THE ENDOCRINOLOGIST'S APPROACH TO A CHILD WITH SHORT STATURE AND THE DIAGNOSIS OF GROWTH HORMONE DEFICIENCY

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Disclosures

- Consulting fees or speaker honoraria:
  - Ascendis, QED, Novo Nordisk, Pfizer, BioMarin
- Research Support
  - BioMarin, NICHD, Pfizer, Novo Nordisk
- Site Investigator for Lumos, Neurocrine, Pfizer, and Novo Nordisk

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Learning Objectives

1. To understand different patterns of growth on growth curves and which ones suggest an underlying endocrine problem
2. To identify the different etiologies of growth hormone deficiency in childhood and the appropriate diagnostic work up
3. To review the impact of growth hormone treatment in growth hormone deficiency and idiopathic short stature

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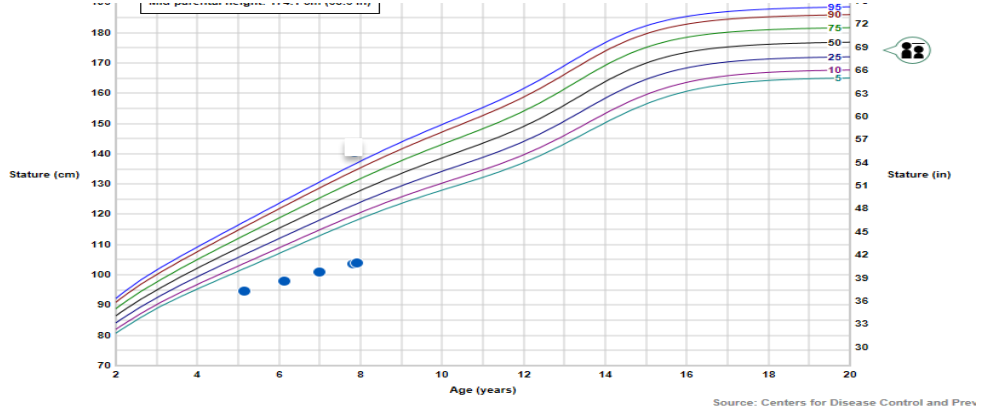
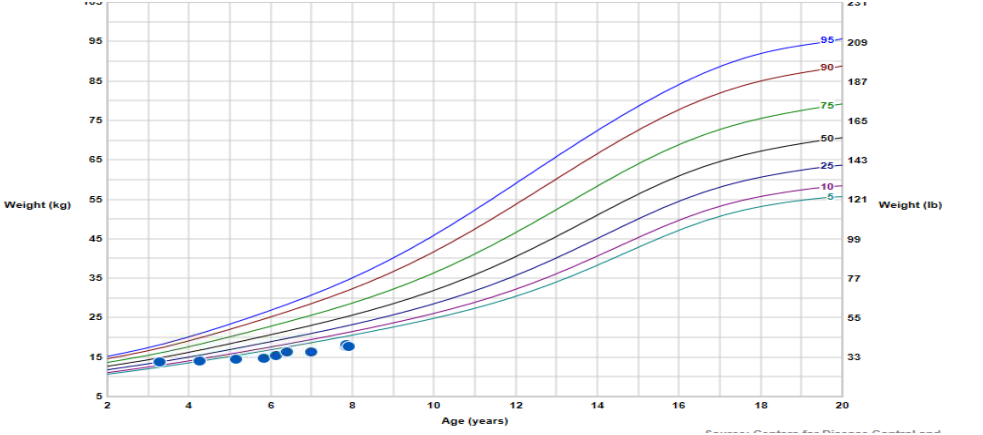
Case #1 – A boy with growth failure

- 7 years 9-month-old male
- PMH: No other medical problems
- Family history of mild pubertal delay
- Pre-pubertal
- Bone age 2-3 years delayed

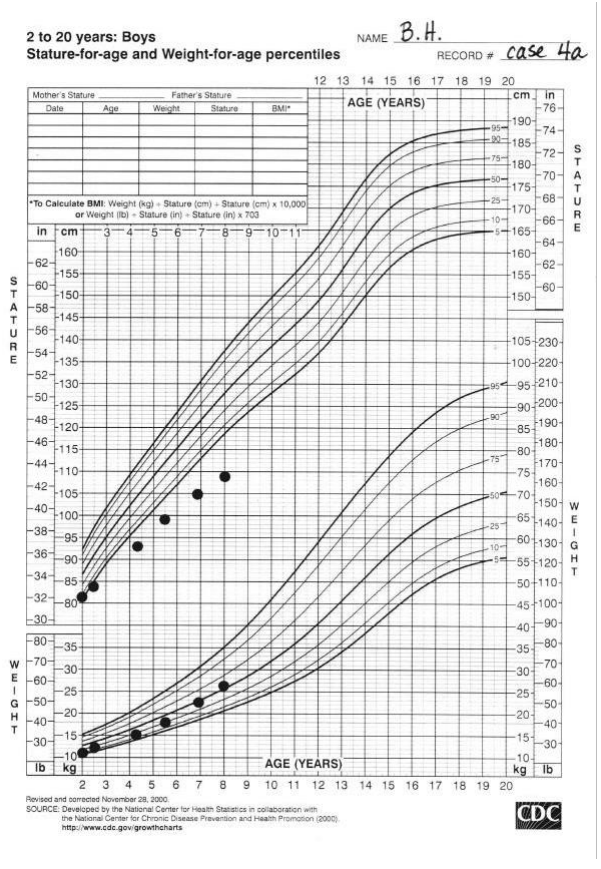
- Low IGF-1
- Dx: Growth Hormone Deficiency
- MRI showed small anterior pituitary

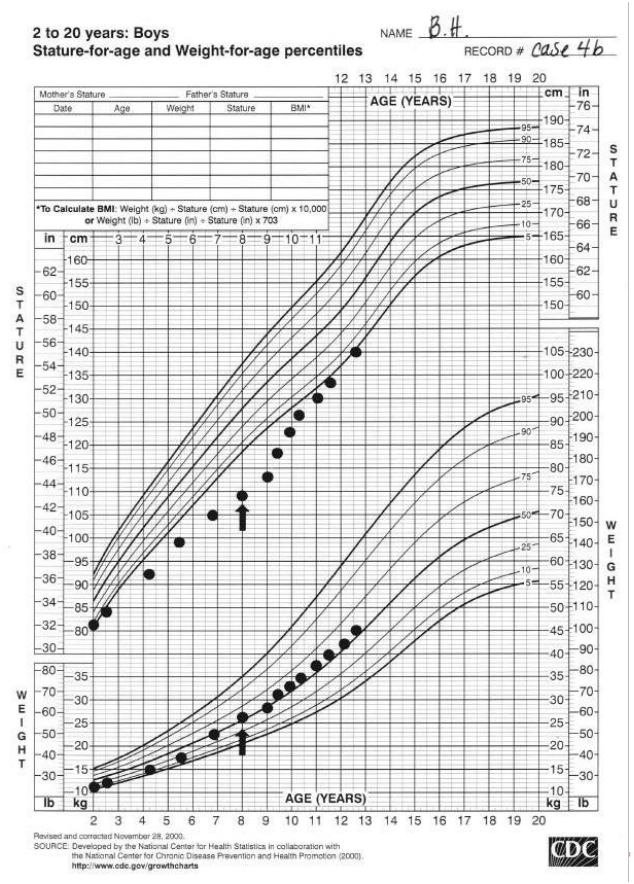




Growth Hormone Deficiency

From Laurie Cohen, MD - PediCases

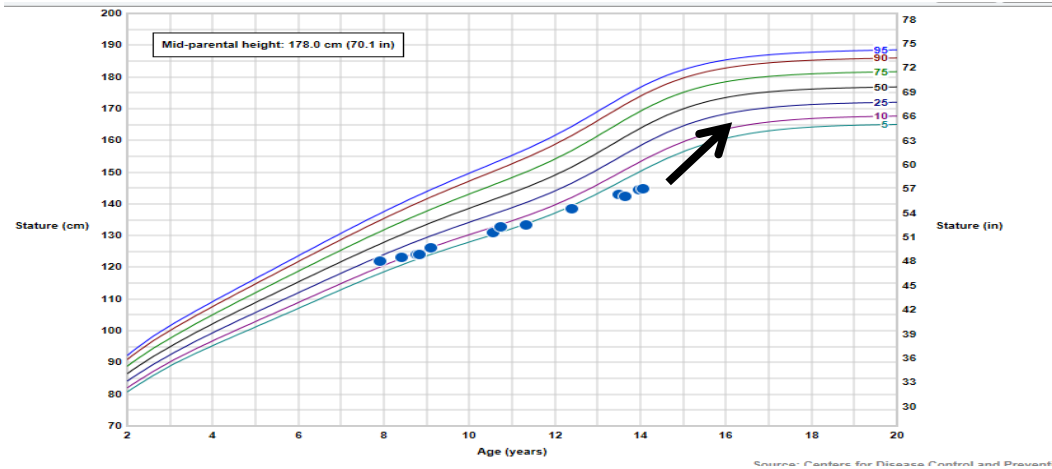


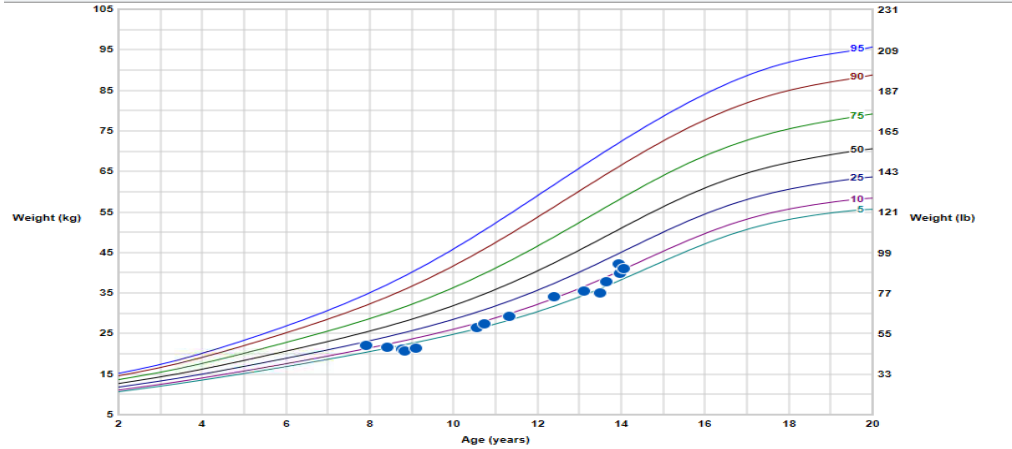


Case #2 – A boy with slowing growth?

- 13 years 7-month-old male
- PMH: ADHD, no other medical problems
- Family history of mild pubertal delay
- Testes 6 ml

- Bone age 12 years
- Constitutional delay of growth and puberty

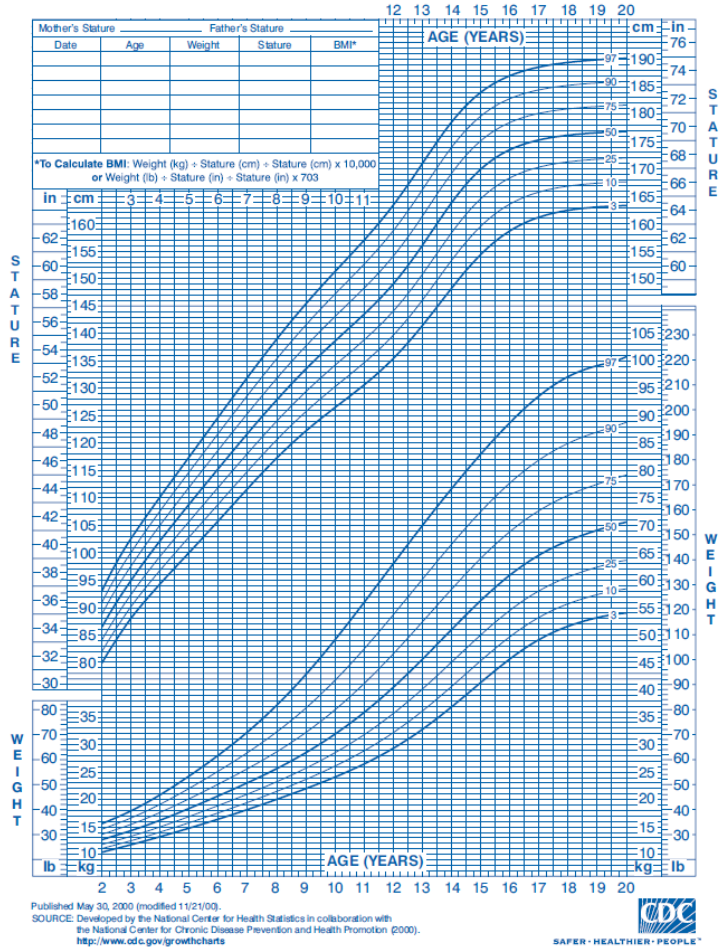




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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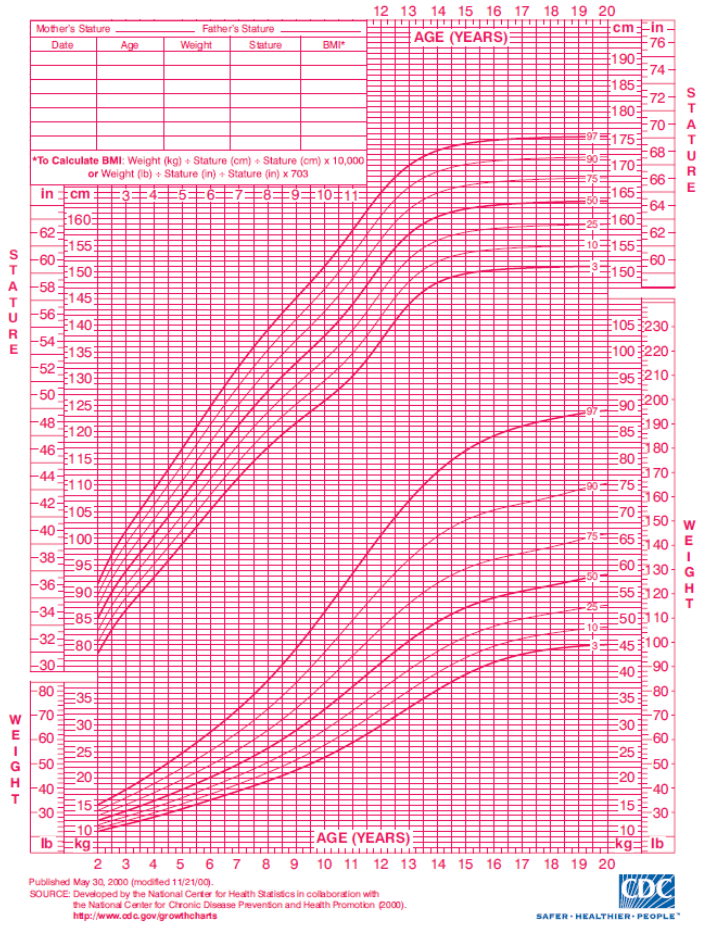
2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
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US Growth Velocity Curves

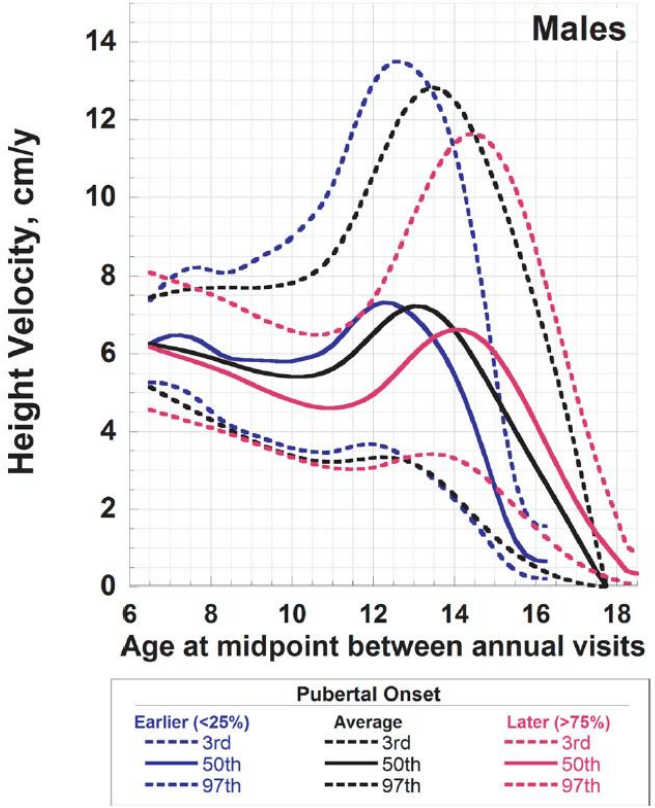


Figure 2. Reference curves for HV for male children aged 6 to19

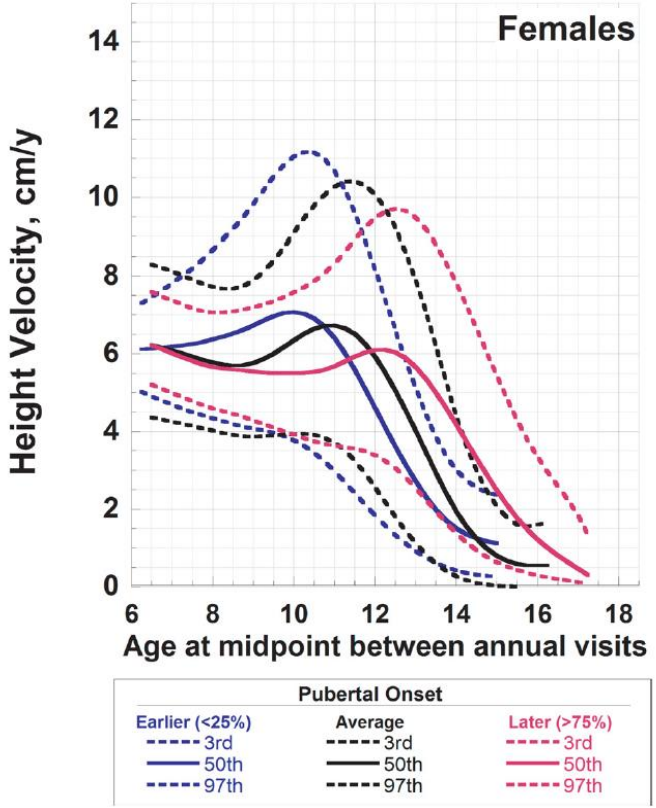
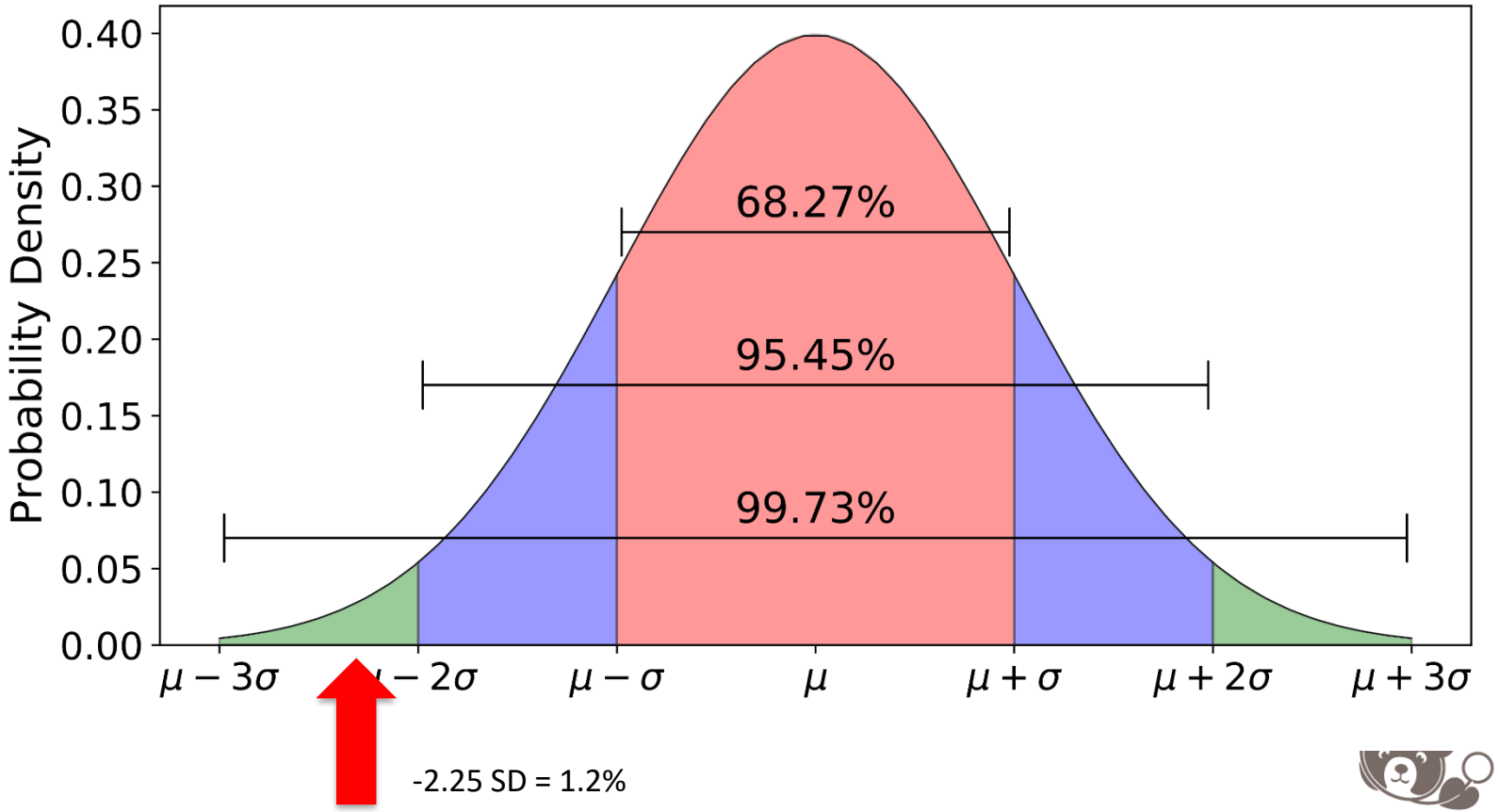


Figure 3. Reference curves for HV for female children aged 6–17

(*J Clin Endocrinol Metab* 99: 2104–2112, 2014)

IDIOPATHIC SHORT STATURE



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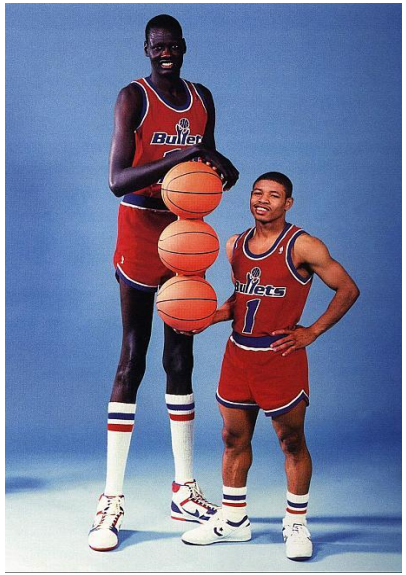
https://towardsdatascience.com/understanding-the-68-95-99-7-rule-for-a-normal-distribution-b7b7cbf760c2

Genetics



HEIGHT

Environment

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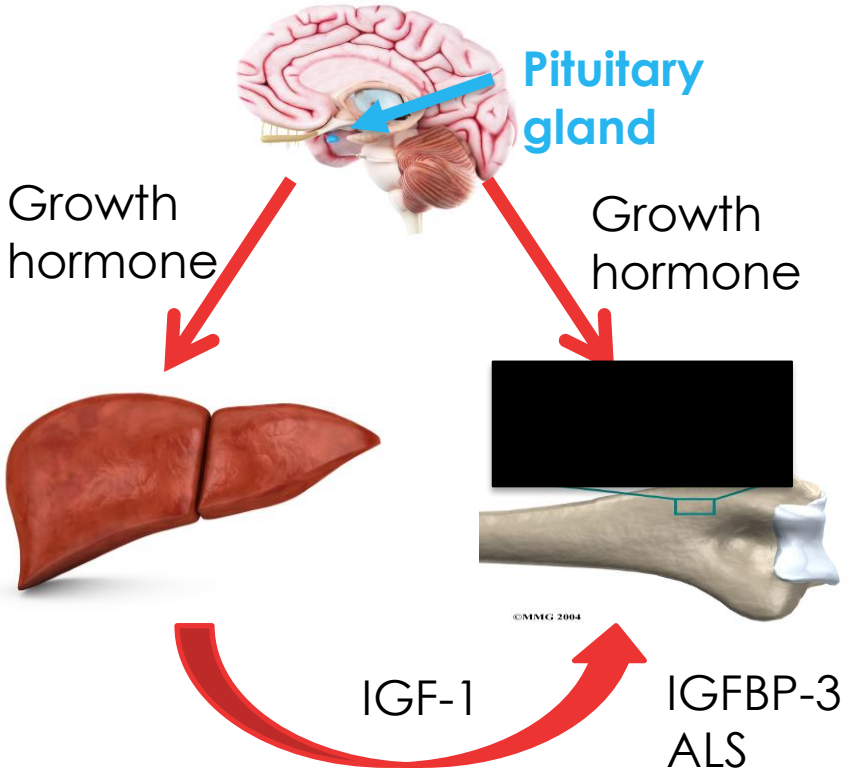
Traditional Endocrinologist View of Growth



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Prevalence, Etiology, and Clinical Presentation (Congenital)

- Isolated
  - Prevalence of 1:4000 to 1:10,000 live births
  - Identified genetic cause in 34% of familial cases and 4% of sporadic cases
  - Most common mutations in *GH1* and *GHRHR* genes
- Multiple pituitary hormone deficiency
  - Due to mutations in pituitary transcription factors (*PROP1*, *POU1F1*, etc)
- May be associated with structural abnormalities of the pituitary gland or optic nerve hypoplasia
- Clinical presentation
  - Postnatal growth failure
  - Jaundice
  - Neonatal hypoglycemia
  - Microphallus

Gregory LC, Dattani MT. *J Clin Endocrinol Metab*. 2020;105(6):e2103-e2120.

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Prevalence, Etiology, and Clinical Presentation (Acquired)

- Intracranial tumors
  - Craniopharyngioma
- Cranial irradiation
- Head trauma
- Clinical presentation
  - Growth failure but with preserved weight gain
  - Delayed bone age
  - Headaches and visual field loss depending on etiology

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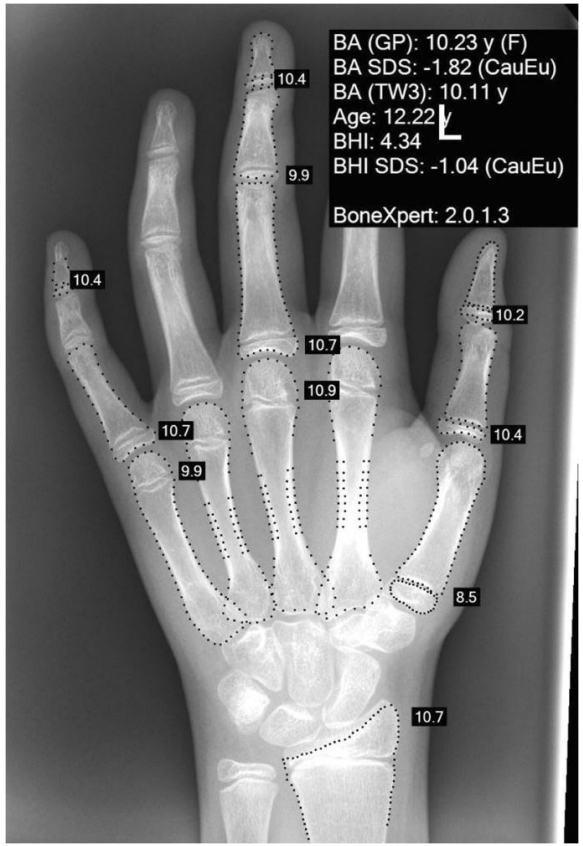
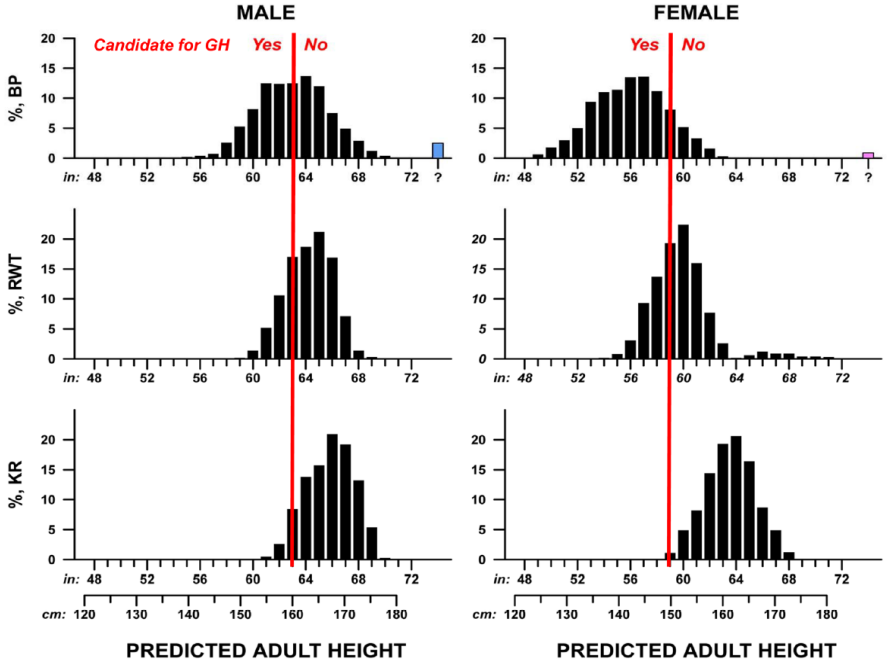
Bone Age





Pediatrics. 2010 November ; 126(5): 938–944. doi:10.1542/peds.2009-3649.

[*European Radiology*](#) **volume 30**, pages504–513 (2020)

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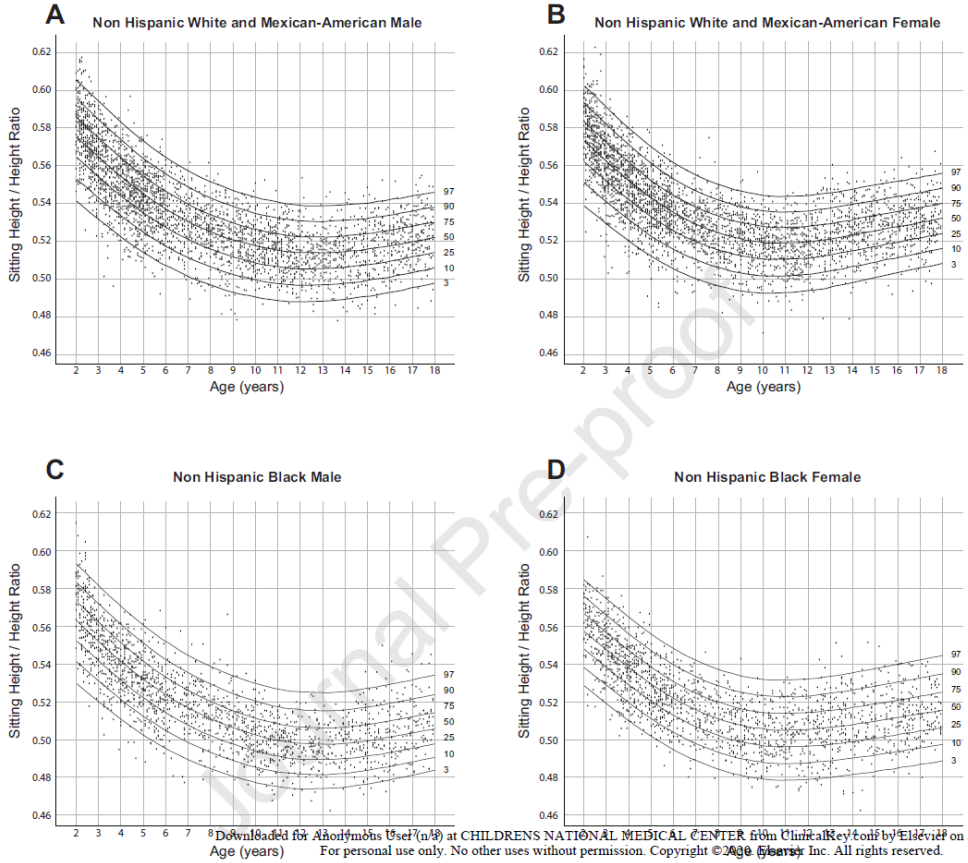
Body Proportions



Hawkes CP et al. Journal of Pediatrics 2020 Nov;226:221-227.

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Mid-Parental Height

- Boys: Average of parents' heights + 2.5 inches
- Girls: Average of parents' heights – 2.5 inches
- Target height: MPH +/- 2 SD (1 SD =~2 inches)
- Yes – this is as dumb as it sounds.

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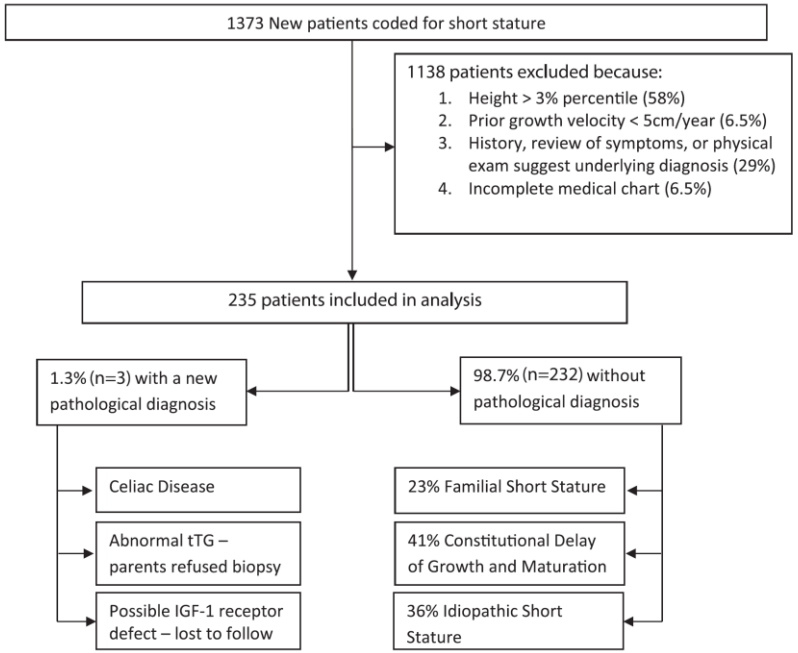
Traditional medical work up in ISS has low yield!

Table I. Demographics and auxologic parameters of 235 asymptomatic short children

Characteristic	Value
Male	72.8%
Age at referral, y	10.1 ± 4.3 (0.8-17.6)
Pubertal status (N = 221)	
Tanner I	60.6%
Tanner II	24.9%
Tanner III	8.6%
Tanner IV	1.8 %
Tanner V	4.1%
Height SDS	−2.5 ± 0.5* (−4.8 to −2.0)
Weight SDS	−2.2 ± 1.1 (−6.8 to 0.5)
BMI SDS	−0.8 ± 1.3 (−5.81 to 2.17)
Growth records available	36.6%
Prior HV, cm/y (averaged over 10.6 ± 2.5 mo)	6.5 ± 2.8 (5 to 14)

Values are percent or mean ± SD (range).
*$P < .05$ between boys and girls (−2.5 ± 0.5 SD vs −2.6 ± 0.5 SD, respectively). No other differences existed between sexes.



Sisley et al. Journal of Pediatrics 2013; 163:1045-51.

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IGF-1 and IGFBP-3

- IGF-1 is an excellent biomarker of GH action.
- It is also affected by nutrition and chronic illness.
- A low IGF-I and/or IGFBP-3 increases the probability of GHD but can be found in numerous conditions.
- IGF-1 >0 SDS essentially rules out GHD.
- IGFBP-3 is more accurate under the age of 3-5 years.
- IGF-1 levels should be assessed by Tanner stage.

Diagnosis, Genetics, and Therapy of Short Stature in Children

Horm Res Paediatr
DOI: 10.1159/000502231

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Growth Hormone Stimulation Testing

2.2.1. We recommend against reliance on GH provocative test results as the sole diagnostic criterion of GHD. (Strong recommendation, ●●●●)

Growth hormone cut-off value for GHD varies:

- United States – Peak GH <10 = GHD
- International Consensus Guidelines picked <7
- Severe GHD is usually <3

Multiple different stimulation agents:

- Arginine
- Glucagon
- Insulin
- L-Dopa
- Clonidine
- Macimorelin Acetate

Horm Res Paediatr
DOI: 10.1159/000452150

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Pubertal Status Affects GH Stimulation Test Results

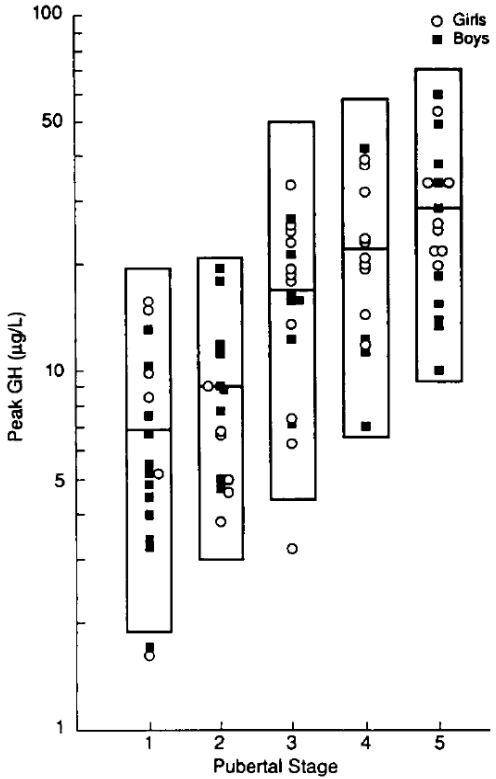

FIG. 1. The effect of pubertal stage on the 95% confidence limits for the peak GH response to exercise, arginine, or insulin. The *boxes* extend from the lower to the upper 95% confidence limit. The *lines in the middle of each box* indicate the mean response. ■, Boys; ○, girls.

Marin et al. JCEM 79: 537-541, 1994.

- 84 healthy children with normal height
- % who failed to achieve a GH peak of 7 mcg/L
  - Tanner 1: 61%
  - Tanner 2: 44%
  - Tanner 3: 11%
  - Tanner 4,5: 0%
- 11 pre-pubertal children were re-tested after estrogen priming and the lower 95% CI limit for GH increased from 1.7 to 7.2 mcg/L

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Sex Steroid Priming for GH Stimulation Tests

2.2.3. We suggest sex steroid priming prior to provocative GH testing in prepubertal boys older than 11 and in prepubertal girls older than 10 years with AH prognosis within –2 SD of the reference population mean in order to prevent unnecessary GH treatment of children with constitutional delay of growth and puberty. (Conditional recommendation, ●●○○)

Horm Res Paediatr
DOI: 10.1159/000452150

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Not All Patients Require Provocative Testing

Patients who meet all 3 of the following criteria:

- Meets auxological criteria
- Hypothalamic-pituitary defect
- **AND** deficiency of ≥ 1 additional pituitary hormone

Newborn with:

- GHD due to hypopituitarism
- Hypoglycemia
- GH concentrations < 5 ng/mL, **AND**
- Deficiency of ≥ 1 other pituitary hormone

- Classical imaging triad
  - Ectopic posterior pituitary
  - Pituitary hypoplasia with abnormal stalk

Grimberg A, et al. *Horm Res Paediatr*. 2016;86:361-397. Collett-Solberg PF, et al. *Horm Res Paediatr*. 2019;92:1-14.

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Brain Imaging in Growth Hormone Deficiency

- Imaging of the brain and in particular the pituitary gland is currently the standard of care after making a diagnosis of growth hormone deficiency.
- It is essential to rule out the possibility of an intracranial tumor such as a craniopharyngioma prior to initiating GH therapy.
- Brain MRIs may also show a structural pituitary abnormality which can assist with the diagnosis of GHD.
- Some experts argue that the likelihood of identifying a pathological cause in cases of isolated mild GHD is quite low, and it is acceptable to skip brain imaging in those cases.

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Dosing of rhGH

- A single subcutaneous daily injection of rhGH can provide physiologic replacement
- Dosing should be based on body weight
  - Starting doses of 0.16 to 0.24 mg/kg/wk
  - Serum IGF-1 levels may be used to monitor adherence and response to GH dose changes
  - Consider decreasing rhGH dose if IGF-1 levels are elevated above +2 or +3 SD
- Discontinue when growth velocity < 2 to 2.5 cm/year
- Check growth every 3 to 6 months
  - Bone age x-rays usually every 1 to 2 years

Grimberg A, et al. *Horm Res Paediatr*. 2016;86:361-397. Collett-Solberg PF, et al. *Horm Res Paediatr*. 2019;92:1-14.

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Monitoring for Adverse Events With rhGH: Pseudotumor Cerebri

- Idiopathic intracranial hypertension (pseudotumor cerebri)
  - Often presents with severe headaches that may be worse in morning or when lying down
  - May present with vomiting, double vision, vision loss
  - Refer to ophthalmologist for funduscopic examination or dilated eye examination to look for signs of papilledema

- rhGH-induced pseudotumor cerebri is dose-related
  - Discontinue rhGH until resolution of symptoms
  - Will usually resolve with discontinuation
  - Reintroduce at lower dose with slower titration

Grimberg A, et al. *Horm Res Paediatr*. 2016;86:361-397. Collett-Solberg PF, et al. *Horm Res Paediatr*. 2019;92:1-14. Rangwala LM, Liu GT. *Survey Ophthalmol*. 2007;52:597-617.

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Monitoring for Additional Adverse Events

- Slipped capital femoral epiphysis
  - Patient with knee or hip pain, or with a new limp; requires x-ray assessment
- Progression of scoliosis
  - Monitor at every follow-up visit
- Monitor for glucose metabolism in patients at increased risk of diabetes due to insulin resistance. Routine monitoring otherwise not necessary
- Counsel patients about the theoretical risk of neoplasia
- Reassess adrenal and thyroid axes after initiation of GH in patients with multiple pituitary hormone deficiencies or anatomic defects of the pituitary gland
- Thyroid function tests should be checked yearly

Grimberg A, et al. *Horm Res Paediatr*. 2016;86:361-397. Collett-Solberg PF, et al. *Horm Res Paediatr*. 2019;92:1-14.

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Early Recognition of GHD and High Adherence to Treatment Affect Outcome

- Earlier age of treatment initiation increases final height outcome.
- Children started on GH prior to the age of 8 years were more likely to achieve a near adult height within the normal range.
- Multiple studies have shown that poor adherence leads to worse growth outcomes.
- Factors that affect adherence include:
  - Age of child
  - Duration of therapy
  - Reluctance to get injections
  - Understanding of consequences of missing therapy
  - Device convenience

Polak M, et al. *Eur J Endocrinol*. 2017;177:421-429. Bagnasco F, et al. *Endocr Pract*. 2017;23:929-941.

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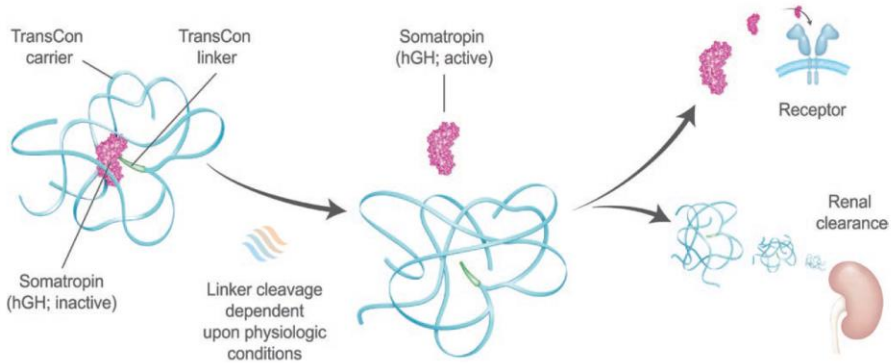
Once Weekly Growth Hormone Has Arrived!



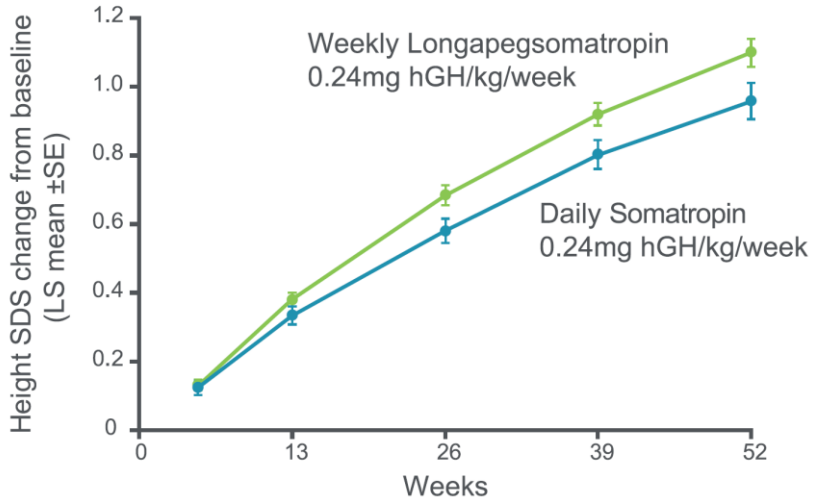


Figure 4. Change from baseline in height SD score.

Thornton PS et al. Journal of Clinical Endocrinology and Metabolism 2021; 106(11):3184-3195.

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Case #3 – Transition to Adult Therapy

- 17-year-old male with a diagnosis of childhood growth hormone deficiency
- Diagnosed at age 10 years when height was -2.5 SD
  - Pre-pubertal
  - IGF-1 <-2 SD
  - Peak growth hormone 8.8 ng/ml
  - Brain MRI normal
  - No other pituitary hormone deficiencies
- Achieved his near-final height
  - Growth velocity 1.2 cm/year over the past year

Does this child need adult growth hormone replacement?

What should be next in his diagnostic workup?

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Adult Growth Hormone Replacement Considerations

- Growth hormone not just for stature
- Adult replacement has positive effects on:
  - Lean body mass/body composition
  - Bone mineral density
  - Lipid metabolism

- PES Guidelines recommend re-evaluation for persistent GHD in persons with GHD and deficiency of only one additional pituitary hormone, idiopathic IGHD, IGHD with or without a small pituitary/ectopic posterior pituitary, and in patients after irradiation.

- Not all patients require re-testing as adults:
  - Patients with multiple (≥ 3) pituitary hormone deficiencies
  - GHD with a documented causal genetic mutation
  - Specific pituitary/ hypothalamic structural defect except ectopic posterior pituitary
- If re-evaluating, start with an IGF-1 level and proceed to GH stimulation testing if low.

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Randomized Controlled Trials of GH in ISS

Table 1 | Characteristics, results, and quality grading of randomised controlled trials of growth hormone therapy in children with idiopathic short stature

Study and group	No	Mean (SD) age at start of therapy (years)	Growth hormone dose (mg/kg/day)	Mean (SD) years of therapy	Mean (SD) height at baseline (SD score)	Mean (SD) adult height (SD score)	Mean (SD) height gain (SD score)	Difference (cases −controls) in adult height (SD score)	Quality
McCaughey et al 1998[9]:									
Treated	8	6.24 (0.38)	0.04	6.2 (range 5.5-6.5)	−2.52 (0.26)	−1.14 (1.06)	1.38 (0.7)	1.23	Low
Untreated	6	6.14 (0.62)	—	—	−2.55 (0.32)	−2.37 (0.46)	0.18 (0.4)	—	
Leschek et al 2004[10]*:									
Treated	22	12.5 (1.6)	0.03	4.4 (1.6)	−2.7 (0.6)	−1.77 (0.80)	0.93 (0.75)	0.57	Moderate
Untreated	11	12.9 (1.1)	—	4.1 (1.7)	−2.8 (0.6)	−2.34 (0.56)	0.46 (0.23)	—	
Albertsson-Wikland et al 2008[11]:									
Treated	49	11.5 (1.3)	0.033 to 0.067	5.64 (1.37)	−2.84 (0.56)	−1.6 (0.68)	1.24 (0.82)	0.6	Moderate
0.033 mg/kg/day	18	11.5 (1.3)	0.033	—	—	−1.7 (0.68)	1.20 (0.82)	0.5	
0.067 mg/kg/day	31	—	0.067	—	—	−1.5 (0.84)	1.30 (0.73)	0.7	
Untreated	19	12 (1.6)	—	—	−2.76 (0.39)	−2.2 (0.75)	0.40 (0.62)	—	

*Placebo controlled trial.

Deodati A, Cianfarani S. BMJ 2011; 342:c7157.

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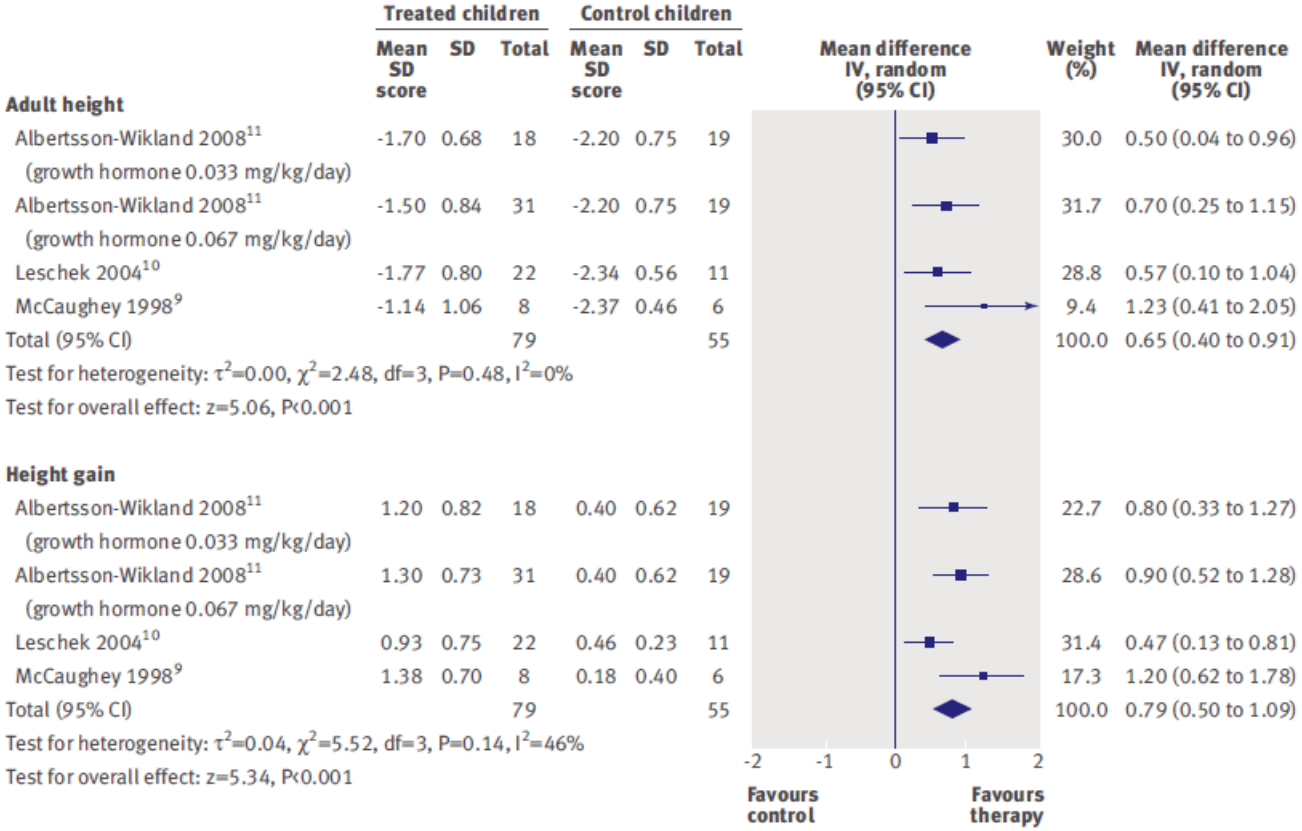

Fig 2 | Effect of long term growth hormone therapy at conventional doses on adult height and height gain in randomised controlled trials. Results of meta-analysis according to random model

~4 cm

Deodati A, Cianfarani S. BMJ 2011; 342:c7157.

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Parental Perspectives on Short Stature and Treatment

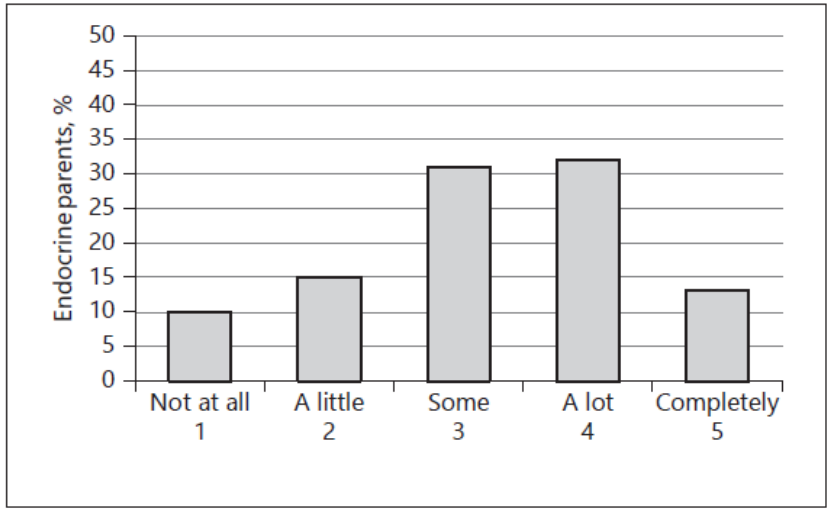

Fig. 2. Endocrine parent ratings of amount of potential improvement of QoL by GH treatment.

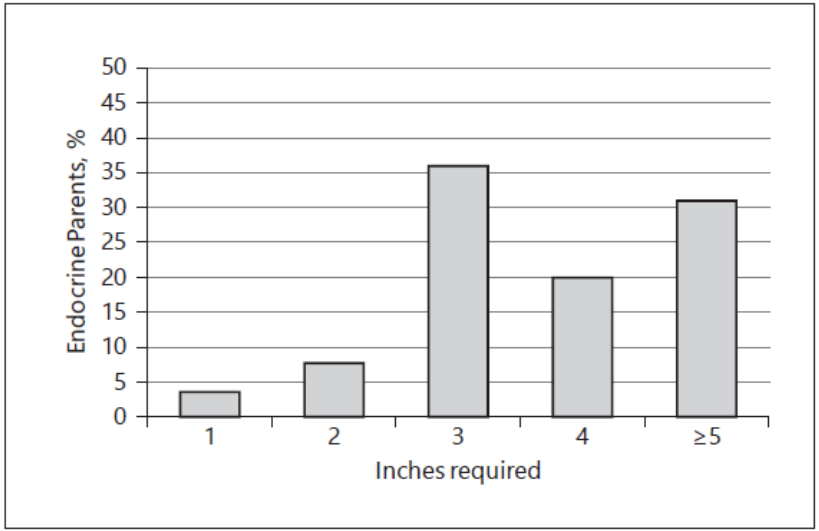

Fig. 3. Endocrine parent ratings of minimum height increase required to improve QoL.

Hitt et al. Hormone Research in Paediatrics 2019;92:311-318.

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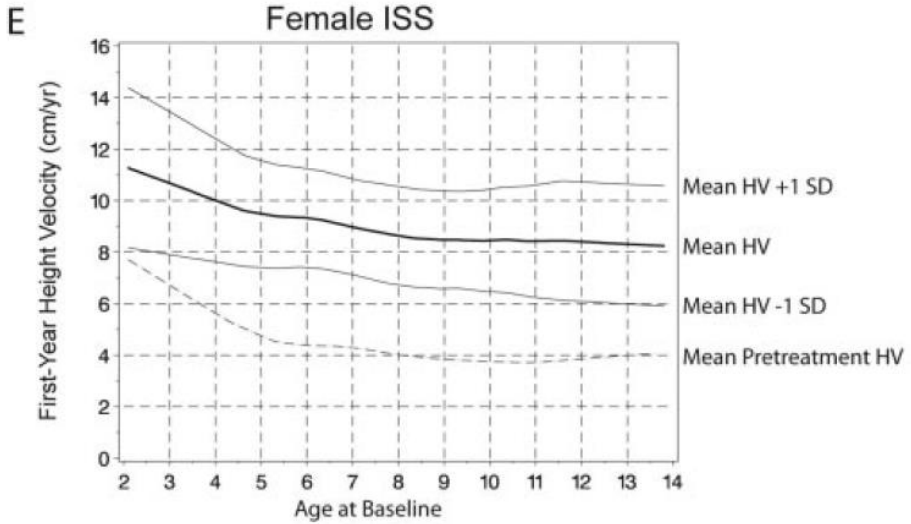
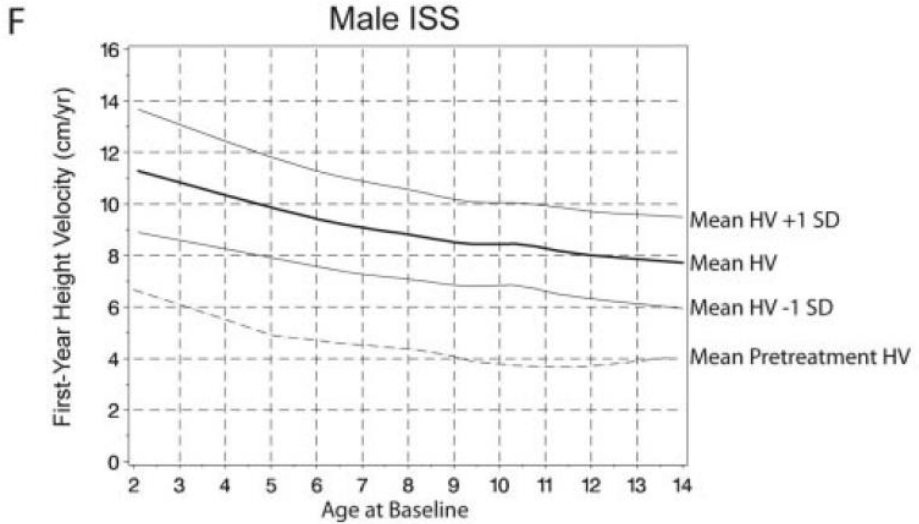
1st Year Growth Velocity Target for ISS





Key Point: Tremendous variability in response

Bakker et al. Journal of Clinical Endocrinology and Metabolism 2008; 93:352-357.

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Predictors of Response to GH Therapy in ISS

Variables	Number	Median	10th percentile	90th percentile
Background				
Birth weight, SDS	594	−0.7	−1.6	0.4
MPH, SDS	657	−1.4	−2.6	0.1
Maximum GH in provocation test, μg/l	657	14.7	10.8	28.7
Sex, male, %		77.6		
Start of GH treatment				
Age, years	657	7.8	4.7	10.6
Bone age, years	291	5.7	2.9	9.0
Height, SDS	657	−2.5	−3.3	−1.8
Weight, SDS	657	−2.3	−3.5	−1.1
Height – MPH, SDS	657	−1.1	−2.6	0.0
Dose of GH, mg/kg/week	657	0.19	0.16	0.30
Injections/week	657	6.0	5.0	7.0
1st year of therapy				
Height velocity, cm/year	657	7.9	6.3	10.1
Change in height, SDS	657	0.52	0.26	0.94

SDS = Standard deviation score; GH = growth hormone; MPH = mid-parental height.

- Age (inverse)
- Weight
- GH Dose
- Distance from MPH
- Explained 39% of variability in response

PHV [cm/year] = 9.3 + (−0.3 × age at start [years]) + (0.31 × weight at start [SDS]) + (0.74 × GH dose [mg/kg/week]) + (−0.33 × (height at start – MPH) [SDS]) ± 1.2.

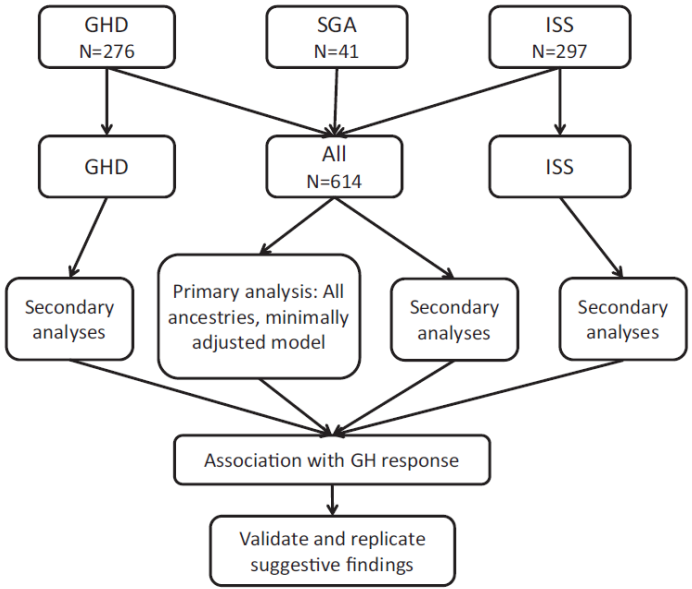
Ranke et al. Hormone Research 2007; 68(2):53-62.

Children's National.

Genetic Predictors of Growth Hormone Response

Table 1. Clinical Characteristics of Participants

	GWAS Cohorts	Replication Cohort
Individuals	614	113
Male	437	73
Female	177	40
Gestational age (weeks)	38.6 (2.9)	37.2 (3.1)
Birth weight (g)	2969 (693)	2754 (809)
Birth weight SDS	–0.70 (1.14)	–0.60 (1.48)
Midparental height (cm)	164.6 (5.8)	161.9 (5.35)
Age at start (years)	8.14 (2.71)	8.31 (2.55)
Average growth hormone dose (mg/kg/week)	0.28 (0.12)	0.29 (0.06)
Height at start (Prader SDS)	–3.00 (0.72)	–3.77 (1.18)
Δ height SDS during first year of therapy	0.78 (0.40)	0.76 (0.72)
ISS	297	42
GHD	276	44
SGA	65	30
SGA & GHD	24	3



Bottom Line: No clear association between common genetic variants and growth hormone response. Previously reported associations were not replicated.

Dauber et al. Journal of Clinical Endocrinology and Metabolism 2020; 105(10):3203-3214.

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Effect of GH Therapy on Quality of Life

- 74 patients treated with GH in France
  - 42 boys, 32 girls
- Diagnoses
  - GHD – 26 (35%)
  - SGA – 24 (32%)
  - Bone Dysplasia – 18 (24%)
  - ISS – 6 (8%)
- Median Height – -2.5 SD
- Baseline Age – 10.9 years

- Overall QOL and social and emotional scales were low in children with the most severe short stature (<-3SD)
- Significant improvements in social and emotional domains after 12 months of treatment.
- Parents also noted improvement in physical domains.
- Moderate correlation between QOL improvement and height SDS gain.

Gonzalez Briceno et al. Journal of Clinical Endocrinology and Metabolism 2019; 104:2103-2111.

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Pediatric Endocrine Society Growth Hormone Guidelines

In the USA, for children who meet FDA criteria, we suggest a shared decision-making approach to pursuing GH treatment for a child with ISS. The decision can be made on a case-by-case basis after assessment of physical and psychological burdens, and discussion of risks and benefits. We recommend against the routine use of GH in every child with HtSDS less than –2.25.

Grimberg et al. Hormone Research in Paediatrics 2016; 86(6):361-397.

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Safety Considerations

- Generally safe medication
- Short term
  - SCFE
  - Increased intracranial pressure
- Long term
  - No clear increased malignancy risk
  - ? Increase CV risk
- Psychological impact
  - Positive
  - Negative

RESULTS A total of 53 444 individuals (3408 patients and 50 036 controls; 67.7% men; mean [SD] age at study end, 25.1 [8.2] years) were followed up for as long as 25 years (median follow-up, 14.9 [range, 0-25] years; total, 795 125 person-years). Among 1809 recorded cardiovascular events, the crude incidence rates were 25.6 events per 10 000 person-years for patients and 22.6 events per 10 000 person-years for controls. The adjusted hazard ratio (HR) for all cardiovascular events was higher in patients compared with controls (HR, 1.69; 95% CI, 1.30-2.19), especially for women (HR, 2.05; 95% CI, 1.31-3.20) compared with men (HR, 1.55; 95% CI, 1.12-2.13). All subgroups had increased HRs (SGA, 1.97 [95% CI, 1.28-3.04]; GHD, 1.66 [95% CI, 1.21-2.26]; and ISS, 1.55 [95% CI, 1.01-2.37]). Longer duration of rhGH treatment (HR, 2.08; 95% CI, 1.35-3.20) and total cumulative dose (HR, 2.05; 95% CI, 1.18-3.55) were associated with higher risk for overall cardiovascular disease. The adjusted HR for severe cardiovascular disease was 2.27 (95% CI, 1.01-5.12).

Tidblad et al. JAMA Pediatrics 2021; 175(2):e205199.

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Conclusions

- Early diagnosis and treatment with rhGH can improve clinical outcomes especially in true growth hormone deficiency
- Diagnosis should take into account growth patterns, biochemical testing, and imaging
- GH stimulation tests should not be the sole diagnostic test used
- A single SC daily injection of rhGH can prove effective in improving height outcomes
- Monitoring medication adherence and counseling patients about the importance of high adherence are key to successful outcomes.
- It is important to verify the diagnosis of growth hormone deficiency at the time of transition to adult care.

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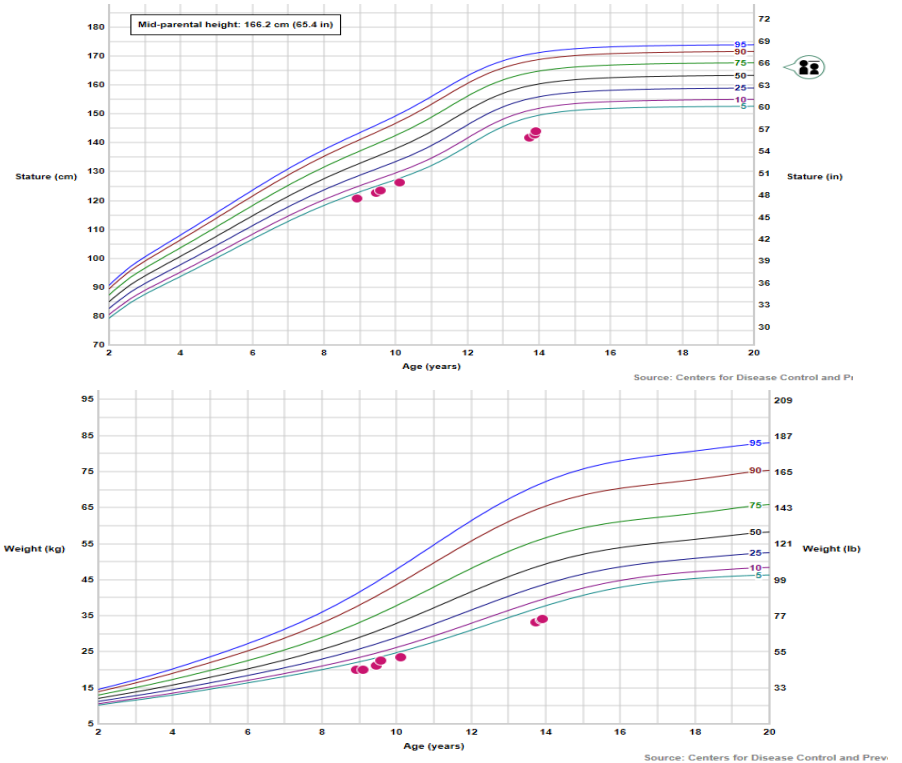
- 13 years 8 month old female
- PMH: No other medical problems
- Had menarche 3 months prior
- Bone age mildly delayed
- Normal IGF-1

- Mosaic Turner Syndrome



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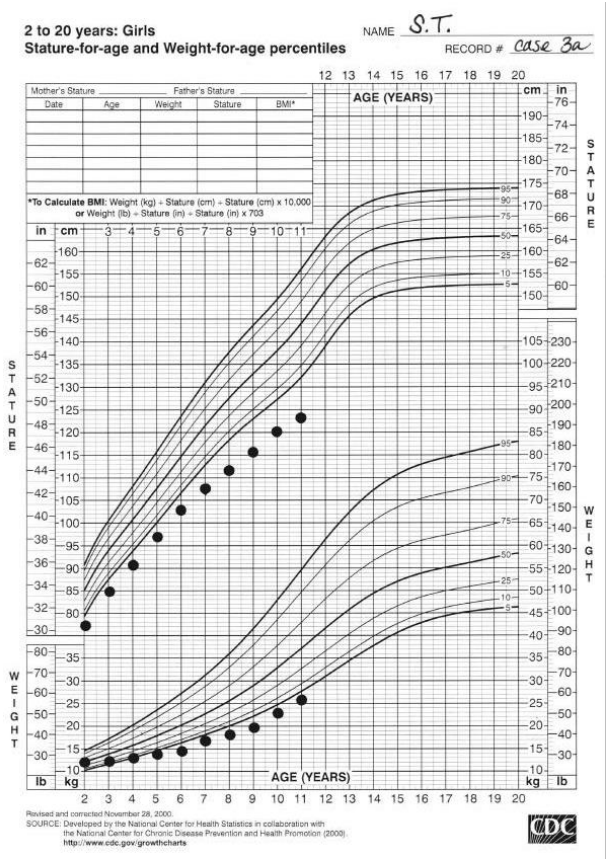
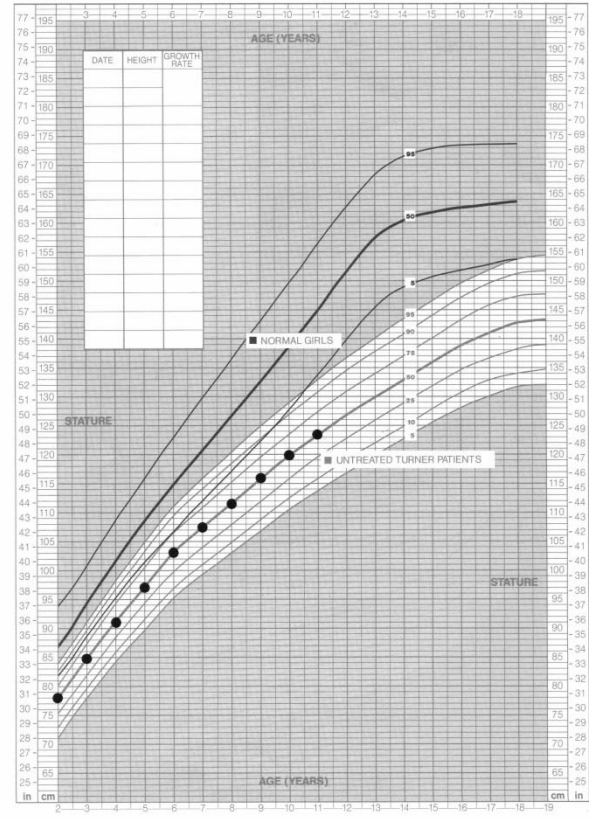
Turner Syndrome





From Laurie Cohen, MD - PediCases

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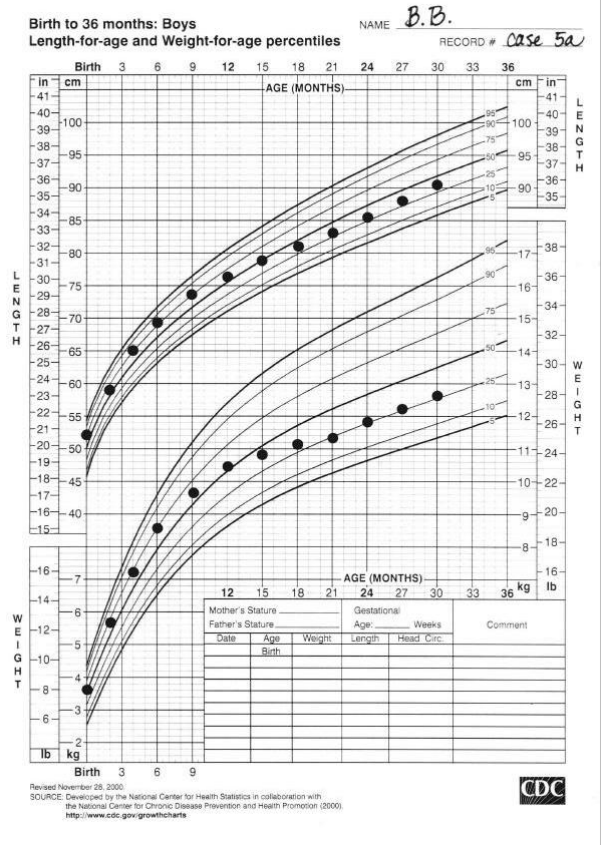

- B.B. is a 30 month old male whose length percentile is decreasing.
- He was the 8 lb. 20½ inch product of a full-term gestation delivered vaginally without complications.
- His past medical history is significant for a few upper respiratory infections, but he has been otherwise healthy.
- His mother is 63", his father is 68".

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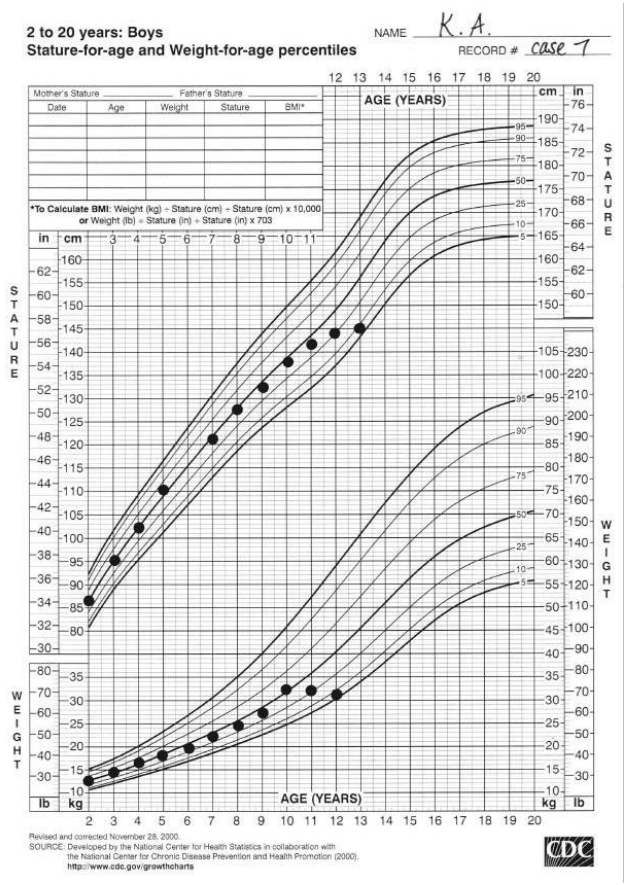

- K.A. is a 13 year old boy with short stature and pubertal delay.
- His past medical history is significant for a seizure disorder and developmental delay.
- His review of systems is positive for a restricted diet; he likes only potato chips. He denies abdominal pain or diarrhea.
- His mother is 5'5", his father is 5'10".
- His physical exam is notable for a gaunt appearance.
- He has 5 cc testes and Tanner II pubic hair.

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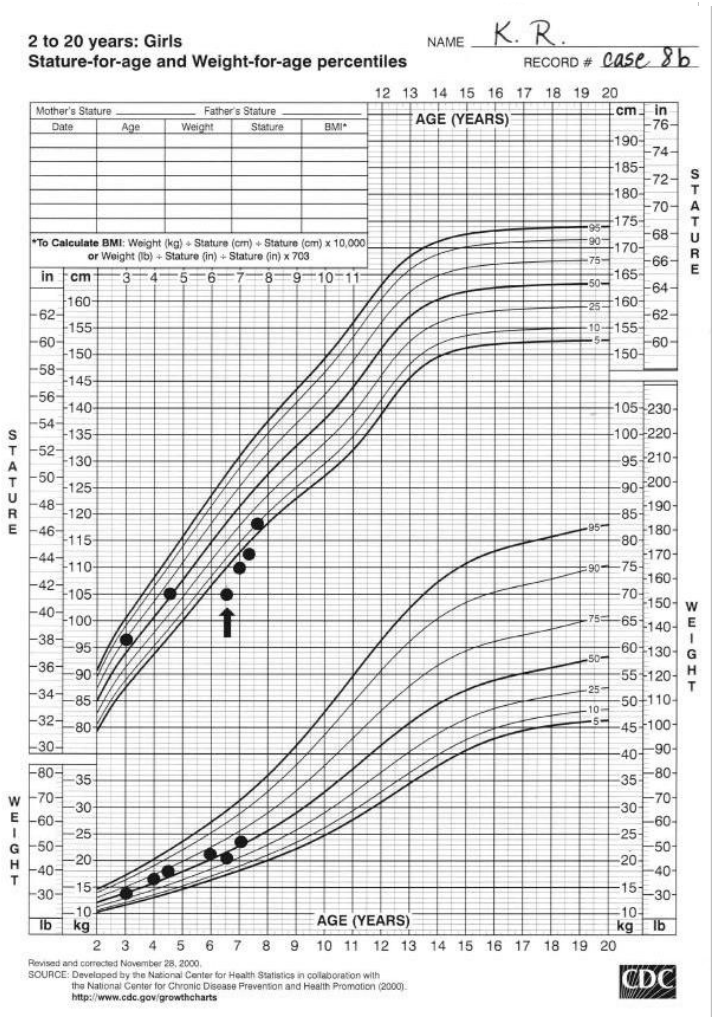

- K.R. is a 6 and 1/2 year old girl presenting with fatigue.
- Her review of systems is positive for cold intolerance, dry skin, and constipation.
- Her physical exam is remarkable for a sallow appearance, waxy dry skin, and coarse hair.
- Her mother is 5'2" and her father is 5'7".

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