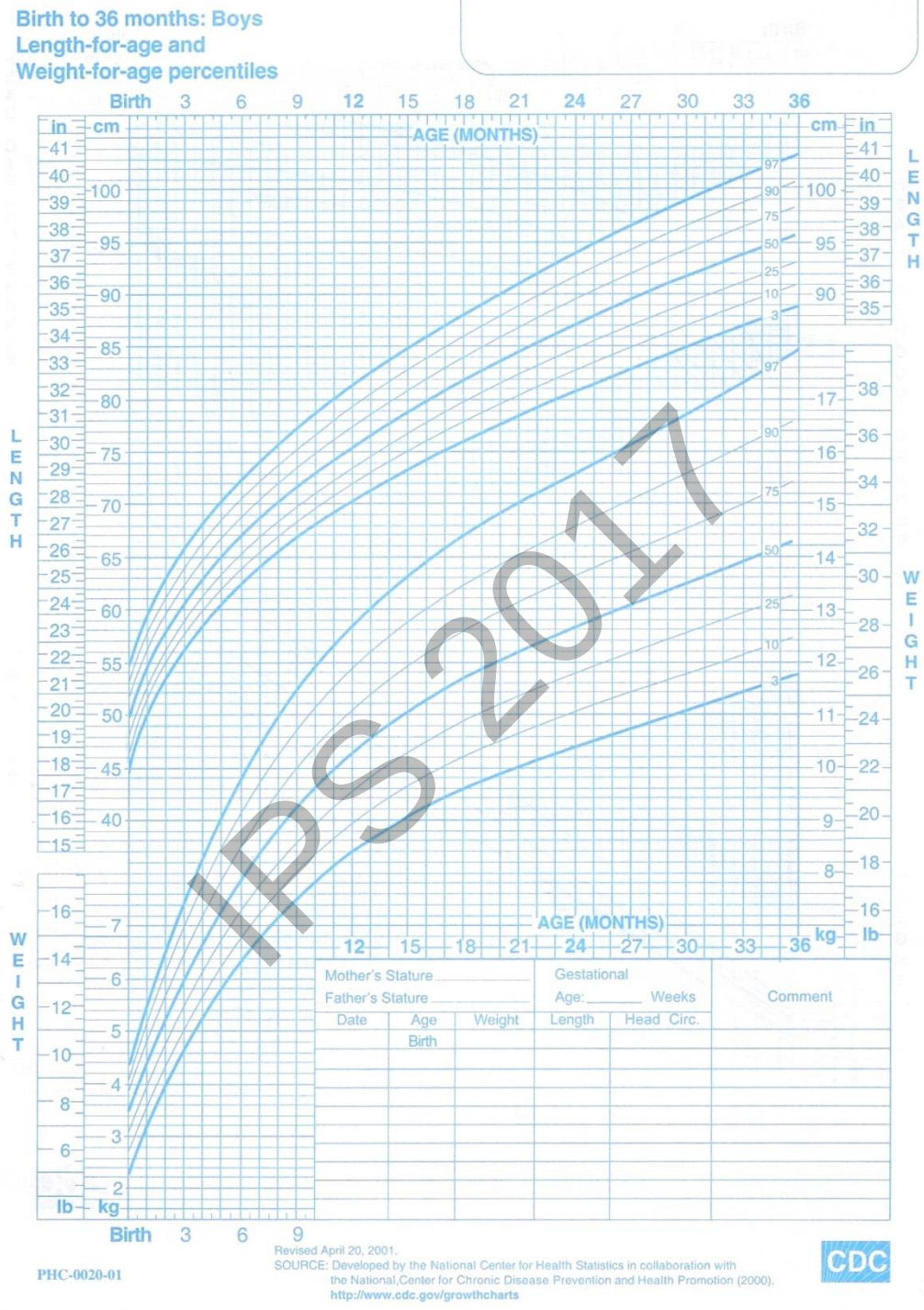
Short Stature

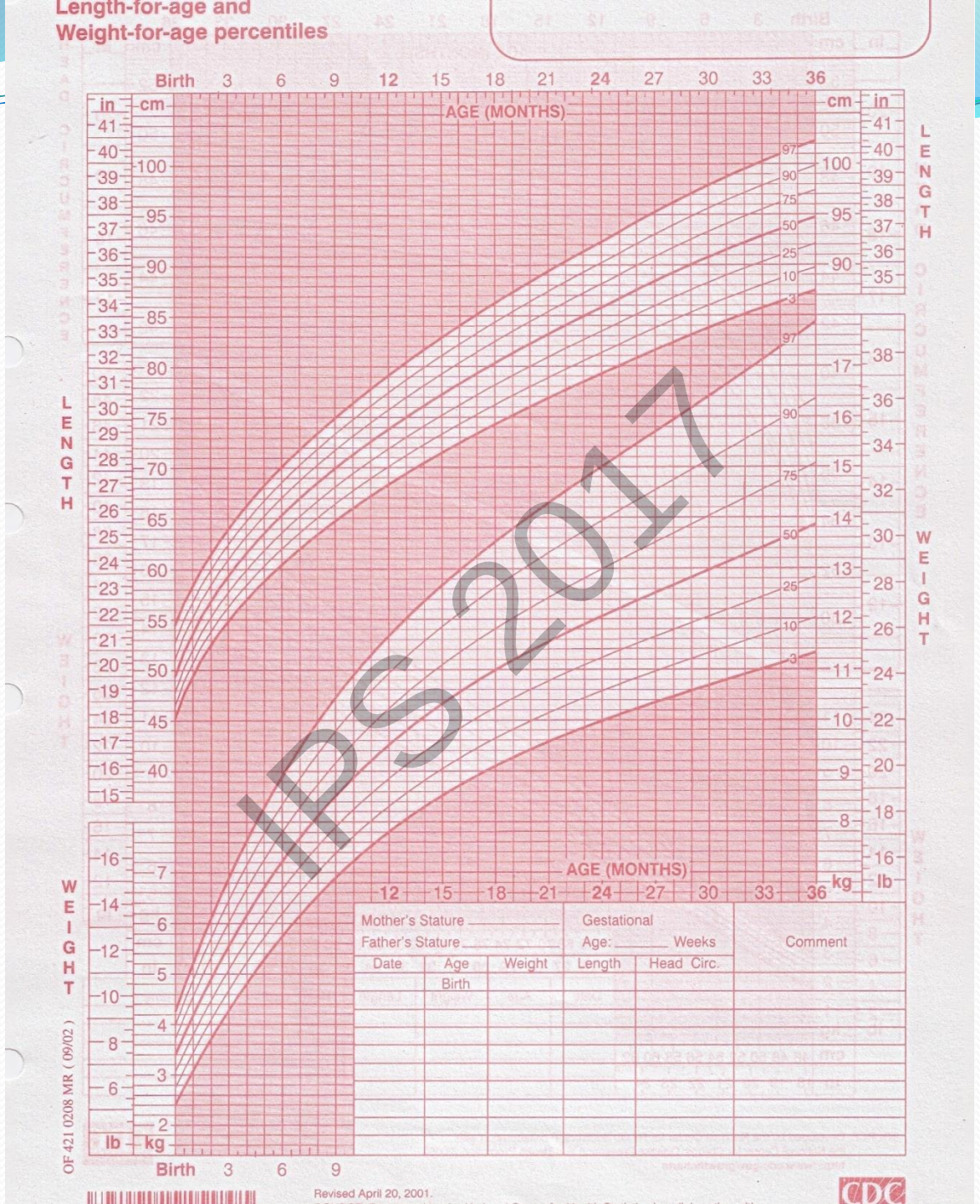
Jamal Al Jubeh, MD, FAAP
Consultant Pediatric Endocrinologist
Acting Chairman of Pediatrics
SKMC, Abu Dhabi, UAE

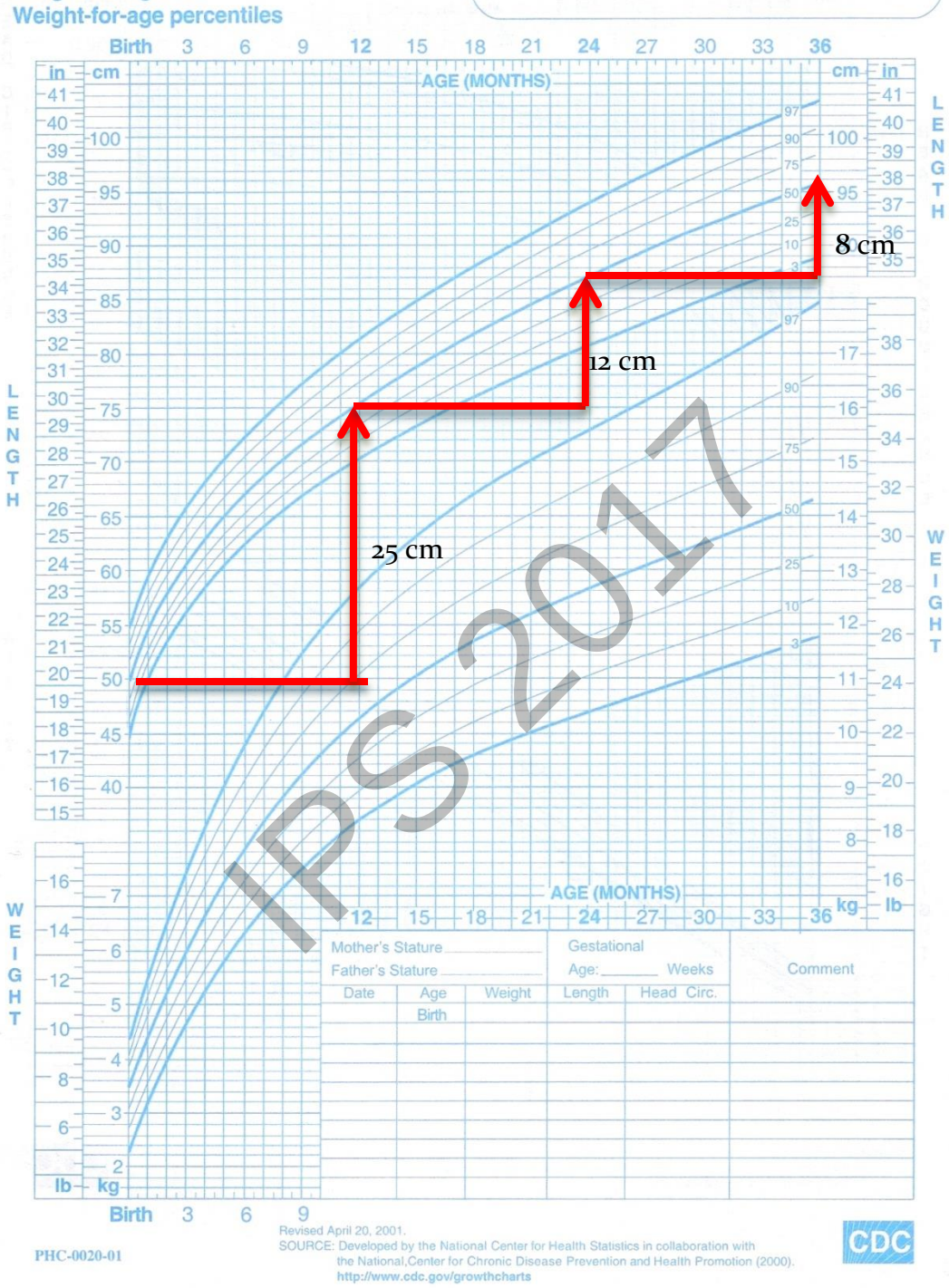
Objectives

- Normal and abnormal growth patterns.
- Short stature and growth failure.
- Causes of growth failure.
- Evaluation process.
- Growth hormone therapy.

What is normal growth?


Birth to 36 months: Boys
Length-for-age and
Weight-for-age percentiles
AGE (MONTHS)
LENGTH
WEIGHT
Mother's Stature
Father's Stature
Gestational
Age: Weeks
Date
Age
Weight
Length
Head Circ.
Comment
Birth
PHC-0020-01
Revised April 20, 2001.
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
CDC


Length-for-age and
Weight-for-age percentiles
Birth 3 6 9 12 15 18 21 24 27 30 33 36
AGE (MONTHS)
in cm
cm in
LENGTH
WEIGHT
97
90
75
50
25
10
3
Mother's Stature
Father's Stature
Gestational
Age: Weeks
Comment
Date
Age
Birth
Weight
Length
Head Circ.
OF 421 0208 MR (09/02)
Revised April 20, 2001.
CDC


Weight-for-age percentiles
Birth 3 6 9 12 15 18 21 24 27 30 33 36
AGE (MONTHS)
LENGTH
WEIGHT
8 cm
12 cm
25 cm
IFS 2017
Mother's Stature
Father's Stature
Gestational Age: Weeks
Comment
Date
Age
Birth
Weight
Length
Head Circ.
PHC-0020-01
Revised April 20, 2001.
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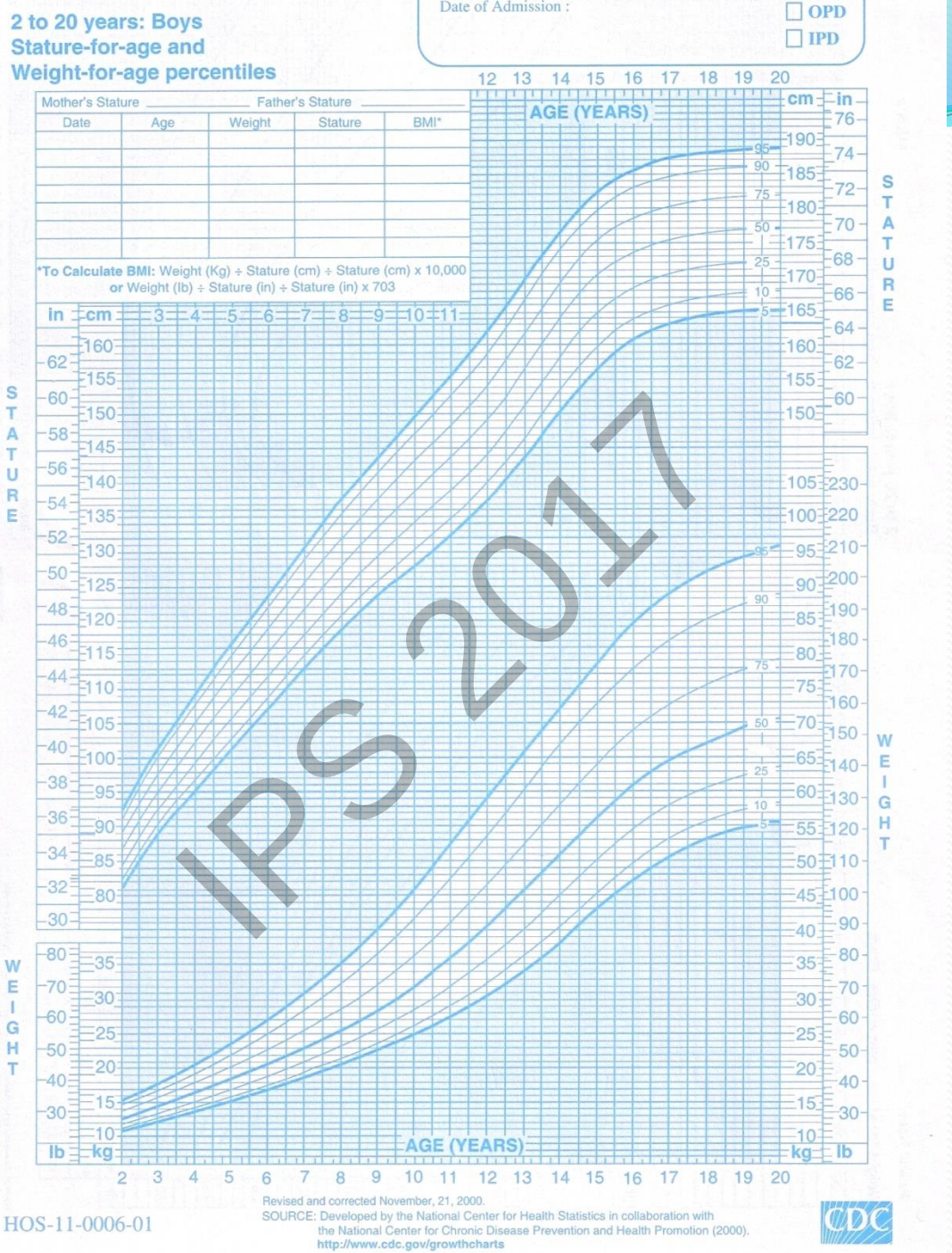
2 to 20 years: Boys
Stature-for-age and
Weight-for-age percentiles
Date of Admission :
OPD
IPD
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (Kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
IPS 2017
Revised and corrected November, 21, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with
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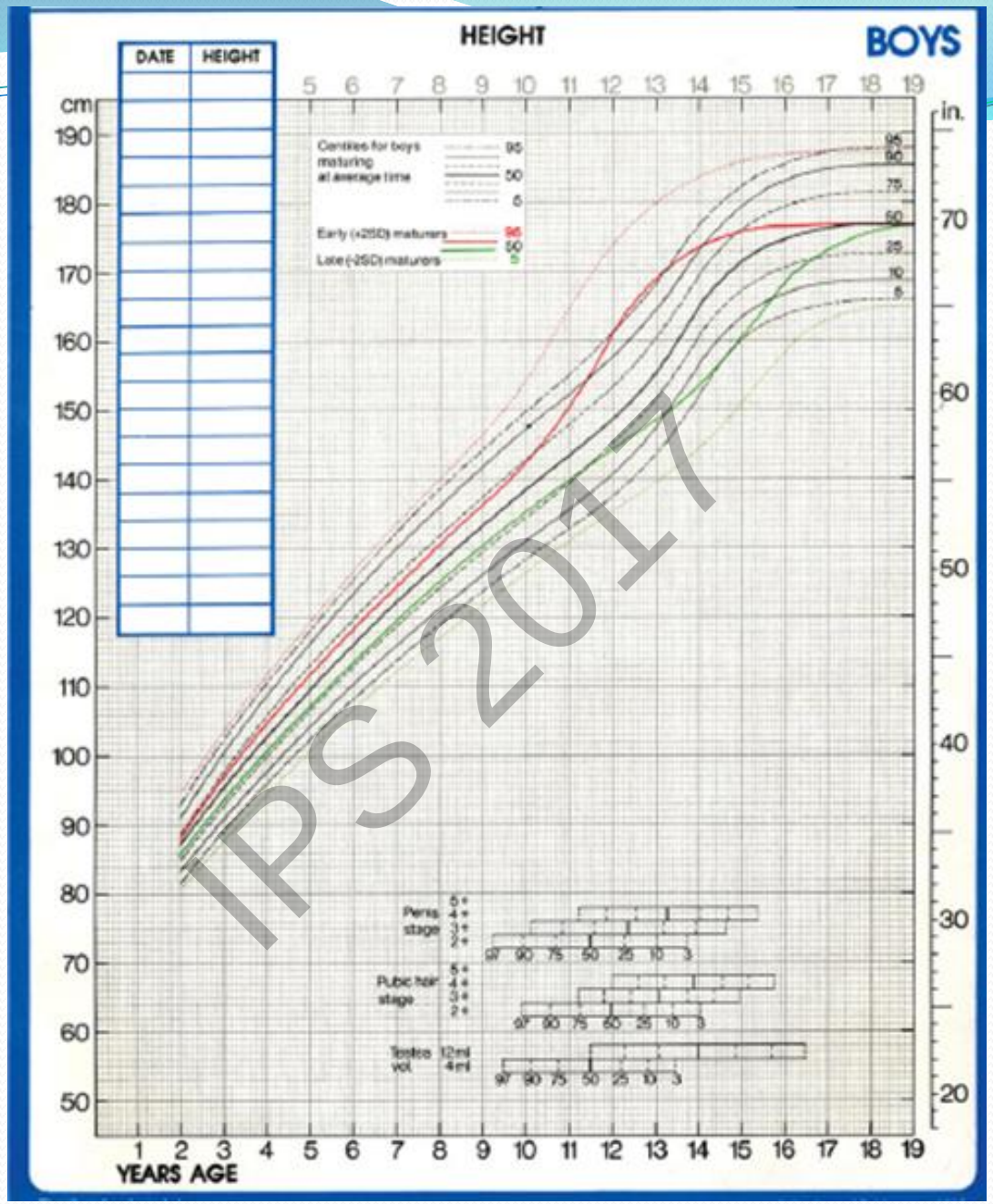
http://www.cdc.gov/growthcharts
HOS-11-0006-01


HEIGHT
BOYS
DATE
HEIGHT
cm
in.
YEARS AGE
IPS 2017

Growth Velocity curves

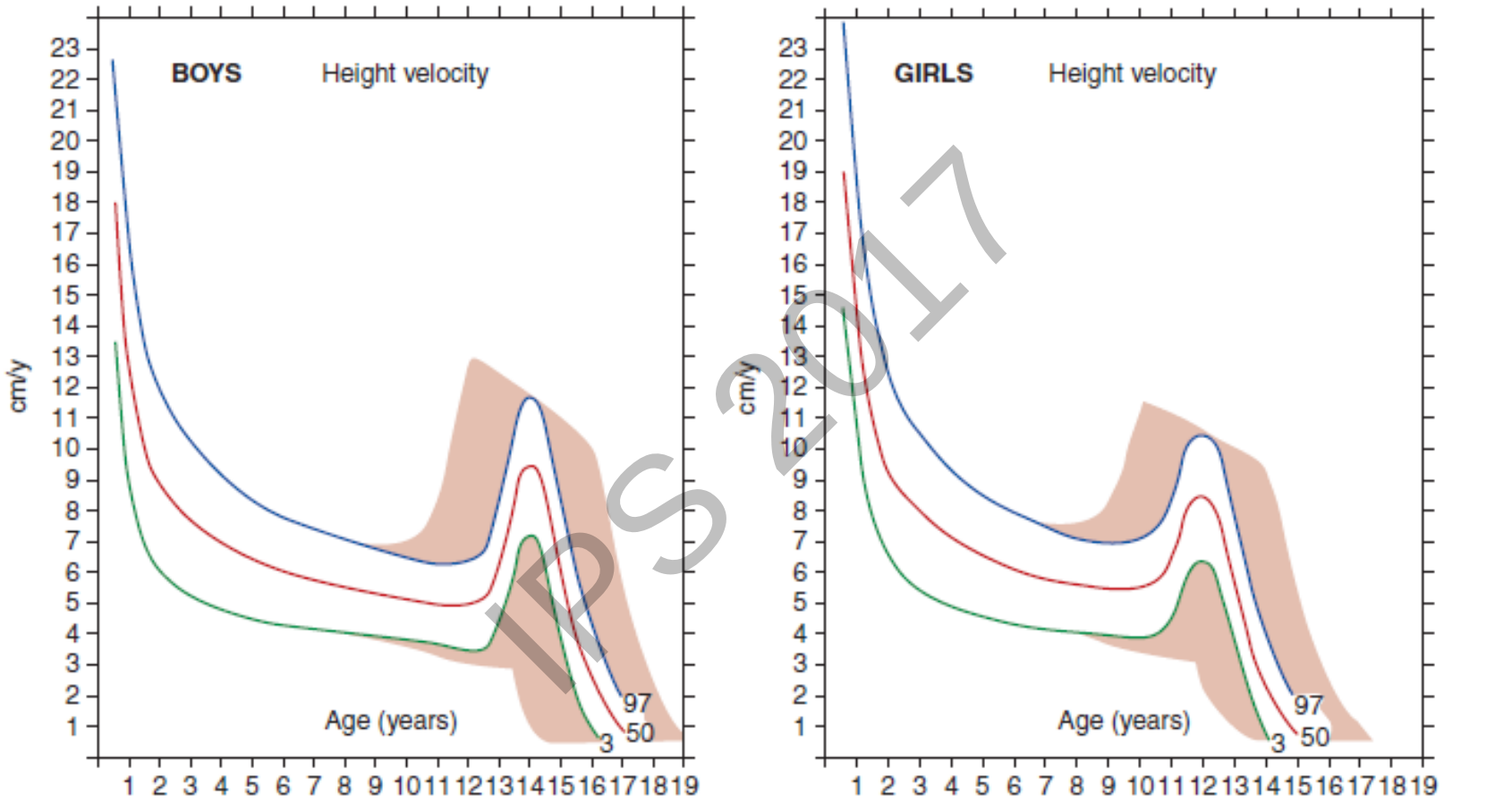


FIGURE 2-2 ■ Ranges of linear growth velocities in males and females. (*Modified from charts prepared by Tanner and Whitehouse, 1976, and reproduced with permission of Tanner JM and Castlemead Publications, Ward's Publishing Services, Herts, UK.*)

Table 1. Normal Growth Velocity at Various Life Stages

Life stage	*Growth velocity per year*
In utero	60 to 100 cm (24 to 40 in)
First year	23 to 27 cm (9 to 11 in)
Second year	10 to 14 cm (4 to 6 in)
Fourth year	6 to 7 cm (2 to 3 in)
Prepubertal nadir	5 to 5.5 cm (2 to 2.2 in)
Pubertal growth spurt	Girls: 8 to 12 cm (3 to 5 in) Boys: 10 to 14 cm (4 to 6 in)

Upper to Lower Extremity Ratios in Boys and Girls

	Boys	Girls
Age (Years)	U/L Ratio	U/L Ratio
Birth	1.70	1.70
1/2	1.62	1.60
1	1.54	1.52
1 1/2	1.50	1.46
2	1.42	1.41
2 1/2	1.37	1.34
3	1.35	1.30
3 1/2	1.30	1.27
4	1.24	1.22
4 1/2	1.22	1.19
5	1.19	1.15
6	1.12	1.10
7	1.07	1.06
8	1.03	1.02
9	1.02	1.01
10	0.99	1.00
11	0.95	0.90
12	0.98	0.99
13	0.97	1.00
14	0.97	1.01
15	0.95	1.01
16	0.99	1.01
17	0.99	1.01

Adapted from Wilkins L. The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. IL: Springfield, Charles C. Thomas, Publisher; 1957.

How to measure length and height?

Measurement of length

Rogol and Hayden www.jpeds.com Vol. 164, No. 5, Suppl. 1

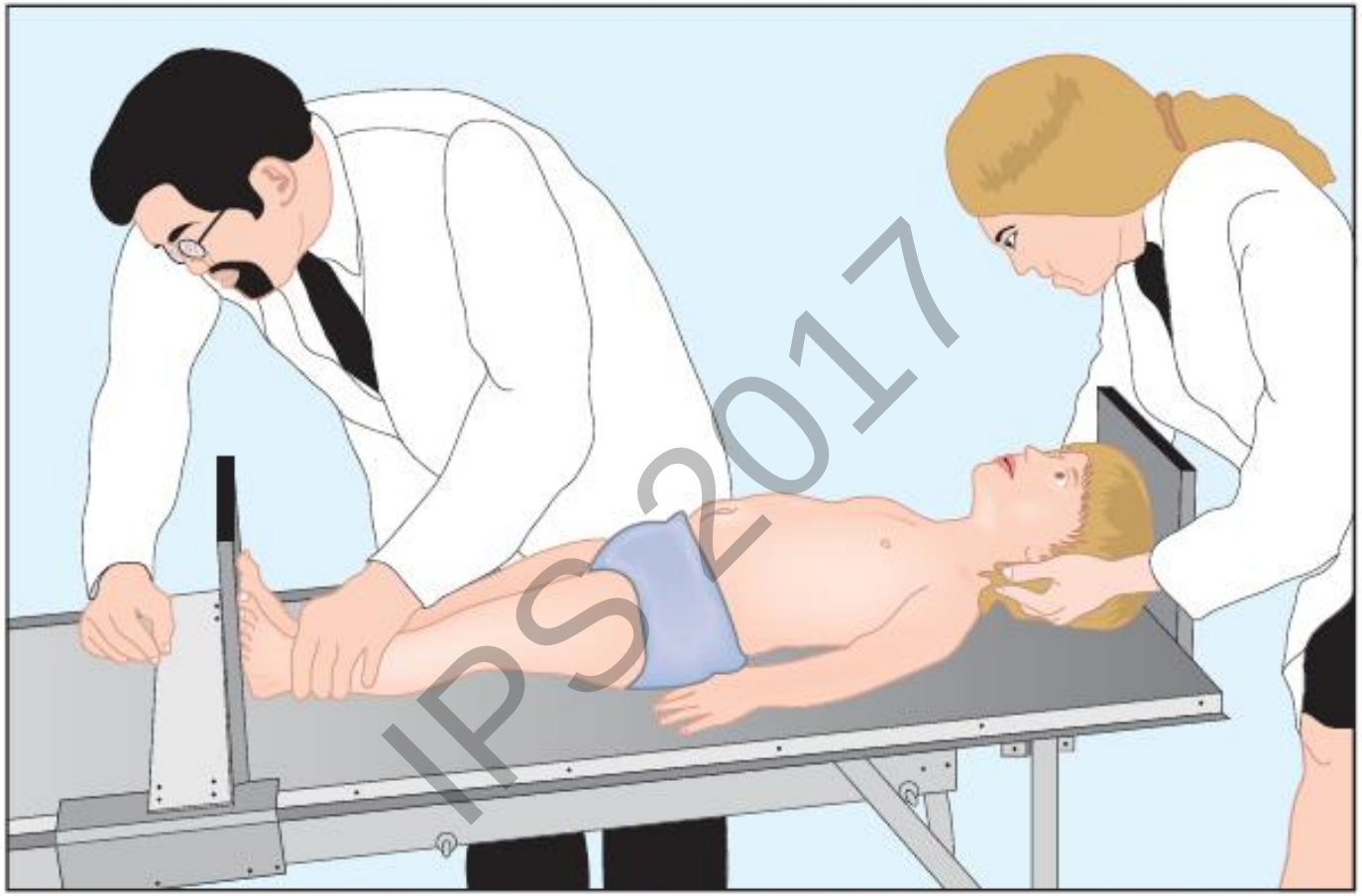
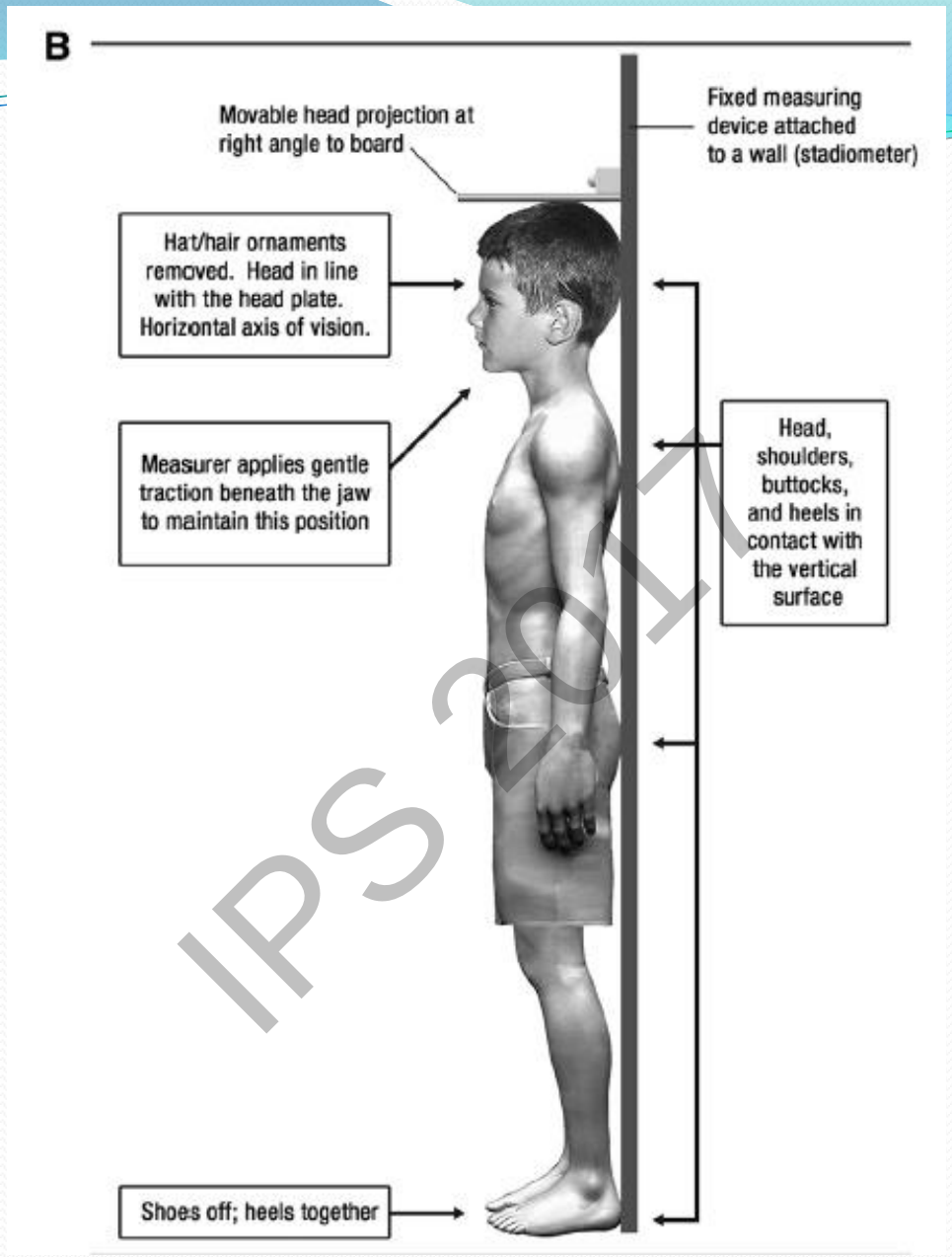


FIGURE 2-3 ■ Measurement of children less than 2 years of age should be obtained in the "Frankfurt plane" which places children in the supine position in full extension and other canthus of the eyes and the external auditory meatus perpendicular to the long axis of the trunk.

Kappy et al. ■ *Pediatric Practice: Endocrinology 2010: 25*



Rogol and Hayden

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Measurement accuracy

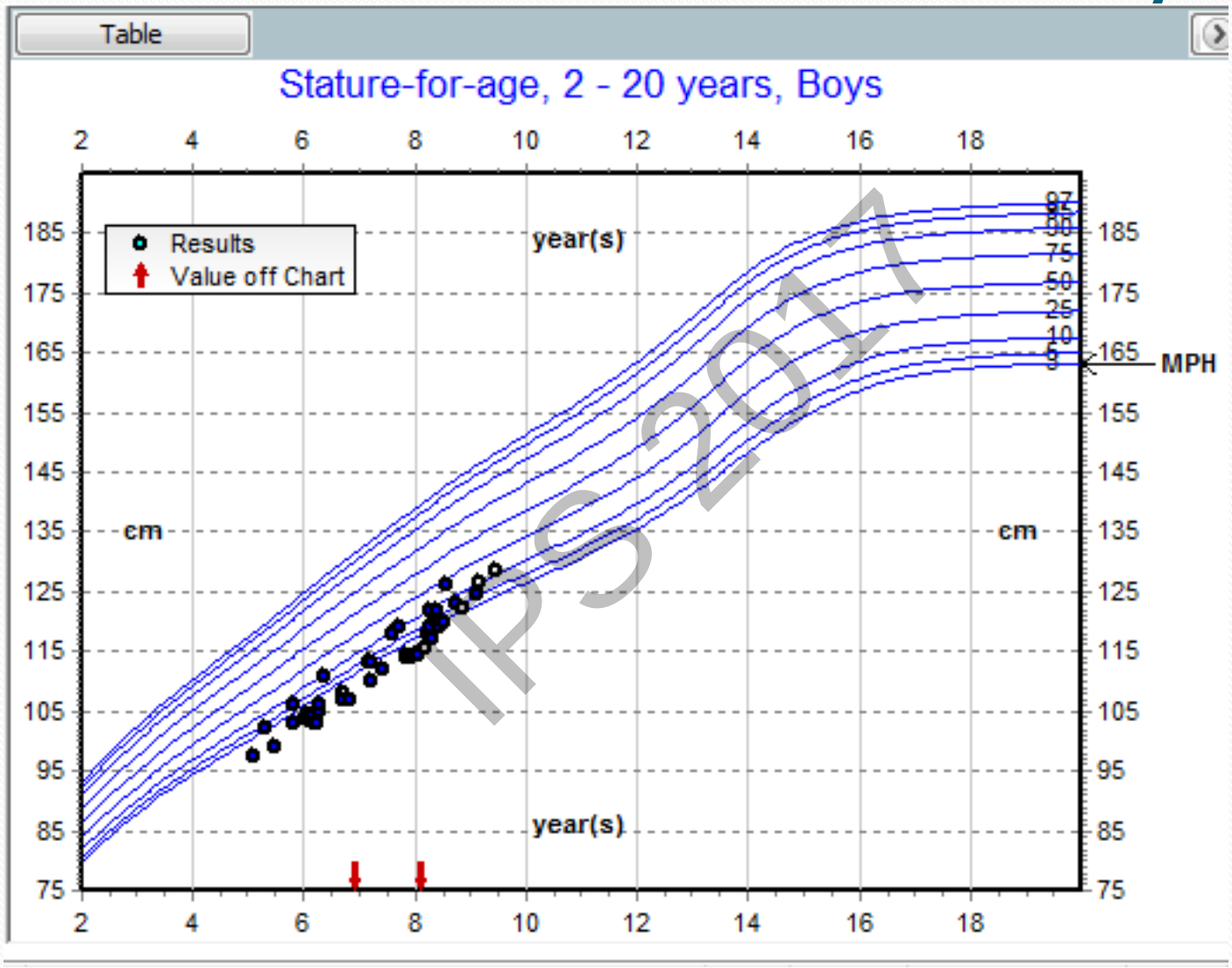
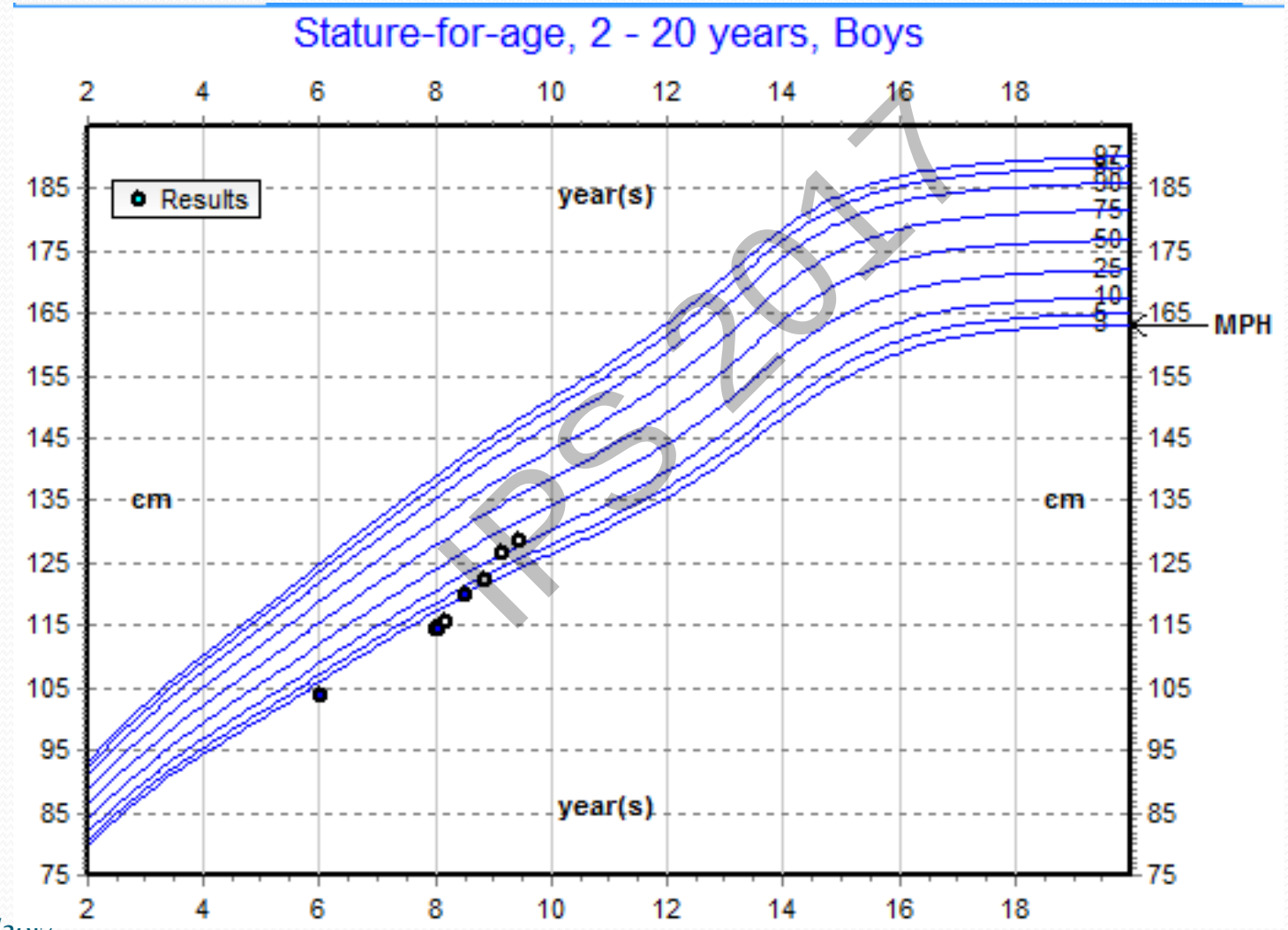


Chart | Calculate GV | Plot All

Stature-for-age, 2 - 20 years, Boys

Date	Age	Value	Centile	z-score/SD	GV	Calculation	Medical Service	Plot
17/03/2013	8 years	(c) 115.40 cm	0.78	-2.42	☐		Paediatrics-Endocrinology	☑
08/04/2013	8 years	118.00 cm	2.58	-1.95	☐		Family Practice	☐
15/04/2013	8 years	119.00 cm	3.26	-1.84	☐		Family Practice	☐
16/04/2013	8 years	122.00 cm	9.48	-1.31	☐		Family Practice	☐
09/05/2013	8 years	117.00 cm	1.38	-2.20	☐		Med-Dermatology	☐
05/06/2013	8 years	122.00 cm	8.25	-1.39	☐		Med-Dermatology	☐
08/06/2013	8 years	120.00 cm	4.08	-1.74	☐		Pharmacy	☐
18/06/2013	8 years	119.00 cm	2.31	-1.99	☐		Family Practice	☐
14/07/2013	8 years	120.00 cm	2.95	-1.89	☐		Paediatrics-Endocrinology	☑
27/07/2013	8 years	126.00 cm	19.87	-0.85	☐		Family Practice	☐
03/10/2013	8 years	123.00 cm	6.58	-1.51	☐		Family Practice	☐
24/11/2013	8 years	(c) 122.40 cm	4.01	-1.75	☐		Paediatrics-Endocrinology	☑
17/02/2014	9 years	124.50 cm	5.59	-1.59	☐		Paediatrics-General	☐
09/03/2014	9 years	(c) 126.60 cm	10.76	-1.24	☐		Paediatrics-Endocrinology	☑
22/06/2014	9 years	(c) 128.40 cm	11.51	-1.20	☐		Paediatrics-Endocrinology	☑


Stature-for-age, 2 - 20 years, Boys
Results
year(s)
cm
year(s)
cm
MPH
97
90
75
50
25
10
5
3
IPS 2017

Short Stature:
Definition, causes and approach

Short Stature

- Height more than 2 SD below mean for the same age and sex compared to genetically relevant population (< 2.3 %)

Growth evaluation

- Accurate measurement of child's height and weight.
- Accurate plotting on appropriate growth chart.
- Assessment of longitudinal growth (growth velocity):
  Accurate heights measured at 6 - 12 month interval
- Measuring parent's height.

Familial (genetic) Short stature

- Parents are short
- Child is growing within target height range.
- Child's bone age = Chronological age

Midparental height (Boys)

- F: Father's height (cm)
  M: Mother's height (cm)

- Midparental height in cm for boys
- = (F + M + 13) / 2

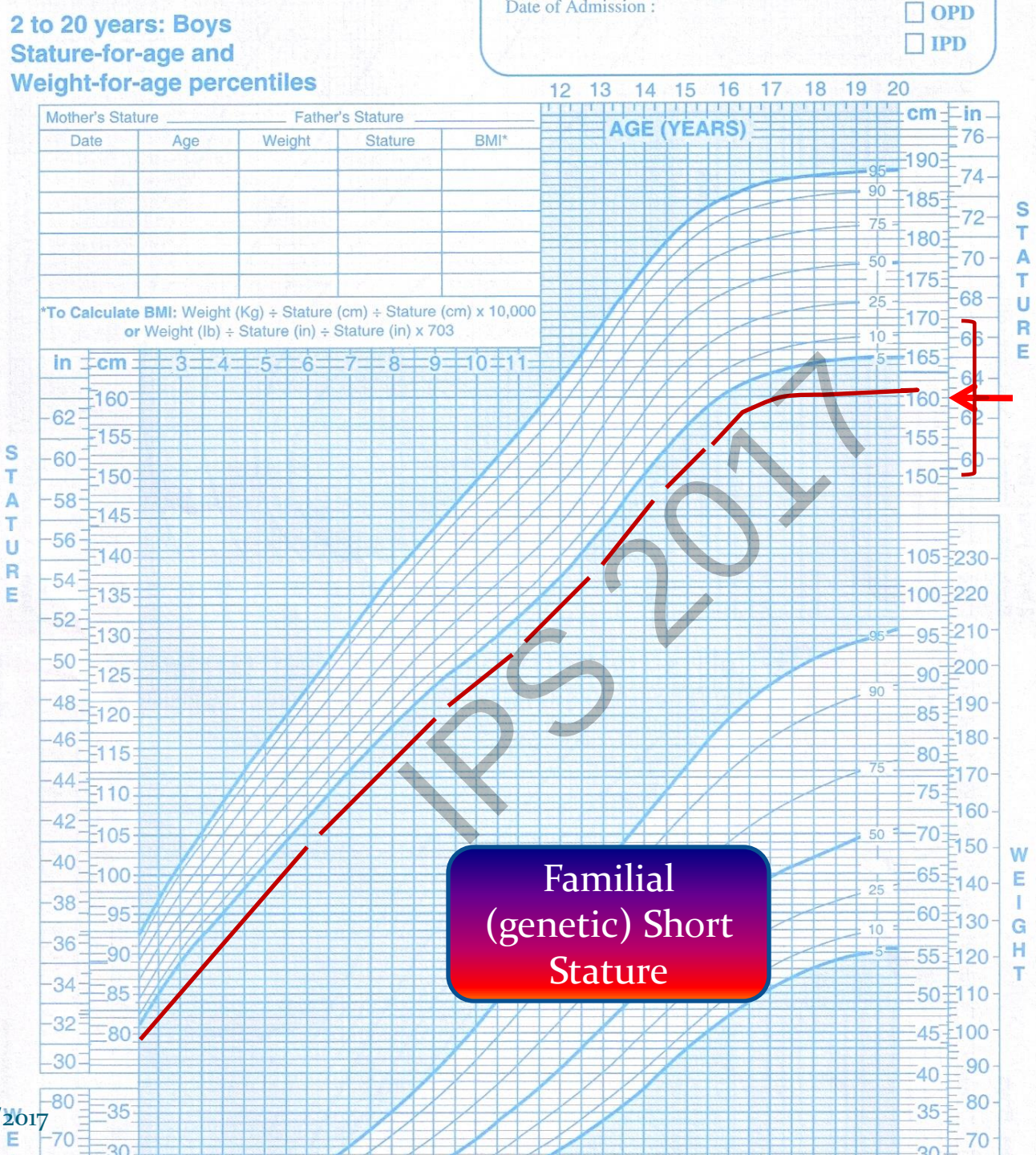
- = (F + M) / 2 + 6.5

Midparental height (Girls)

- F: Father's height (cm)
  M: Mother's height (cm)

- Midparental height in cm for Girls
- = (F + M - 13) / 2

- = (F + M) / 2 - 6.5


2 to 20 years: Boys
Stature-for-age and
Weight-for-age percentiles
Date of Admission :
OPD
IPD
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (Kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
IPS 2017
Familial (genetic) Short Stature

Constitutional Delay of Growth and Puberty (CDGP)

- Normal growth velocity.
- Delayed bone age.
- Delayed puberty (Often runs in the family)
- Normal adult (final) height


2 to 20 years: Boys
Stature-for-age and
Weight-for-age percentiles
Date of Admission :
OPD
IPD
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
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AGE (YEARS)
STATURE
WEIGHT
IPS 2017
Constitutional
Growth Delay
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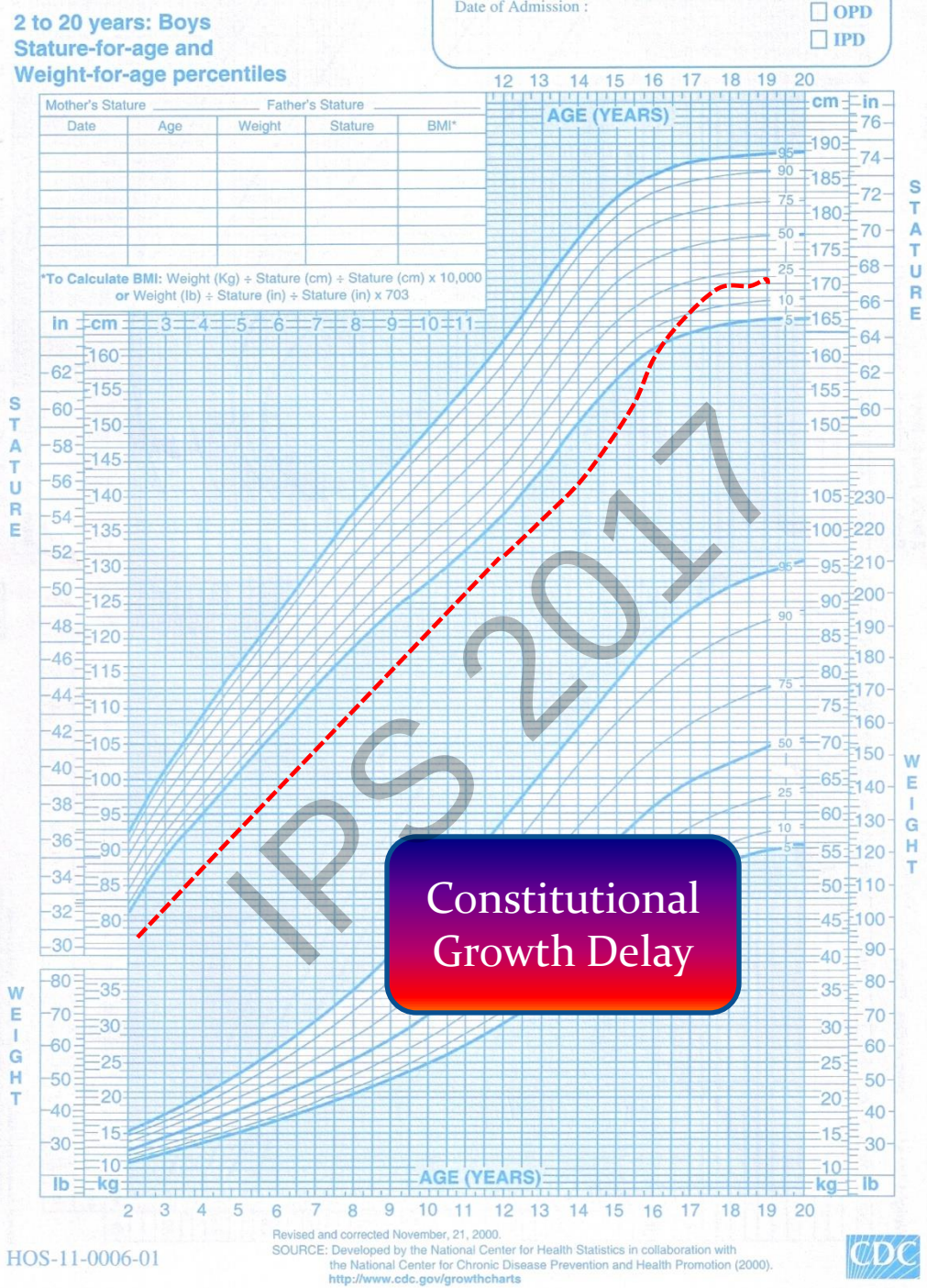
http://www.cdc.gov/growthcharts
HOS-11-0006-01
CDC


2 to 20 years: Boys
Stature-for-age and
Weight-for-age percentiles
Date of Admission :
OPD
IPD
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (Kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
IPS 2017
Constitutional
Growth Delay
Revised and corrected November, 21, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with
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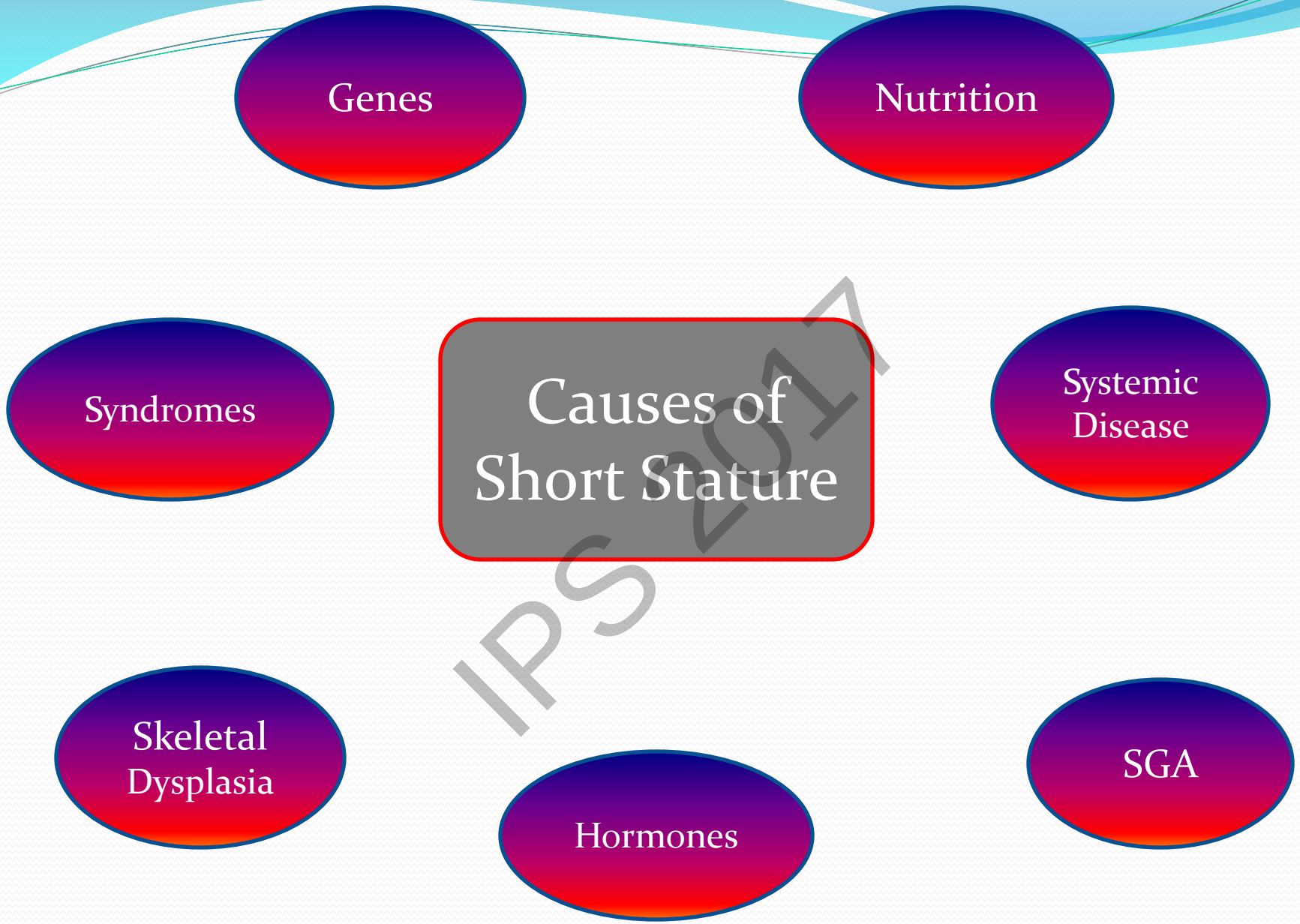
http://www.cdc.gov/growthcharts
HOS-11-0006-01
CDC

What are the causes of short stature?


Genes
Nutrition
Syndromes
Causes of Short Stature
Systemic Disease
Skeletal Dysplasia
Hormones
SGA

Systemic Diseases

GI

- Celiac Disease
- Malabsorption
- IBD

Renal

- CKD
- Renal Tubular Acidosis

Hem / ONC

- Thalassemia
- SCD
- Malignancy

Pulmonary

- Cystic Fibrosis
- Severe Asthma

Metabolic

- Organic Acidemia
- GSD

Cardiac

- Congenital Heart disase

Endocrine

- Hypothyroidism
- Hypopituitarism
- Isolated growth hormone deficiency
- GH insensitivity (Laron dwarfism)
- Cushing syndrome
- Poorly controlled type 1 diabetes mellitus - Mauriac syndrome
- Rickets
- Idiopathic short stature

Evaluation of Short Stature

Should be based on findings from History and Physical Exam

Evaluation of Short stature

- CBC, ESR
- Electrolytes & Renal Panel, Ca, Phos.
- Thyroid (TSH, FT4)
- Celiac Screen:
  - (Tissue transglutaminase antibodies).
- Chromosomal analysis (girls).
- IGF-1, IGF-BP3
- Bone Age X ray.

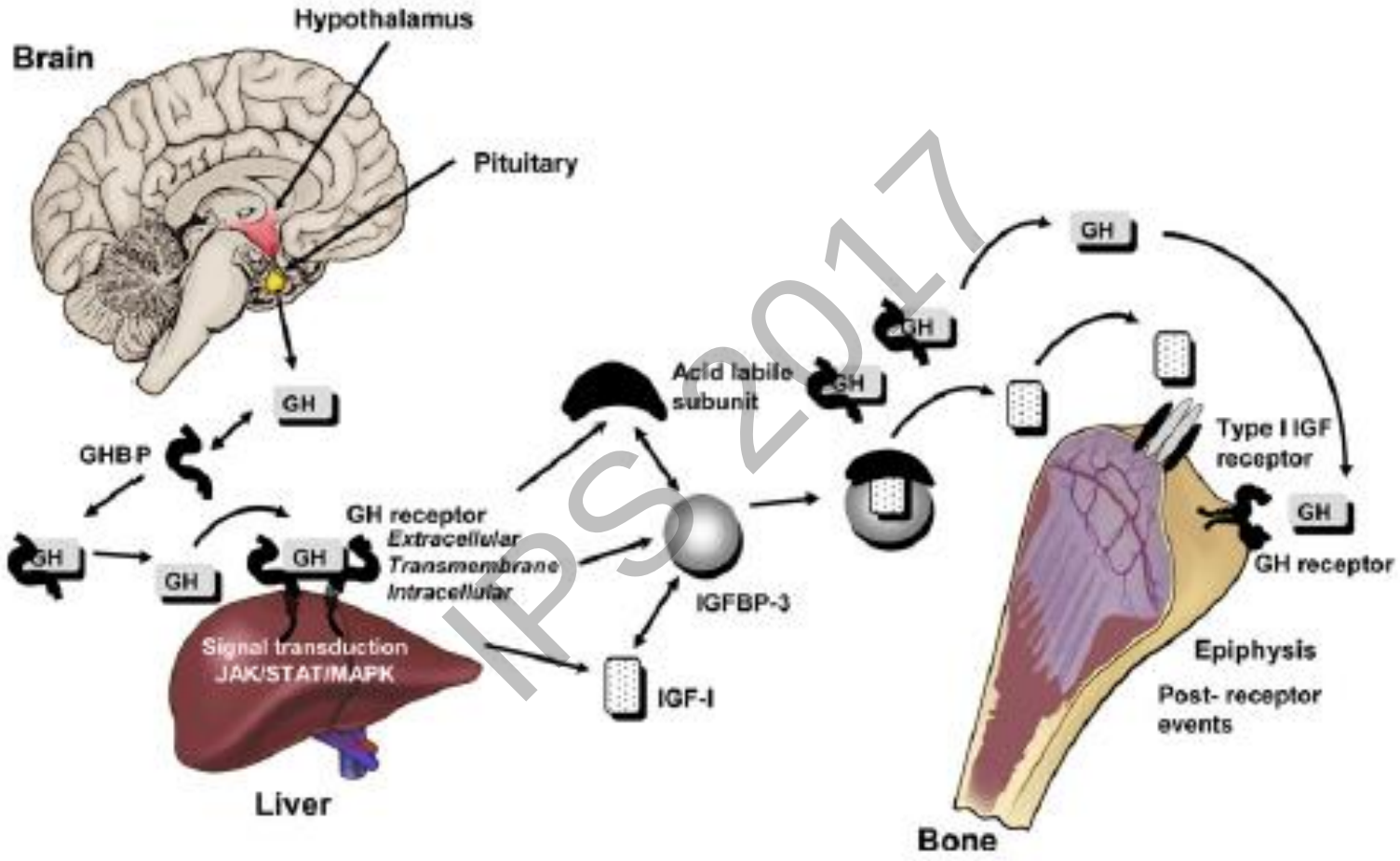
Differential diagnosis of low circulating IGF-I concentration

- GH deficiency
- GHR dysfunction (GH resistance/insensitivity)
- Post-GHR signaling defect (STAT5b)
- *IGF1* gene defect
- ALS deficiency
- Hepatic insufficiency (eg, cirrhosis)
- Malnutrition
- Hypothyroidism
- Delayed puberty
- Poorly controlled diabetes mellitus
- Chronic illness
- Glucocorticoid therapy

Endocrinol Metab Clin N Am 41 (2012) 265–282

GH – IGF1 Axis

GH – IGF1 axis



Endocrinol Metab Clin N Am 36 (2007) 131–186

Defects in GH/IGF axis

Table 1
Phenotypes of patients with defects in GH/IGF axis

Condition	Affected Gene	Prenatal Growth	Postnatal Growth	GH/IGF Axis	Other Features
GH insensitivity, Laron syndrome	*GHR*	Normal	↓↓↓↓	GH ↑ IGF-I ↓ IGFBP-3 ↓	Hypoglycemia common; affected usually homozygous
STAT5b deficiency	*STAT5b*	Normal	↓↓↓↓	GH ↑ IGF-I ↓ IGFBP-3 ↓	Immune deficiency; affected usually homozygous
IGF-I gene mutation	*IGF1*	↓↓↓	↓↓↓	GH ↑ IGF-I ↓ IGFBP-3 NI	Deafness, microcephaly, carbohydrate intolerance; affected usually homozygous
Russell-Silver syndrome	*IGF2* via abnormal cytosine methylation	↓↓↓	↓↓↓↓	GH NI IGF-I NI IGFBP-3 NI	Dysmorphic features and body asymmetry; normal IGF-II levels
ALS deficiency	*IGFALS*	Normal	↓–↓↓	GH NI IGF-I ↓ IGFBP-3 ↓ ALS undetectable	Phenotype similar to constitutional delay of growth and adolescence; affected usually homozygous
IGF resistance	*IGF1R*	↓↓–↓↓↓	↓↓↓	GH NI- ↑ IGF-I NI- ↑ IGFBP-3 NI- ↑	Variable effect on intellect/mental status; usually hemizygous, heterozygous, or compound heterozygote

Abbreviations: ALS, acid-labile subunit; IGFBP-3, insulin-like growth factor binding protein 3; IGF1R, type I IGF receptor; NI, normal; STAT, signal transducer and activator of transcription.

Endocrinol Metab Clin N Am 41 (2012) 265–282

When to suspect Growth Hormone Deficiency (GHD)?

- Low growth velocity.
- Low IGF-1, IGF-BP3
- Delayed bone age.
- Other causes were excluded
- ± Evidence of pituitary abnormality.

How to confirm GHD?

- Growth hormone stimulation testing:
- Arginine,
- Clonidine.
- Glucagon
- Levodopa
- Insulin / hypoglycemia

Tests to Provoke Growth Hormone Secretion

Stimulus	Dosage	Times Samples Are Taken (min)	Comments
Exercise	Step climbing; exercise cycle for 10 min	0, 10, 20	Observe child closely when on the steps
Levodopa	< 15 kg: 125 mg 10-30 kg: 250 mg > 30 kg: 500 mg,	10, 60, 90	Nausea, rarely emesis
Clonidine	0.15 mgs/m^2	0, 30, 60, 90	Tiredness, postural hypotension
Arginine HCl (IV)	0.5 g/kg (mas 30 g) 10% arginine HCl in 0.9% NaCl over 30 min	0, 15, 30, 45, 60	
Insulin (IV)	0.05-0.1 unit/kg	0, 15, 30, 60, 75, 90, 120	Hypoglycemia, requires close supervision
Glucagon (M)	0.03 mg/kg (max 1 mg)	0, 30, 60, 90, 120, 150, 180	Nausea, occasional emesis
GHRH (IV)	1 (g/kg)	0, 15, 30, 45, 60, 90, 120	Flushing, metallic taste

Tests should be performed after an overnight fast. Many investigators suggest that prepubertal children should be "primed" with gonadal steroids, eg, 5 mg Premarin orally the night before and the morning of the test or with 50 to 100 µg/d ethinyl estradiol for 3 consecutive days before testing or 100 ng depot testosterone 3 days before testing. This, of course, alters patient's steady state and performs the provocative test in a steroid-rich environment. Patients must be euthyroid at the time of testing.

Documentation of appropriate lowering of blood glucose is recommended. If GHD is suspected, the lower dosage of insulin is usually administered, especially in infants. D10W and glucagon should be available.

If GHD is confirmed

- MRI of brain (hypothalamus / pituitary)
- Start GH therapy.

The Story of hGH

- 1958: Cadaveric GH was first used.
- 1980s: Trials of Recombinant GH.
- 1985: Creutzfeldt-Jakob's disease reported in a number of patients using Cadeveric GH.
- 1985: Recombinant GH was approved starting era of unlimited supplies and expanded use

rhGH associated adverse events

- Impaired insulin sensitivity.
- Benign Intracranial Hypertension
- Slipped capital femoral epyphysis
- Scoliosis
- Features of acromegaly
- Sudden death in Prader Willi Syndrome
- No evidence of increase in cancer risk
- High cost is a major issue

What determines response to GH?

- Diagnosis.
- Correction of other underlying problems.
- Age at initiation of treatment.
- Dose.
- Adherence.

Table 1 Approved indications for GH use in the USA and Europe

Indication	Year of FDA approval
GH-deficiency states	
Childhood growth-hormone deficiency	1985 (E)
Adult growth-hormone deficiency	1996 (E)
Pubertal dosing	2000
Non-GH-deficiency states	
Chronic kidney disease	1993 (E)
Turner syndrome	1996 (E)
AIDS wasting	1996
Prader–Willi syndrome	2000 (E)
Small for gestational age	2001 (E)
Idiopathic short stature	2003
Small bowel syndrome	2004
SHOX deletion	2006 (E)
Noonan syndrome	2007

Abbreviations: E, Europe; FDA, US Food and Drug Administration; GH, growth hormone.

Drug Design, Development and Therapy 2011:5

FDA-Approved Indications for Growth Hormone Therapy

Indication	Dosage*
GHD	0.16-0.30 mg/kg/wk also dosed as 0.024-0.034 mg/kg/d
PWS	Up to 0.24 mg/kg/wk (or body surface area-based dosing at ~1 mg/m^{2}BSA/day)
SGA/IUGR	Up to 0.48 mg/kg/wk
Turner syndrome	Up to 0.33-0.47 mg/kg/wk also dosed as up to 0.067 mg/kg/d)
Noonan syndrome	Up to 0.066 mg/kg/d
ISS	Up to 0.47 mg/kg/wk
Chronic renal insufficiency	Up to 0.35 mg/kg/wk (dose should be given 4 h after dialysis)
AIDS wasting	Consult adult text
Adult GHD	Starting 0.2 mg/d (range 0.15-0.30 mg/d) increase by increments of 0.1-0.2 mg/d every 1-2 m or starting 0.006 mg/kg/d up to 0.025 mg/kg/day depending on age
SHOX deficiency	Up to 0.35 mg/kg/wk

**Depending on which brand of GH used the dosing may vary within the range listed.*

Table 3. GH doses recommended for different indications

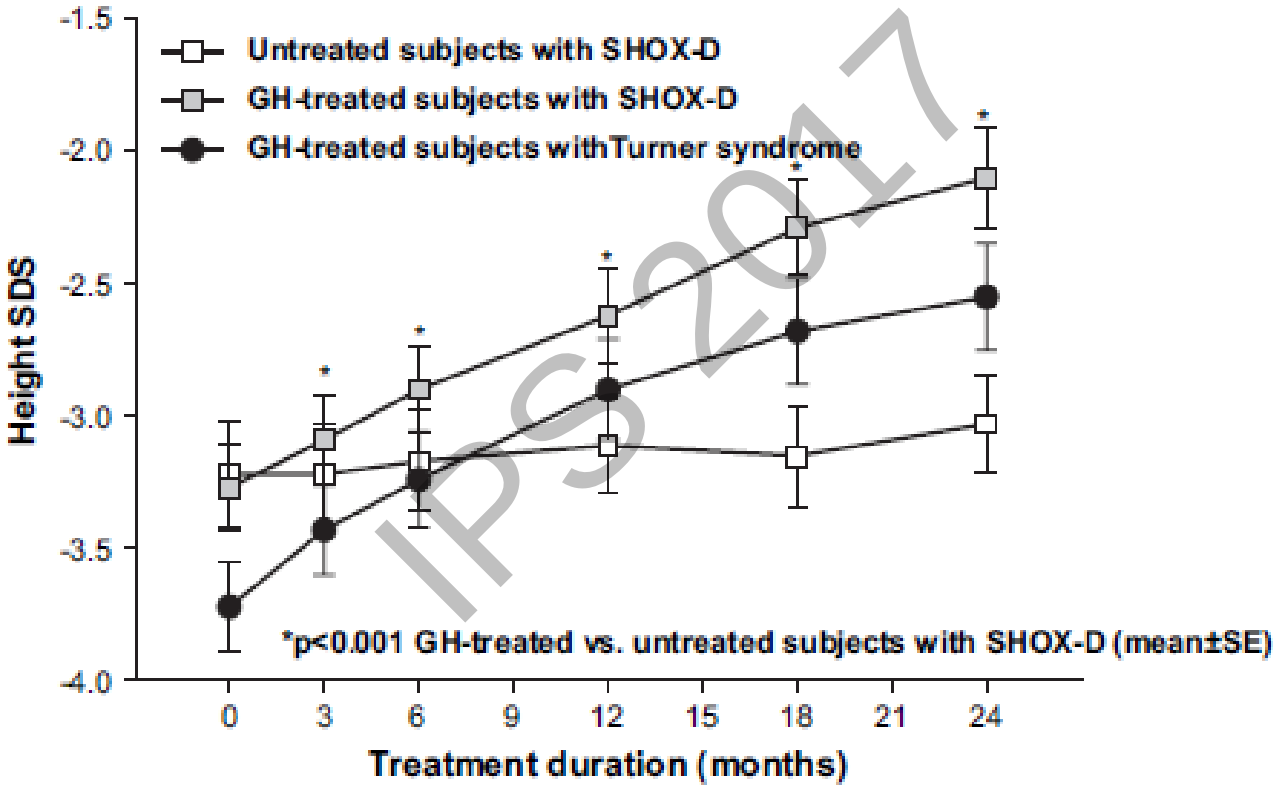
Indication	Europe (EMA) µg/kg/day	Japan (PMDA) mg/kg/week	USA (FDA)[1]	
			mg/kg/week	µg/kg/day
GHD	25–35[2]	0.175	0.16–0.30[2]	23–43
PWS	35	0.245	0.24	34
TS	45–50	0.35	0.33–0.47	47–67
CRI	45–50	0.175–0.35	0.35	50
SGA	35	0.23–0.47	0.47–0.48	67–69
SHOX haploinsufficiency	50	not approved	0.35	50
ISS	not approved	not approved	0.30–0.47	43–67
NS	not approved	not approved	up to 0.46	up to 66

Not all brands have been approved for each indication. GH dose = mg/kg/week:7 = µg/kg/day.
PWS = Prader-Willi syndrome; CRI = chronic renal insufficiency; NS = Noonan syndrome.
[1] Dose ranges reflect FDA-approved doses for same indication by different companies.
[2] May be increased in puberty in USA up to 0.70 mg/kg/week (100 µg/kg/day).

Towards Optimal Treatment with GH in Short Children and Adolescents

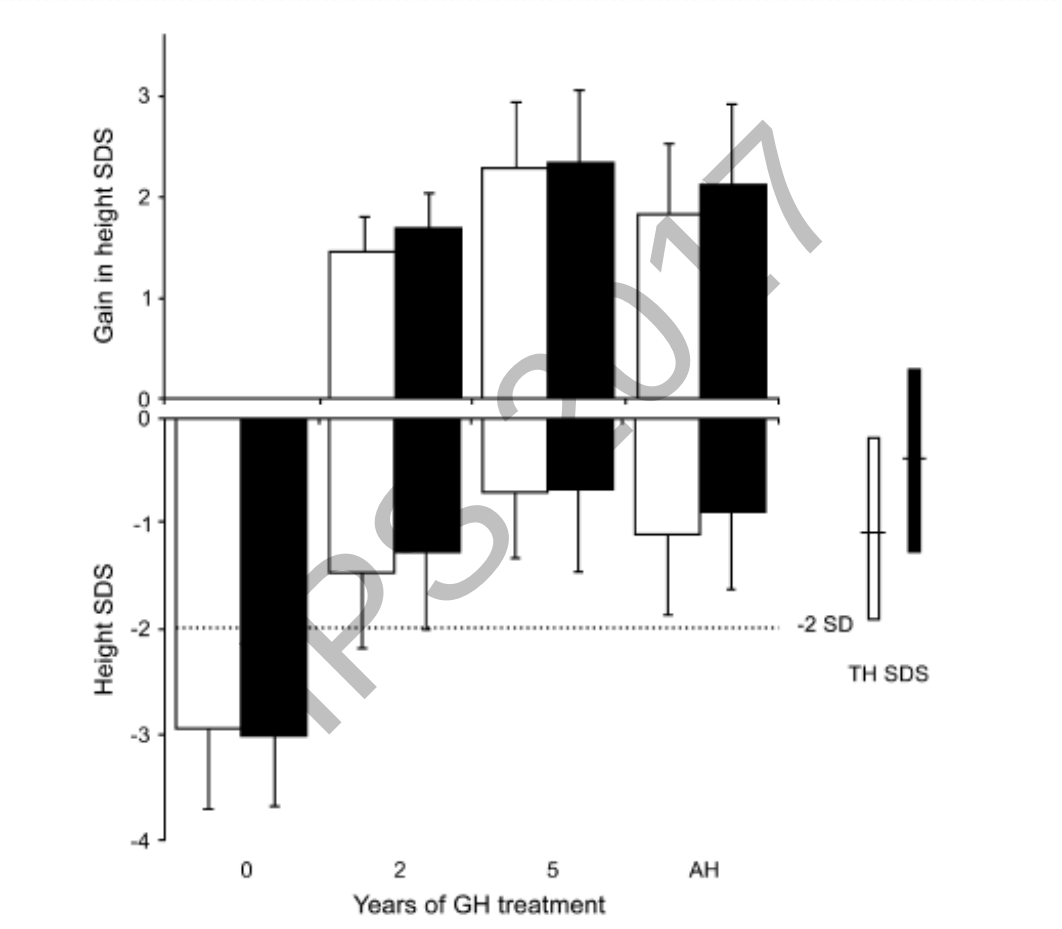
Horm Res Paediatr 2013;79:51–67
DOI: 10.1159/000347121

GH in TS and SHOX-D

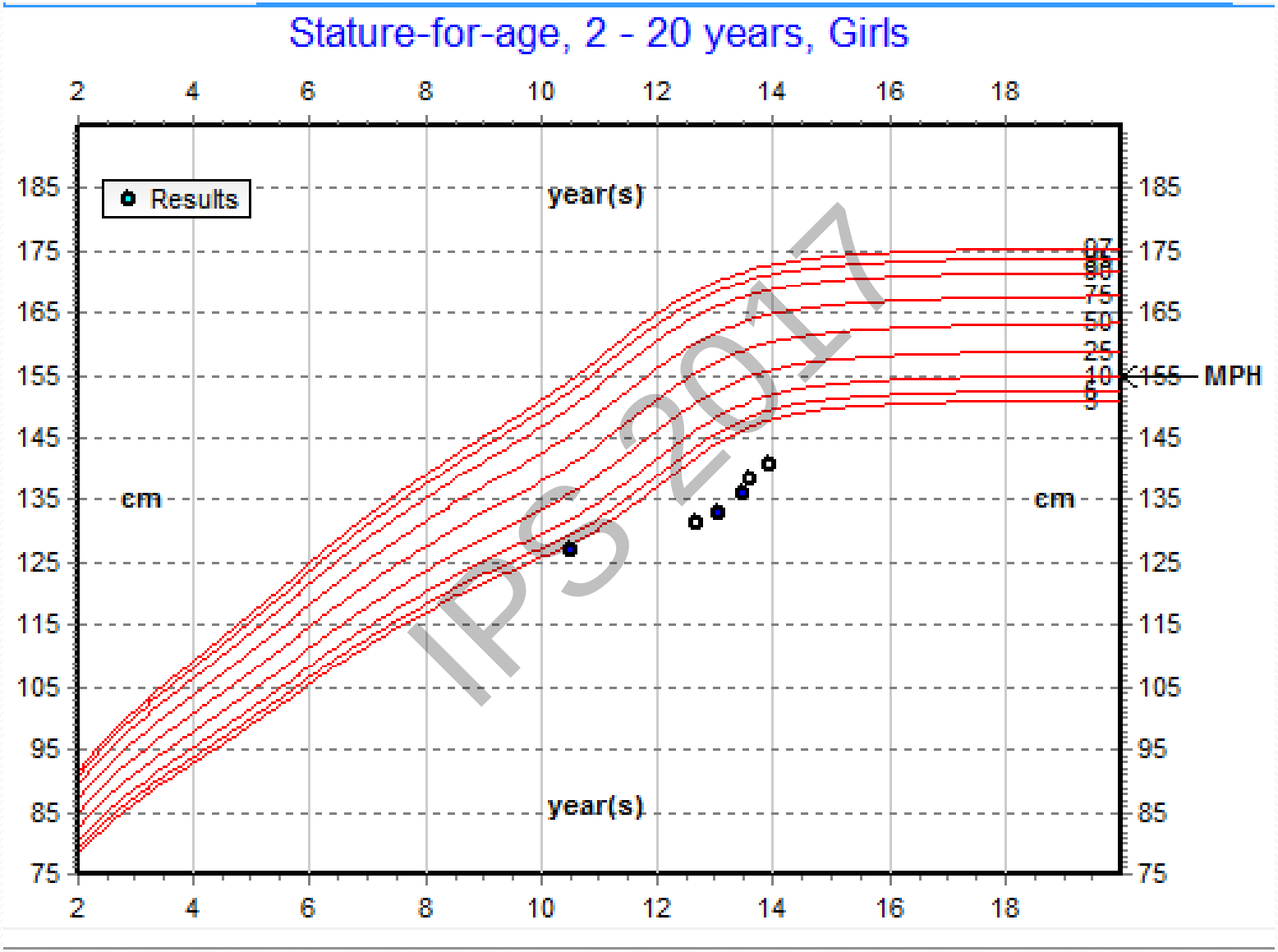


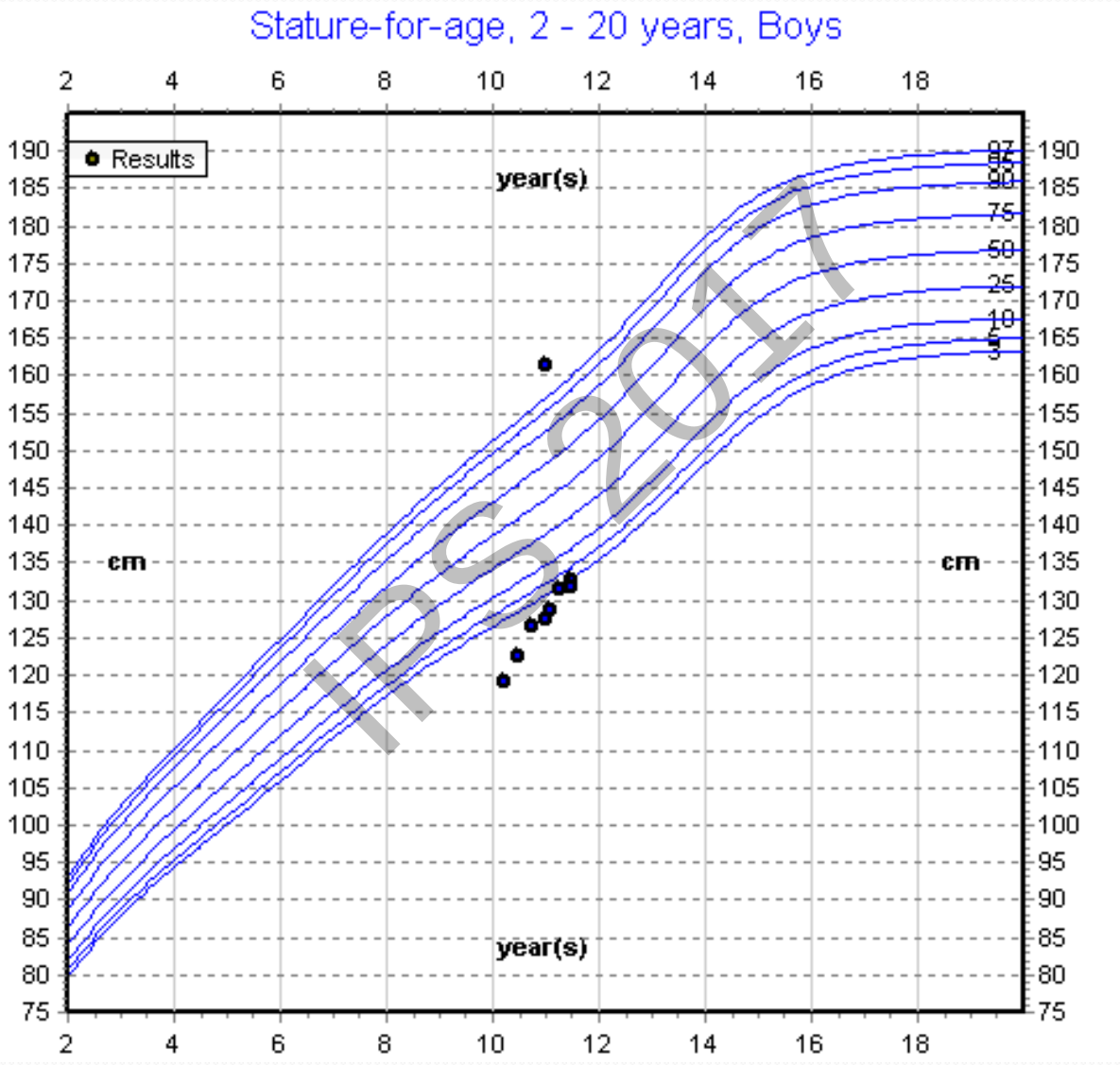
J Clin Endocrinol Metab 2007;92:222;

GH in SGA children

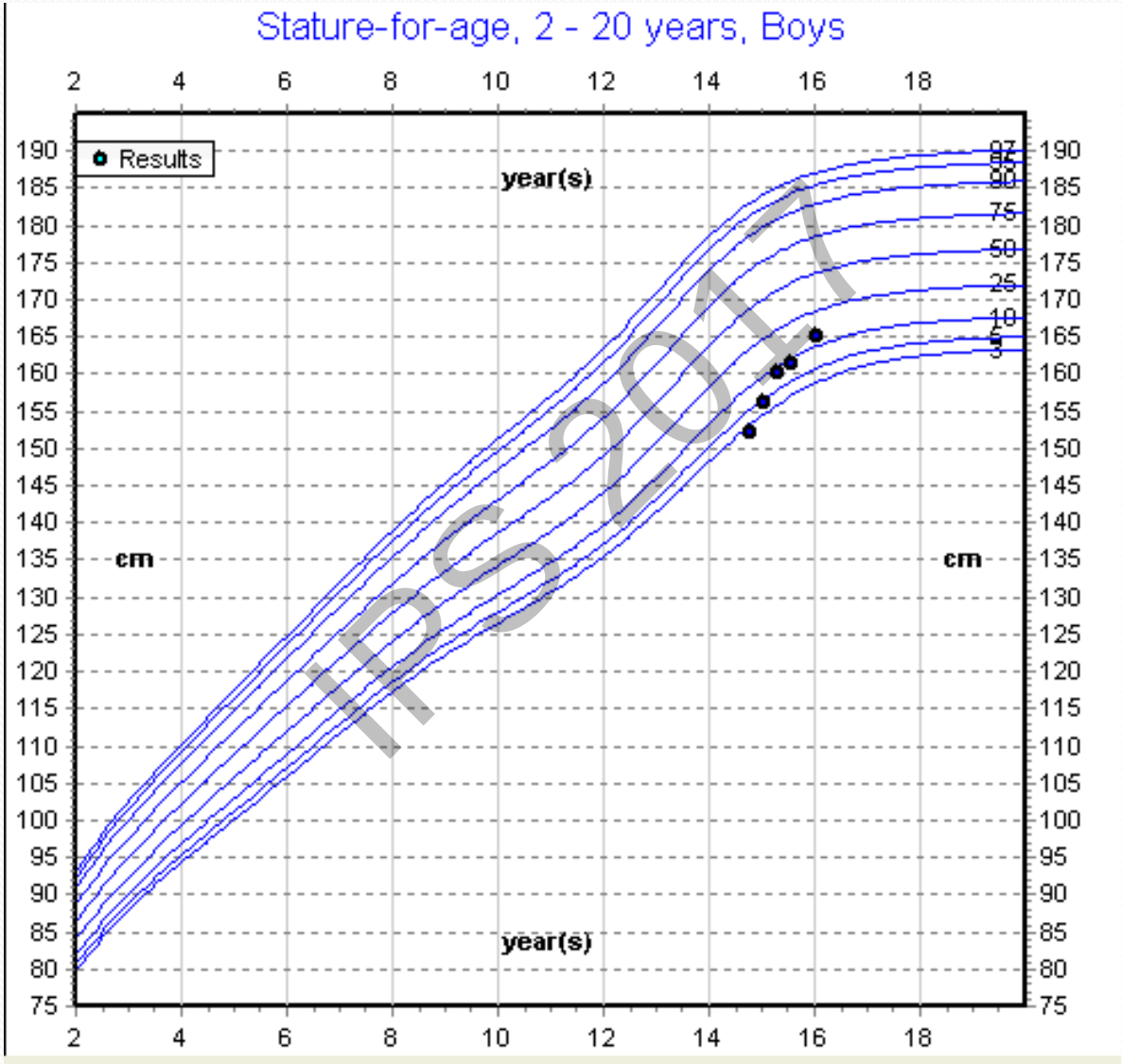


J Clin Endocrinol Metab 2003;88:3587

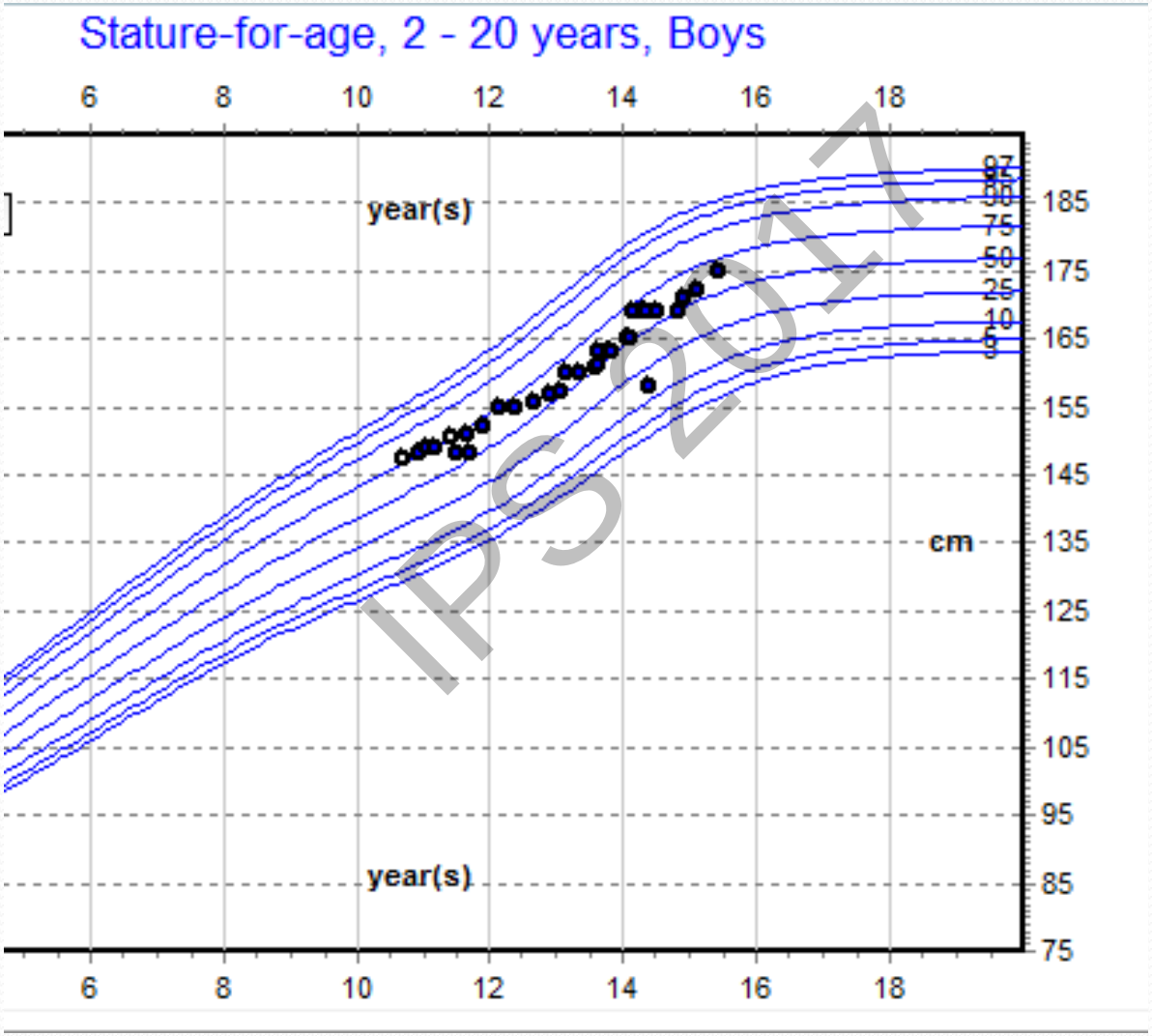

Stature-for-age, 2 - 20 years, Girls
Results
year(s)
cm
MPH
IPS 2017


Stature-for-age, 2 - 20 years, Boys
Results
year(s)
cm
year(s)
cm
97
95
90
75
50
25
10
5
3
IPS2017

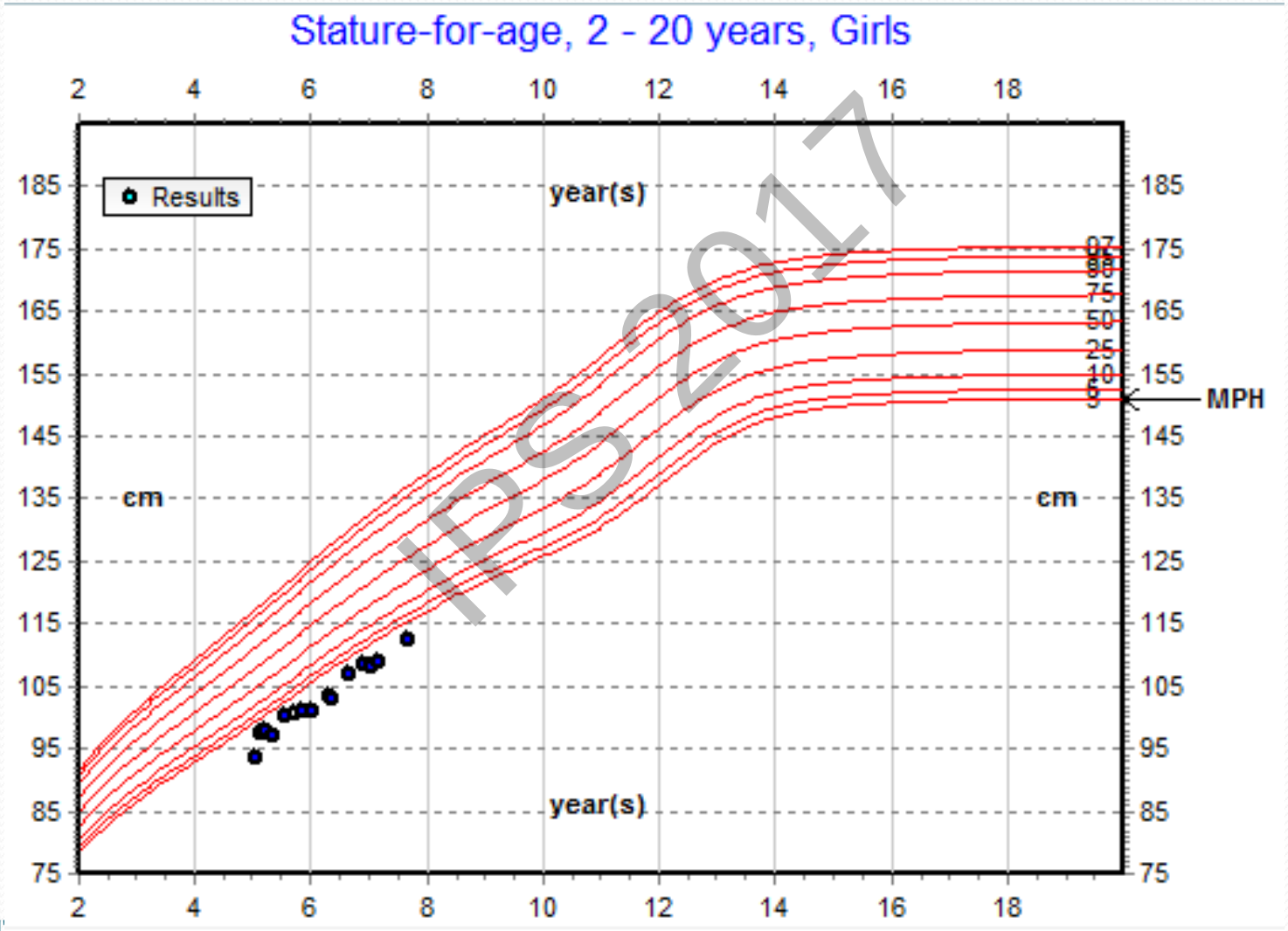
Constitutional growth delay



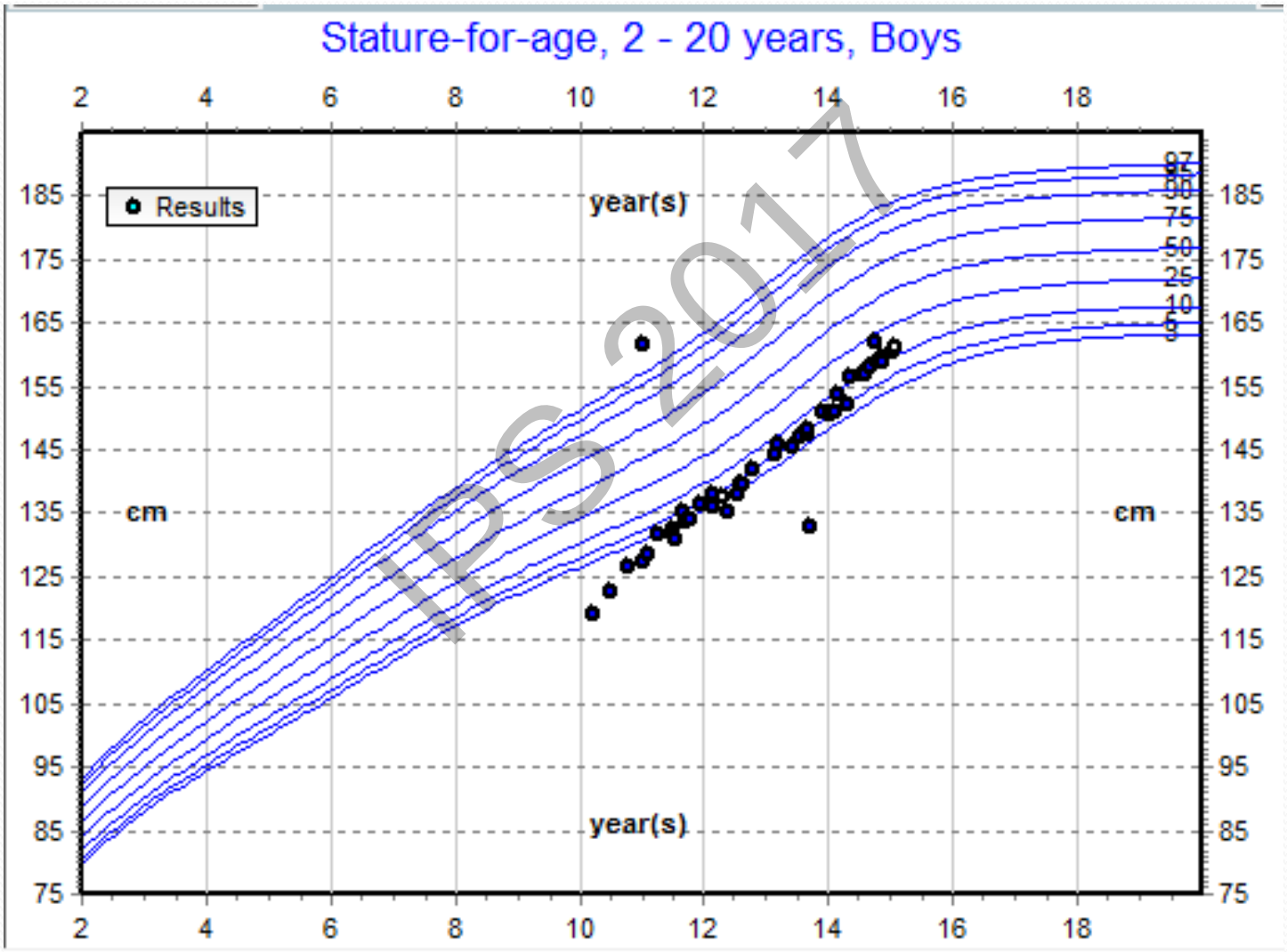
Poorly controlled diabetic

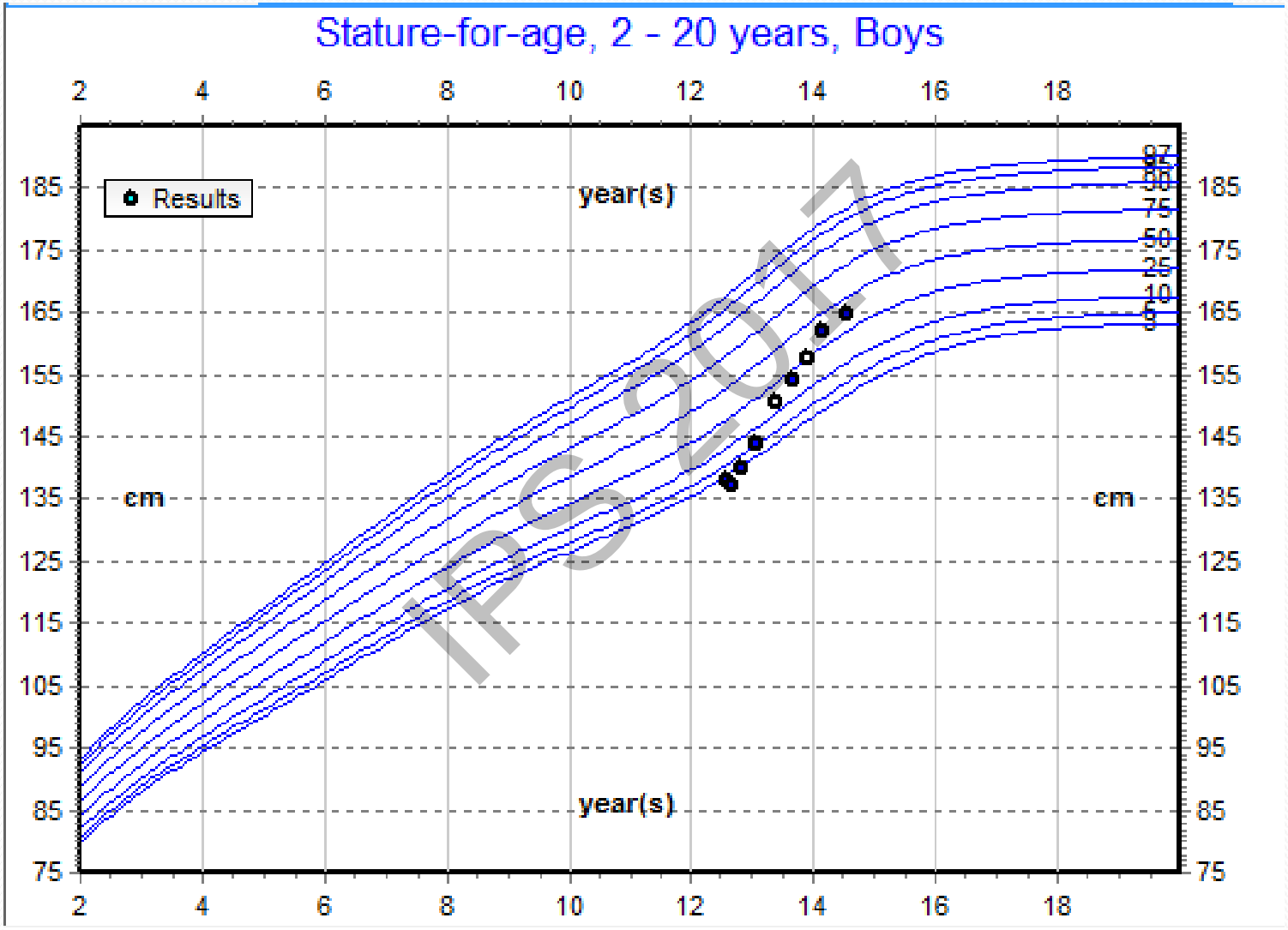


Familial short stature



GHD


Stature-for-age, 2 - 20 years, Boys
Results
year(s)
cm
year(s)
cm
97
90
75
50
25
10
3
185
175
165
155
145
135
125
115
105
95
85
75
2
4
6
8
10
12
14
16
18


Stature-for-age, 2 - 20 years, Boys
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year(s)
cm
year(s)
cm
IPS 2017
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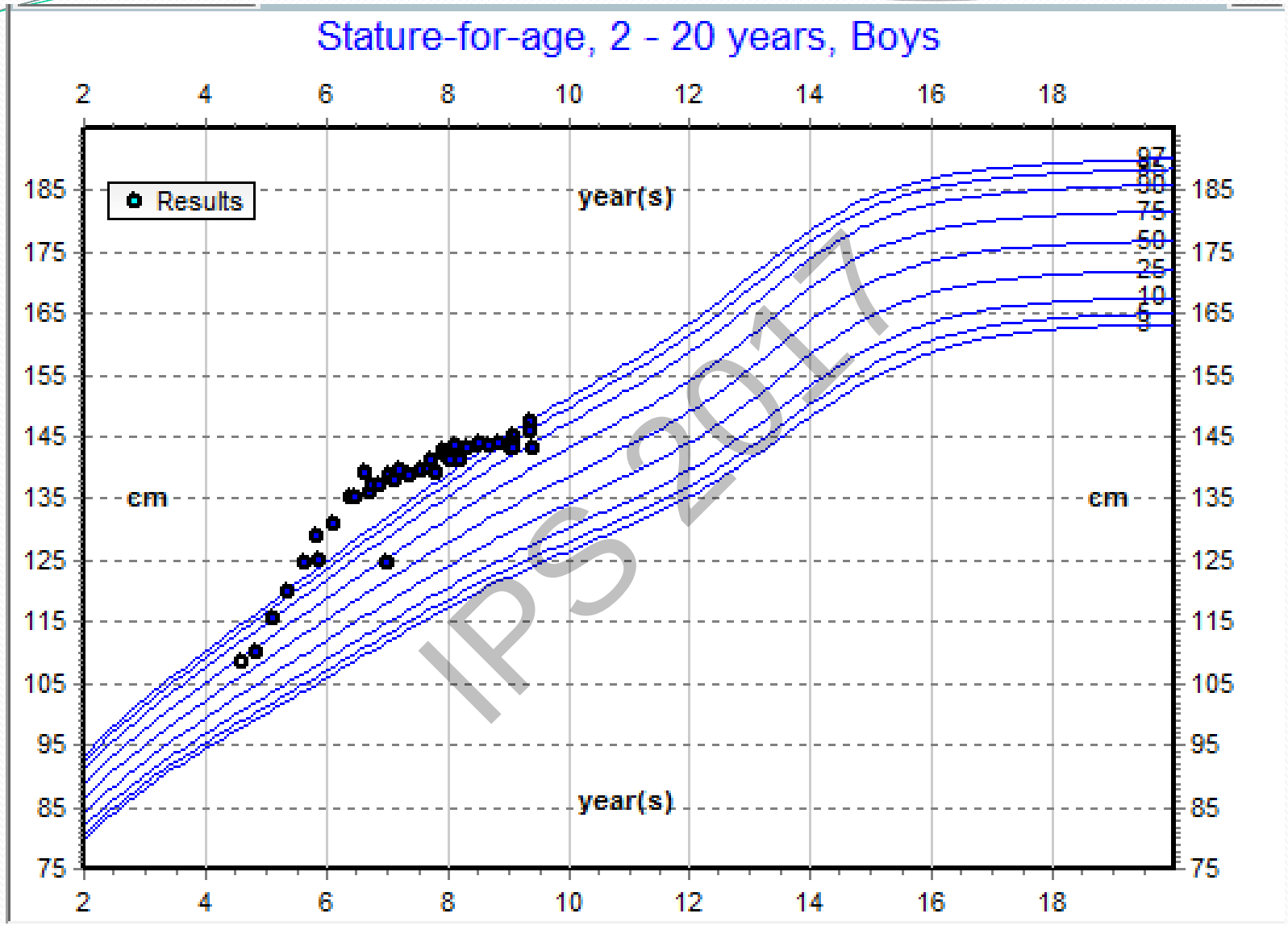
135
125
115
105
95
85
75
97
95
90
75
50
25
10
5
3

Chart | Calculate GV | Plot All

Stature-for-age, 2 - 20 years, Boys

Date	Age	Value	Centile	z-score/SDS	GV	Calculation	Medical Service	Plot
15/09/2012	12 years	138.00 cm	2.15	-2.02	☐		Paediatrics-Endocrinology	☑
09/10/2012	12 years	137.00 cm	1.54	-2.16	☐		Paediatrics-Endocrinology	☑
09/12/2012	12 years	140.00 cm	2.90	-1.90	☐		Paediatrics-Endocrinology	☑
10/03/2013	13 years	143.80 cm	5.33	-1.61	☐		Paediatrics-Endocrinology	☑
07/07/2013	13 years	(c) 150.60 cm	14.56	-1.06	☑		Med-Endocrinology	☑
09/10/2013	13 years	154.00 cm	19.29	-0.87	☐		Paediatrics-Endocrinology	☑
08/01/2014	13 years	(c) 157.70 cm	26.00	-0.64	☐		Paediatrics-Endocrinology	☑
13/04/2014	14 years	162.00 cm	34.09	-0.41	☐		Paediatrics-Endocrinology	☑
30/08/2014	14 years	164.80 cm	36.99	-0.33	☑	12.4 CM/YEARS	Paediatrics-Endocrinology	☑


Stature-for-age, 2 - 20 years, Boys
Results
year(s)
cm
year(s)
cm
97
95
90
75
50
25
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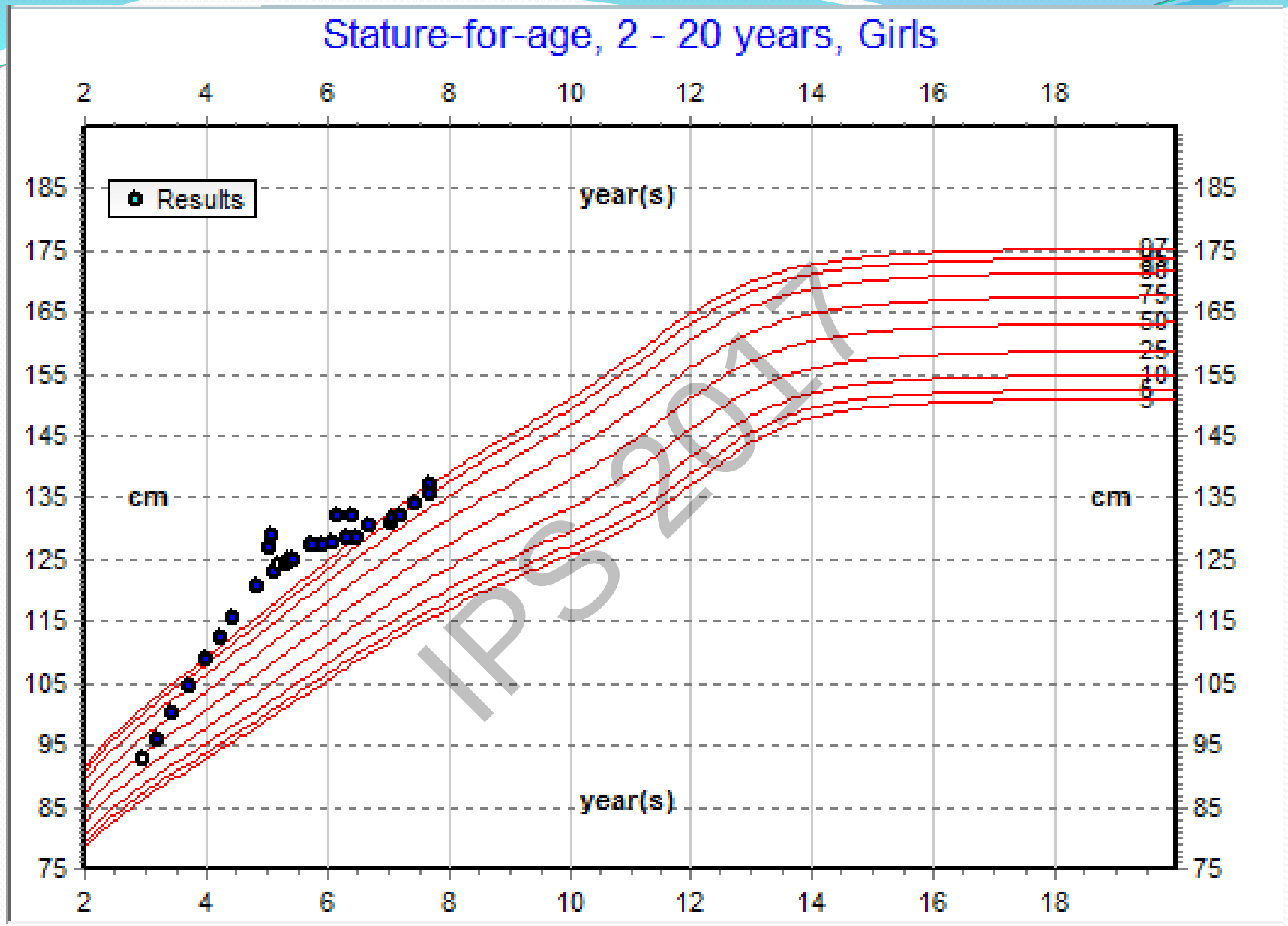
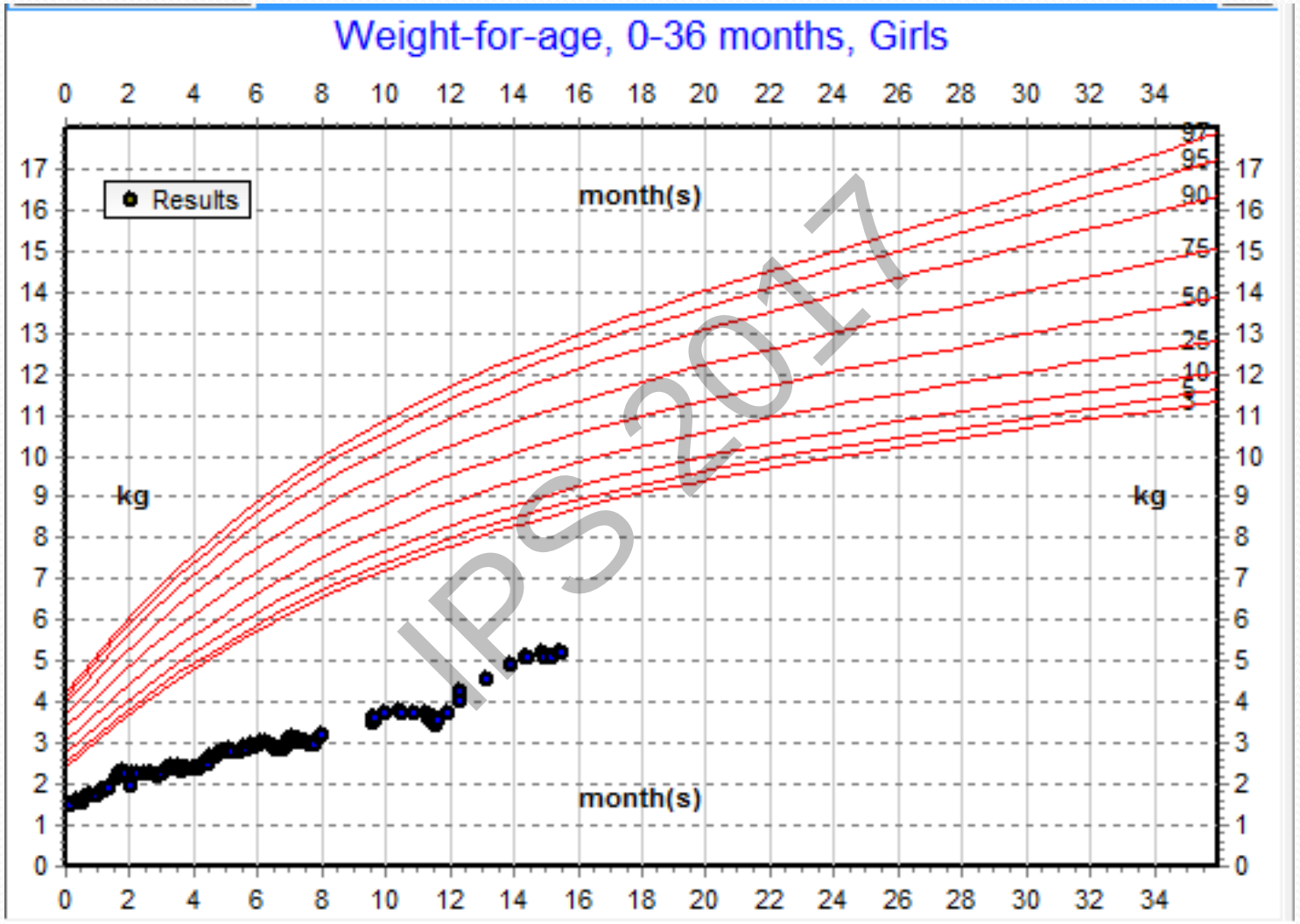
5
3
IPS 2017


Stature-for-age, 2 - 20 years, Girls
Results
year(s)
cm
cm
year(s)
IPS 2017
2
4
6
8
10
12
14
16
18
185
175
165
155
145
135
125
115
105
95
85
75


Weight-for-age, 0-36 months, Girls
Results
month(s)
kg
97
95
90
75
50
25
10
5
3
IPS 2017
month(s)
kg

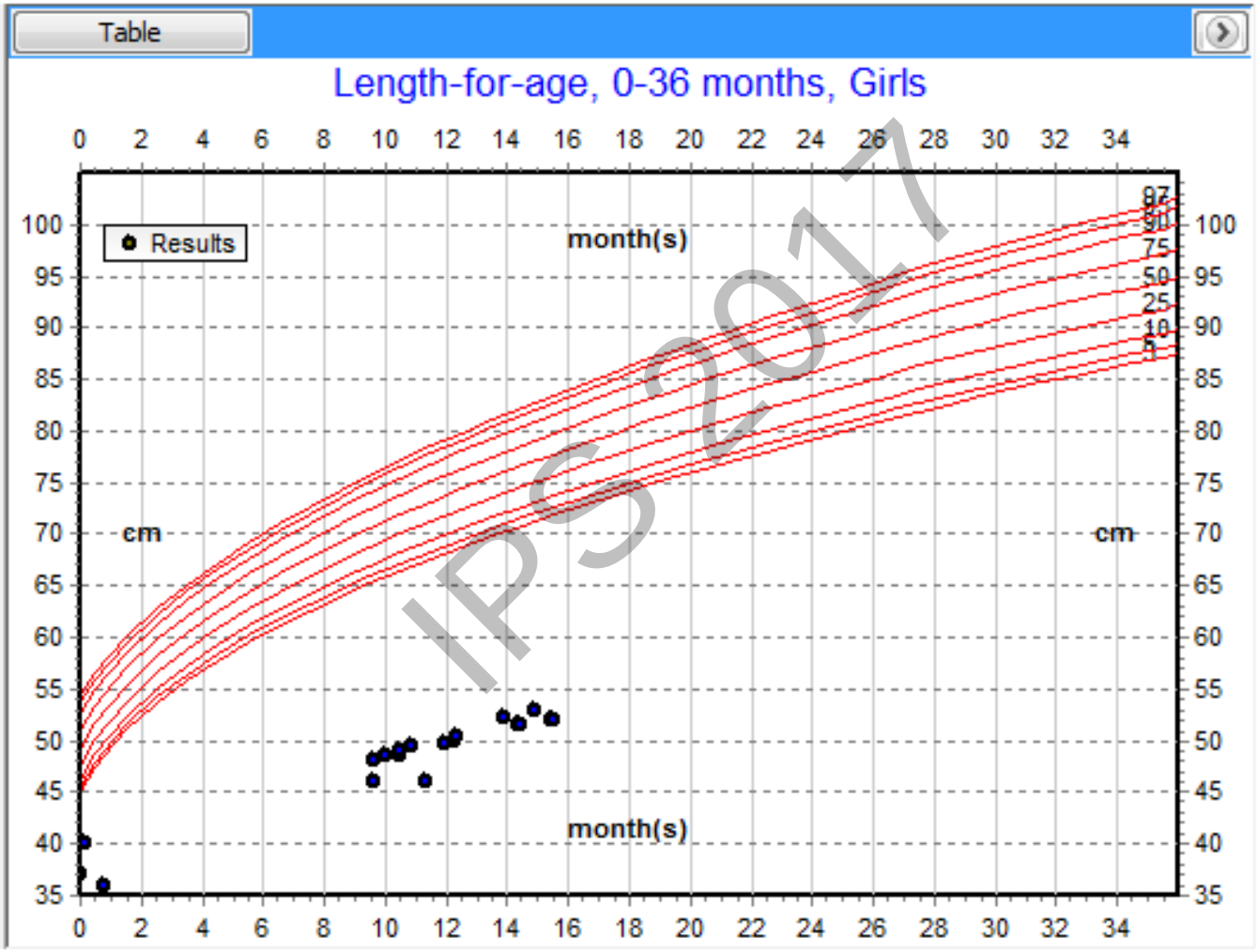
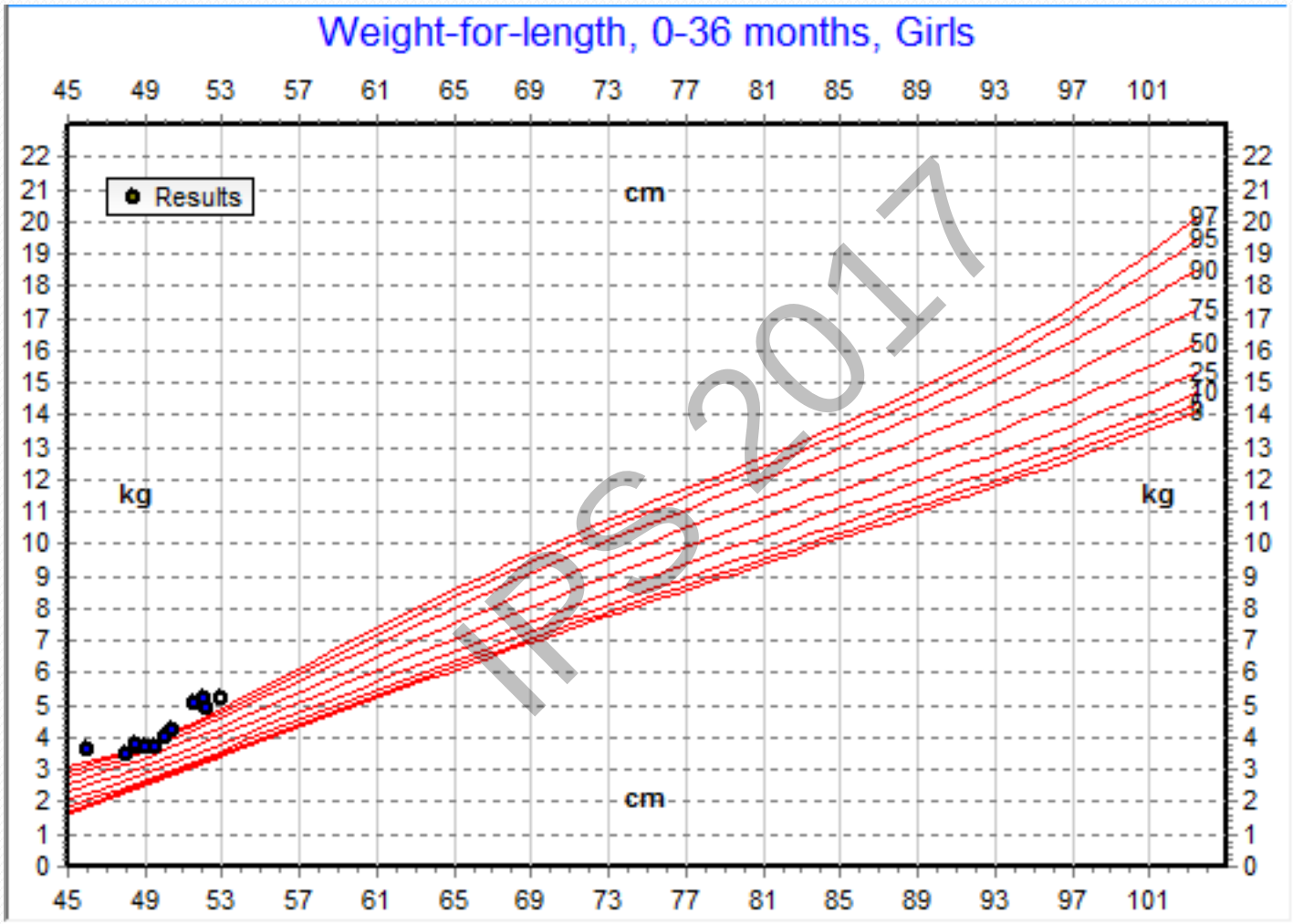


Table
Length-for-age, 0-36 months, Girls
Results
month(s)
cm
cm
month(s)
97
90
75
50
25
10
5
IPS 2017


Weight-for-length, 0-36 months, Girls
Results
cm
kg
kg
cm
97
95
90
75
50
25
10
5
3
IPS 2017

Special considerations .. TS

Special considerations .. TS

- Thyroid
- Celiac
- Timing of Estrogen

Special considerations .. CKD

Special considerations .. CKD

- Nutrition
- Anemia
- Metabolic acidosis
- Hypocalcemia

Special considerations … PWS

- Extreme obesity
- Sleep apnea
- Uncontrolled diabetes

Other treatment considerations

- Oxandrolone
- Testosterone
- IGF-1
- GnRH analogues
- Aromatase inhibitors

Deining successful 1st year response to GH

- Change in Ht SDS > 0.5
- Ht velocity increment more than 3 cm/yr
- Ht velocity SDS more than +1

Conclusion

- It is important to recognize Normal pattern and variants of Growth
- Accurate measurement and monitoring of GV.
- The majority of short children do not have endocrine cause.
- Diagnosing GHD is not easy task and is subject to false results
- Approved indications for GH have expanded over the years
- Long term safety of GH is still unknown


Thank You
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