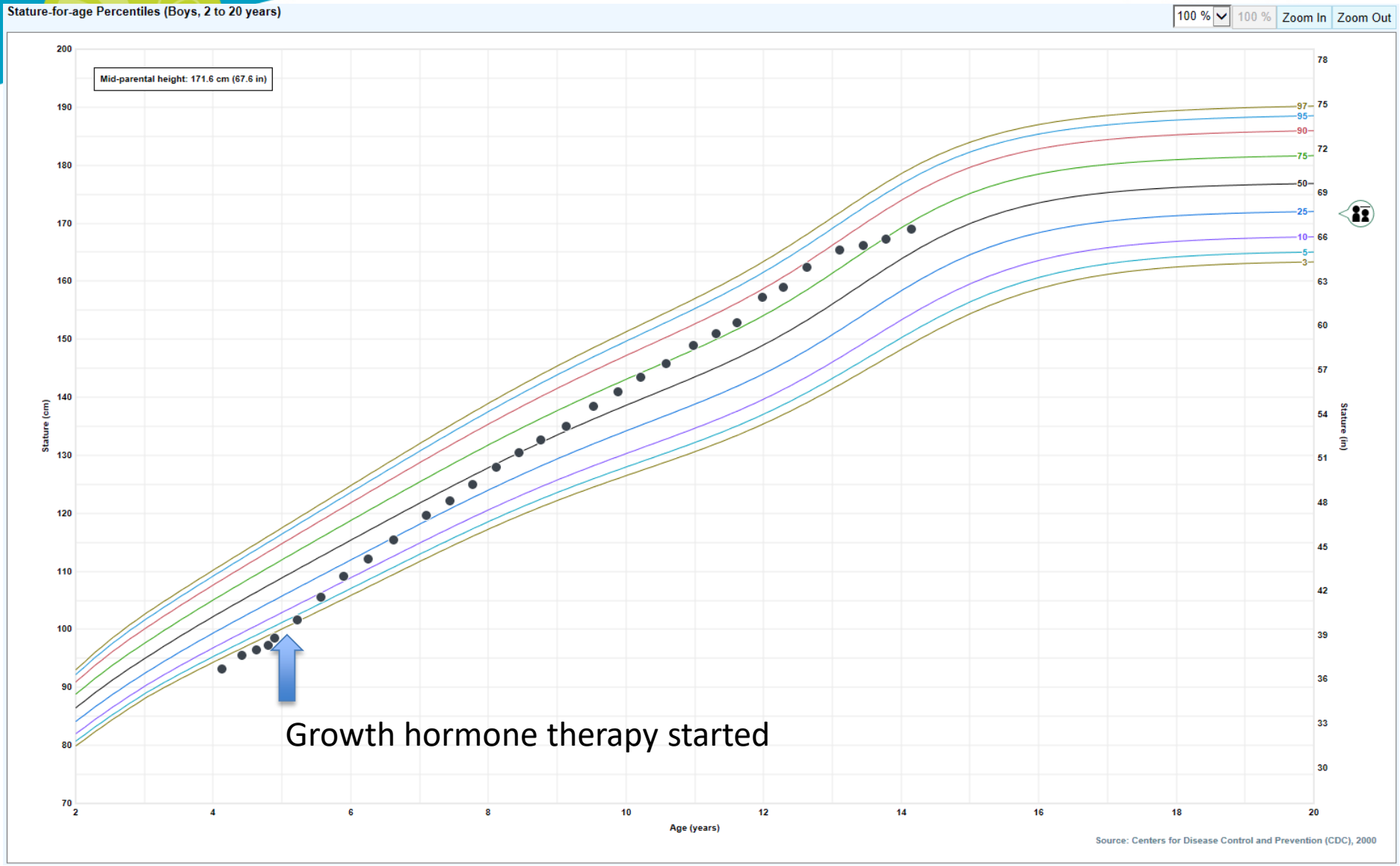


Mecasermin (Increlex)

- Contains human IGF-1, produced by recombinant DNA technology.
- For children with primary insulin-like growth factor deficiency
- Given subcutaneously twice a day (with breakfast and dinner)
- Adverse effects:
  - Hypoglycemia
  - Tumor Growths. Several cases of cancerous tumors have been observed.
  - Similar to growth hormone therapy

Aromatase Inhibitors (Boys)

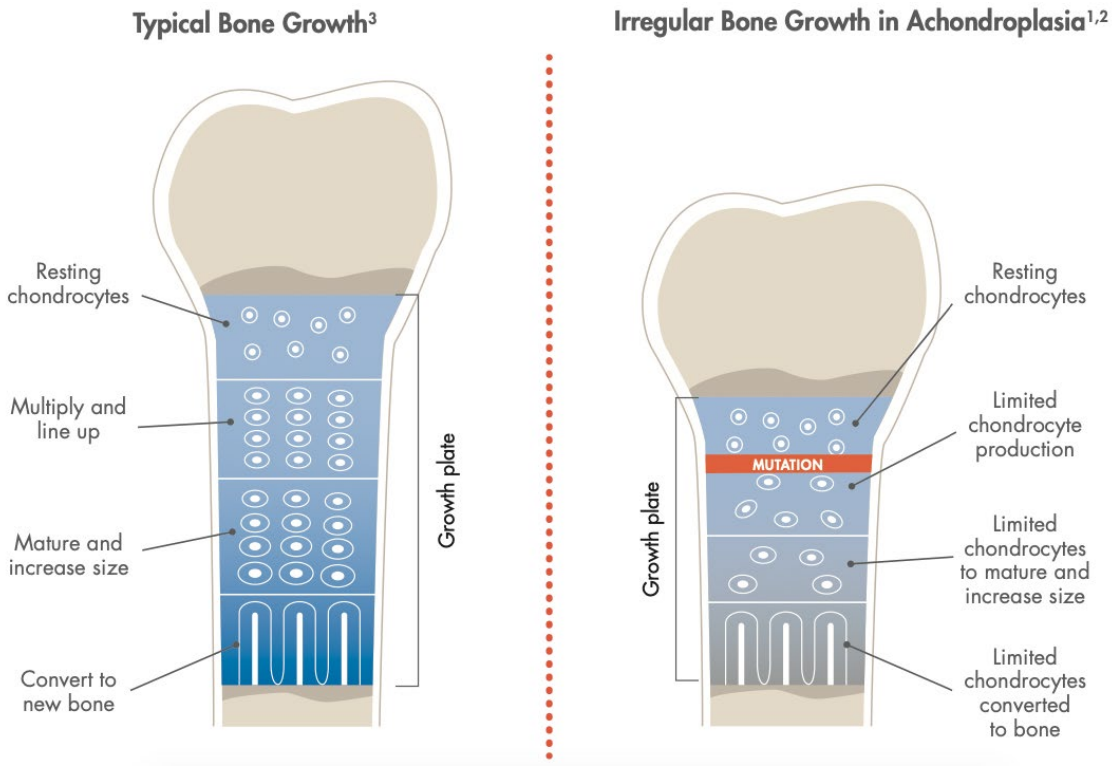
- Anastrozole, Letrozole.

Testosterone ↛ Estradiol

- Off-label Use
  - Drugs used to treat hormone receptor-positive breast cancer.
- Mechanism
  - Estrogen is one of the main regulators of bone maturation and closure of growth plate.
  - Aromatase converts testosterone to estradiol.
  - Aromatase inhibitor can delay growth plate closure.
- Adverse Effects:
  - Weight gain, elevated cholesterol, acne, flushing, joint pain, and mood changes.

Vosoritide

- Treatment of achondroplasia
- Phase III clinical Trials
- C-type natriuretic peptide analogue
  - Reduces the effects of overactive FGFR3



- Savarirayan R et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. The Lancet. Volume 366. Issue 10252. P684-692, SEPTEMBER 05, 2020
- BioMarin.Com

Thank you. Questions?

- Providence Pediatric Endocrinology
  - Two locations:
    - West: St Vincent
    - East: Clackamas
  - Phone: 503-216-6050
  - Fax: 971-282-0106
  - Epic code: REF70J
  - Epic code for RD: REF30H
  - E-Consult: Pediatric Endocrinology