Growth hormone therapy

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

Objectives

- Approved indications for GH therapy.
- Case studies of GH therapy
- Monitoring response to therapy
- Adverse effects
- Long term safety

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

- What are the adverse effects of GH?

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.

- What are the approved indications for GH therapy?

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

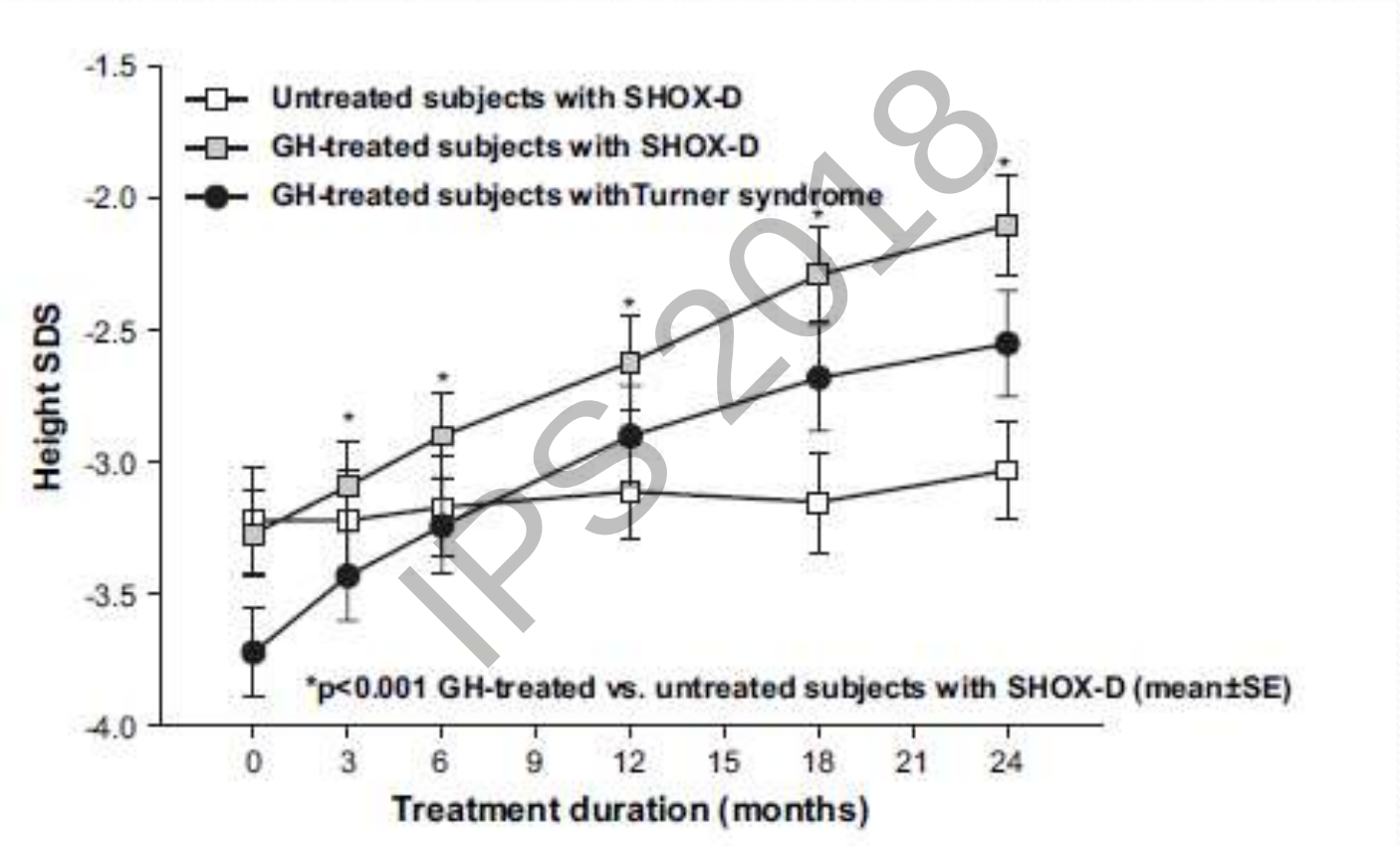
Indication	Europe (EMA) µg/kg/day	Japan (PMDA) mg/kg/week	USA (FDA)[1]	
			mg/kg/week	µg/kg/day
GHD	25–35[2]	0.175	0.16–0.30[2]	23–43
PWS	35	0.245	0.24	34
TS	45–50	0.35	0.33–0.47	47–67
CRI	45–50	0.175–0.35	0.35	50
SGA	35	0.23–0.47	0.47–0.48	67–69
SHOX haploinsufficiency	50	not approved	0.35	50
ISS	not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

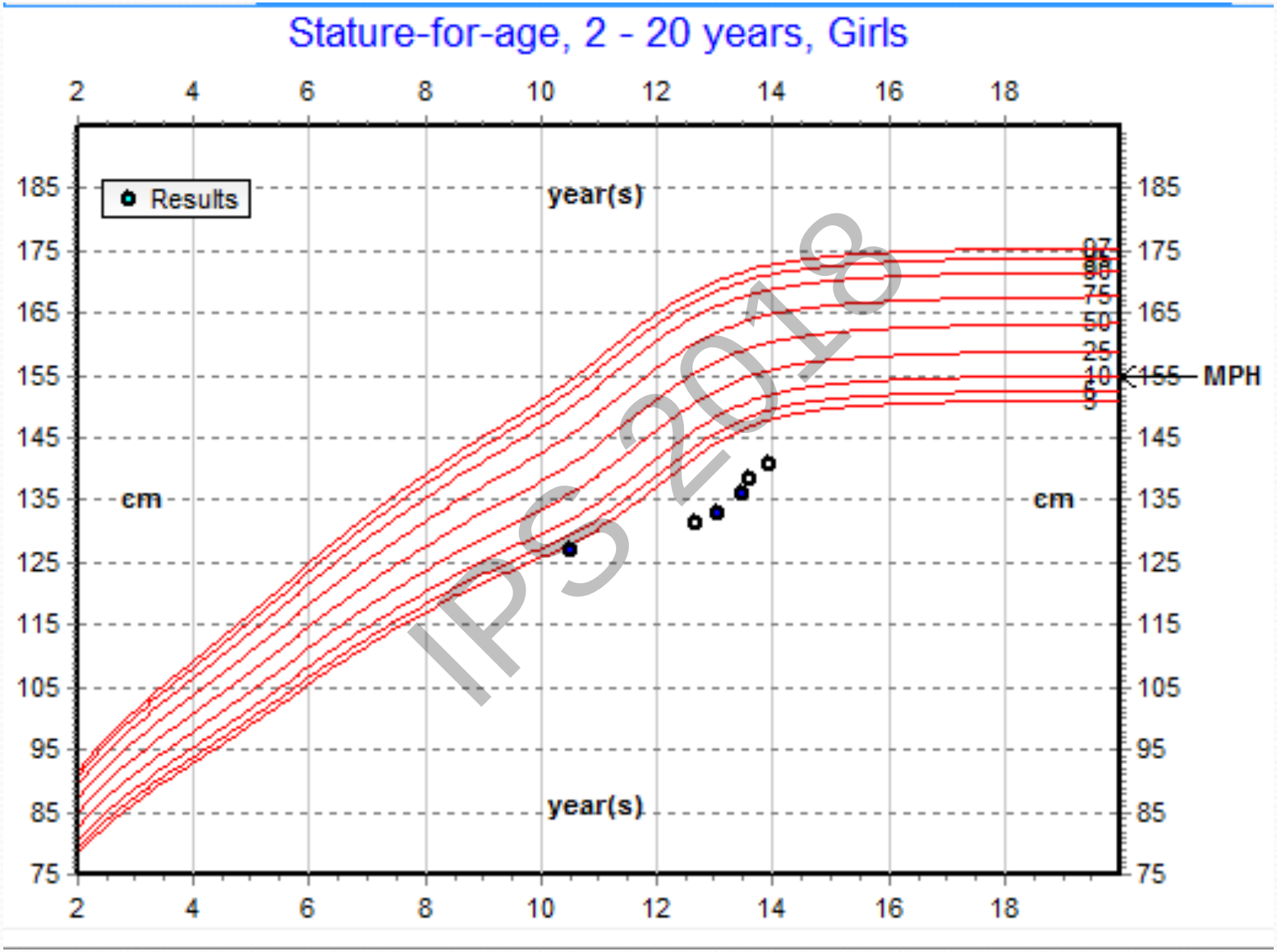
Towards Optimal Treatment with GH in Short Children and Adolescents

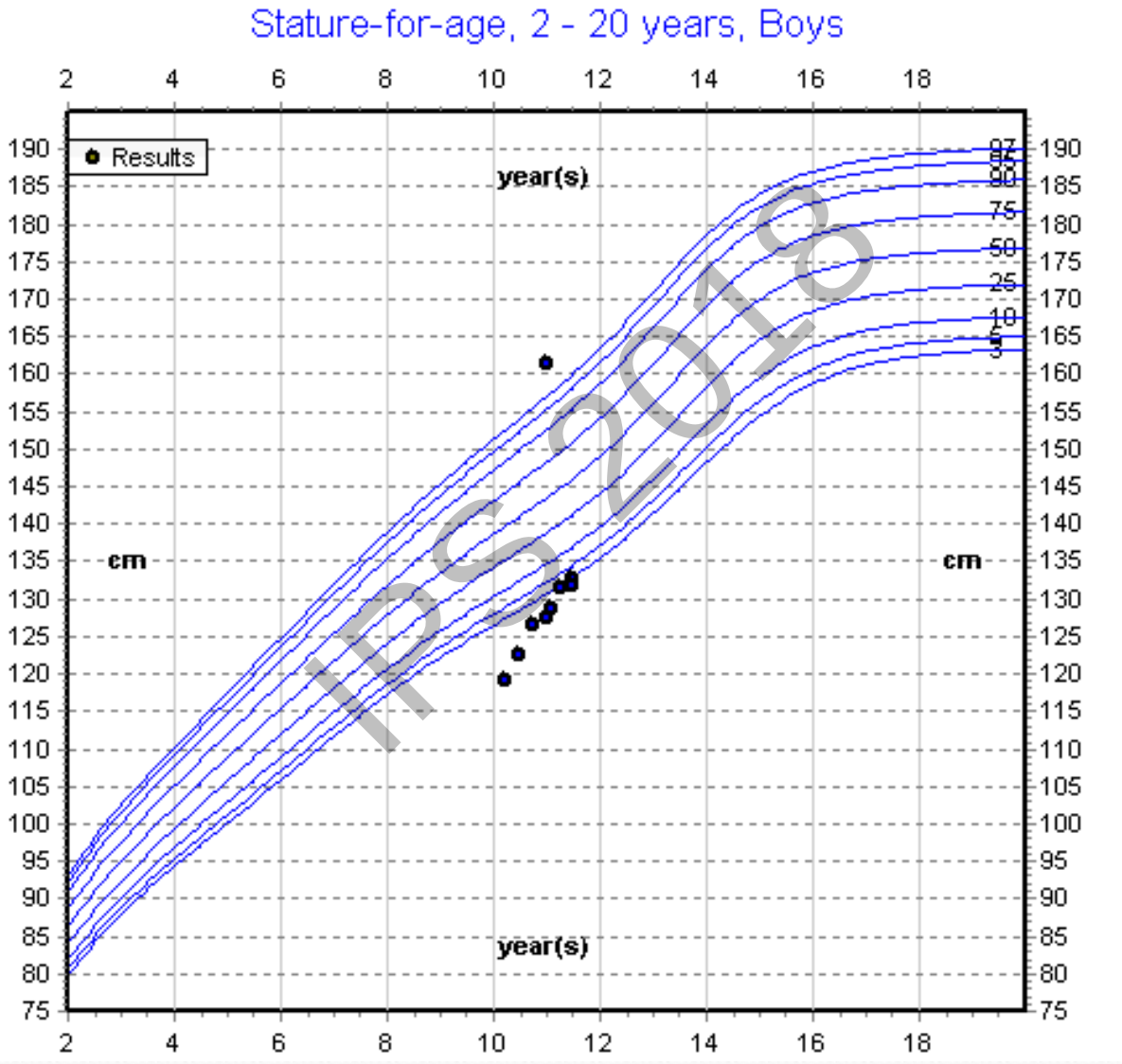
Horm Res Paediatr 2013;79:51–67
DOI: 10.1159/000347121

GH in TS and SHOX-D

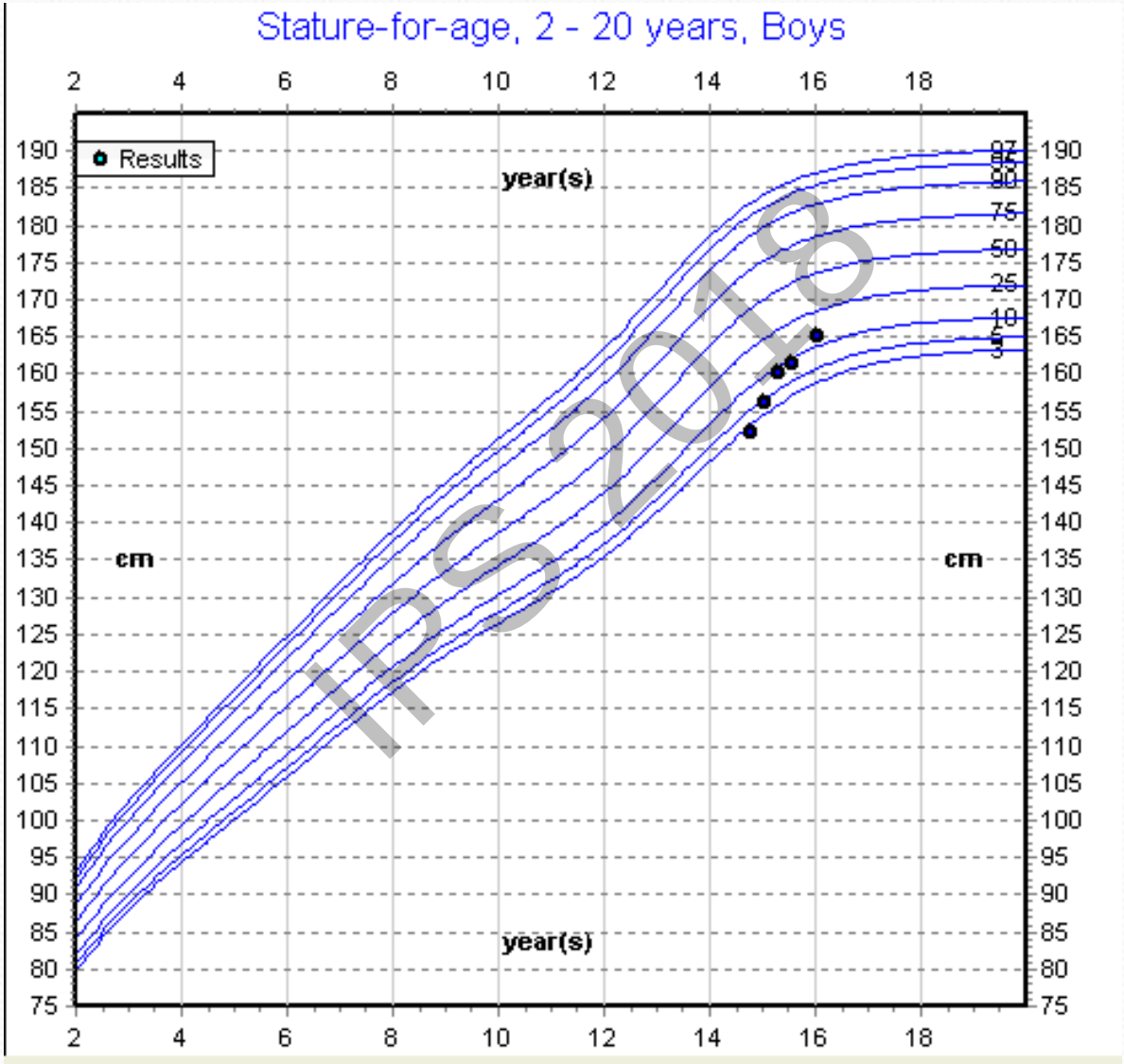


J Clin Endocrinol Metab 2007;92:222;

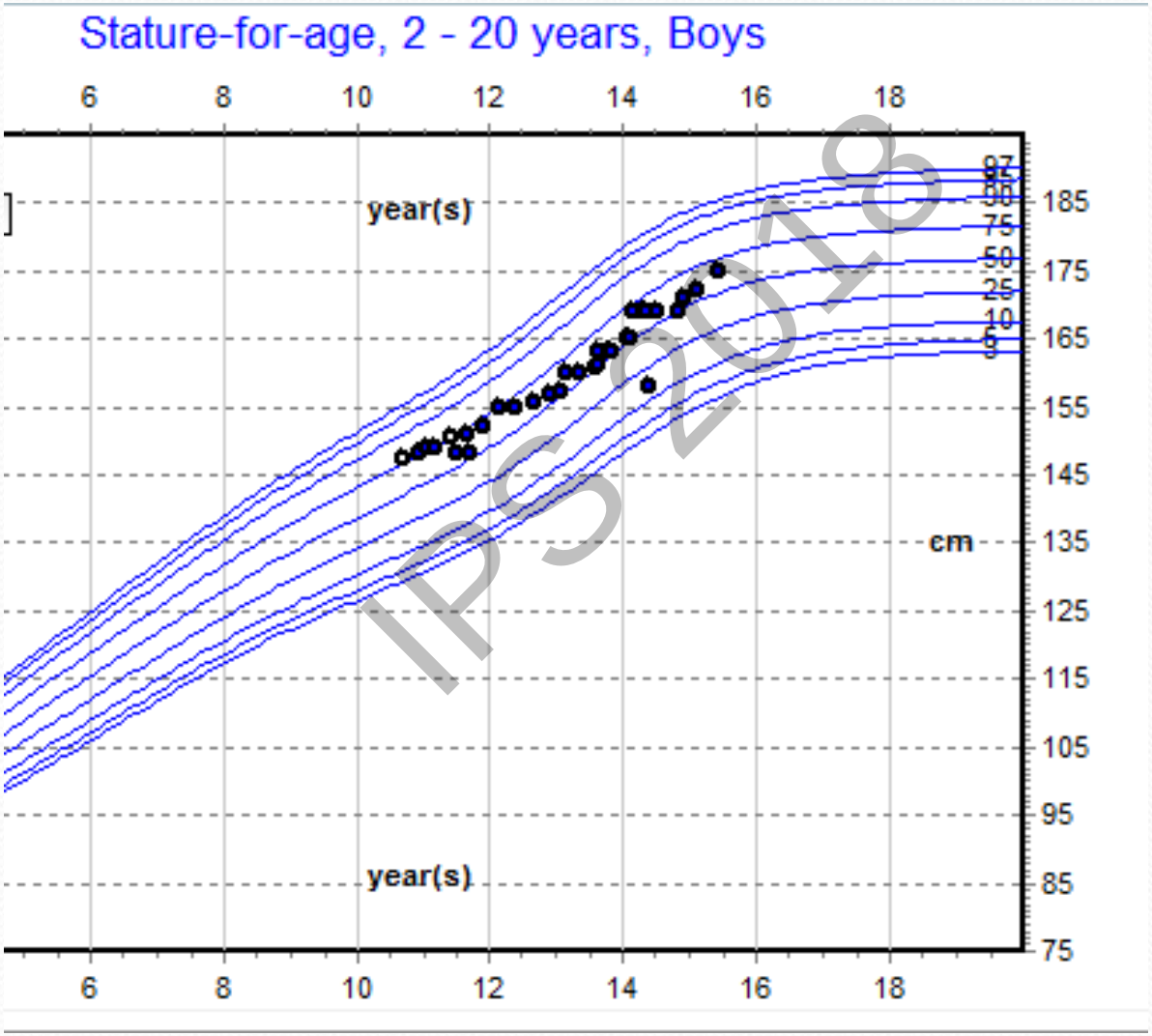

Stature-for-age, 2 - 20 years, Girls
Results
year(s)
cm
MPH
IPS 2018


Stature-for-age, 2 - 20 years, Boys
Results
year(s)
cm
year(s)
cm
97
95
90
75
50
25
10
5
3
IPS 2018

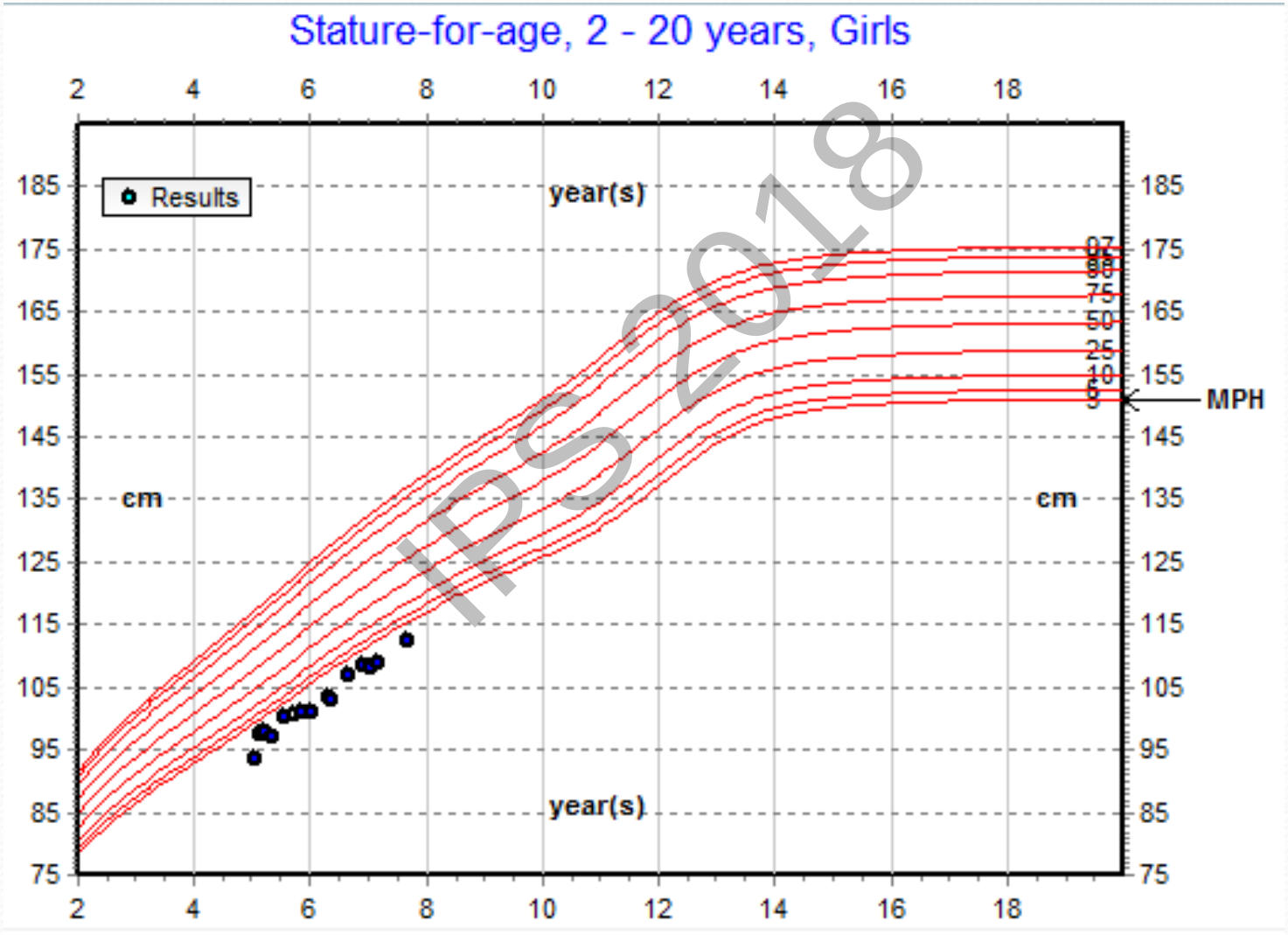
Constitutional growth delay



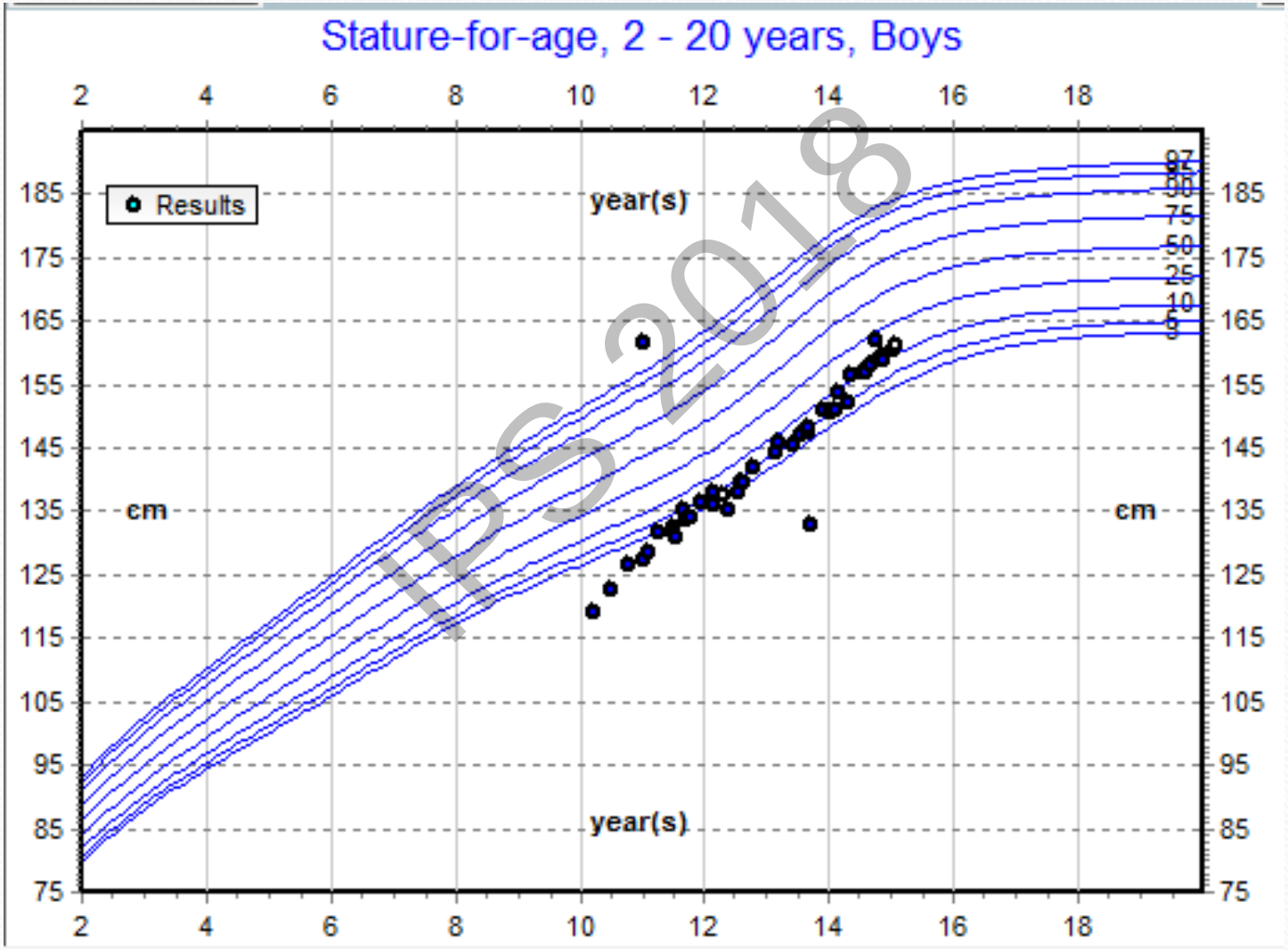
Poorly controlled diabetic



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
BS 2018

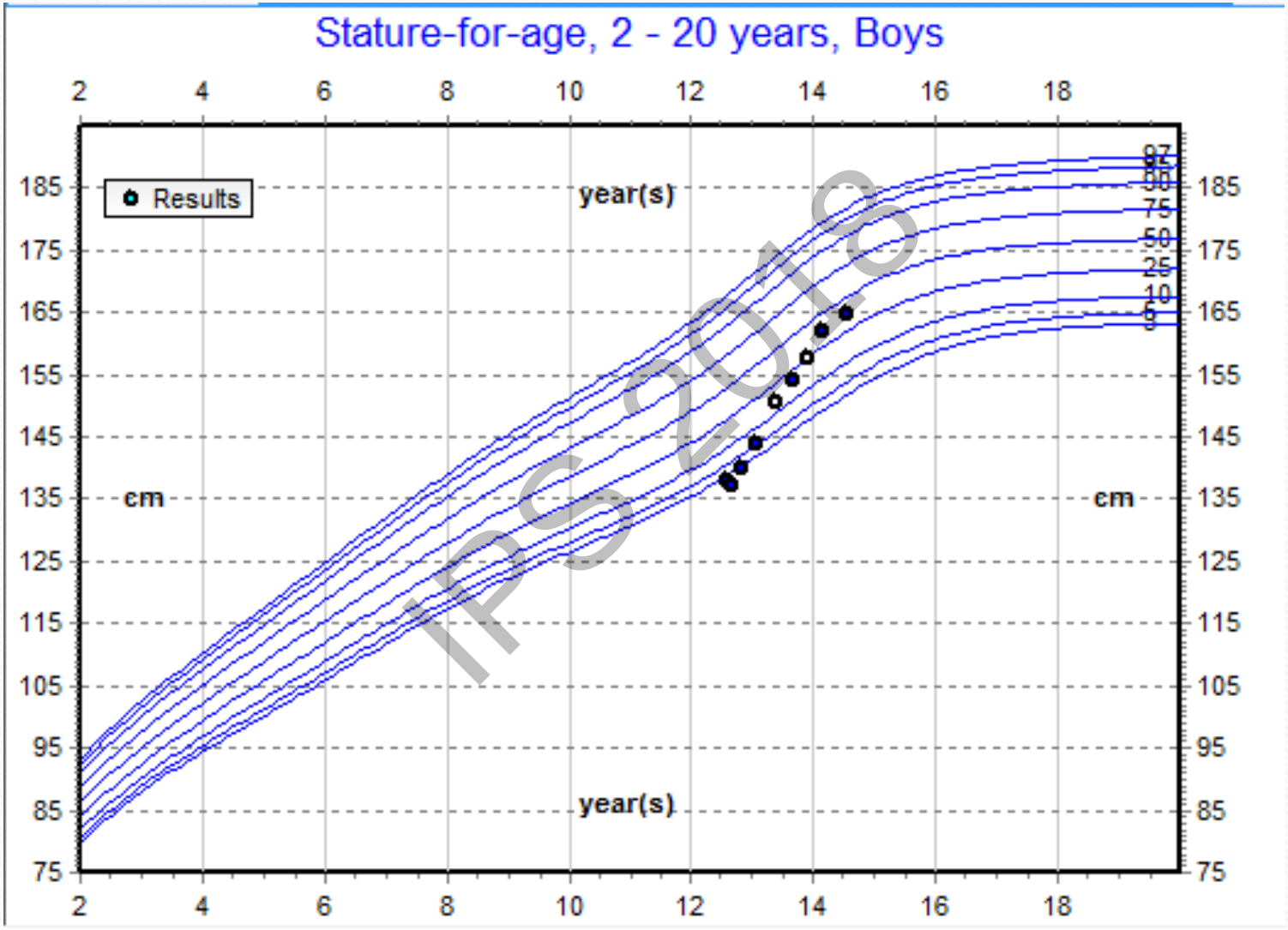
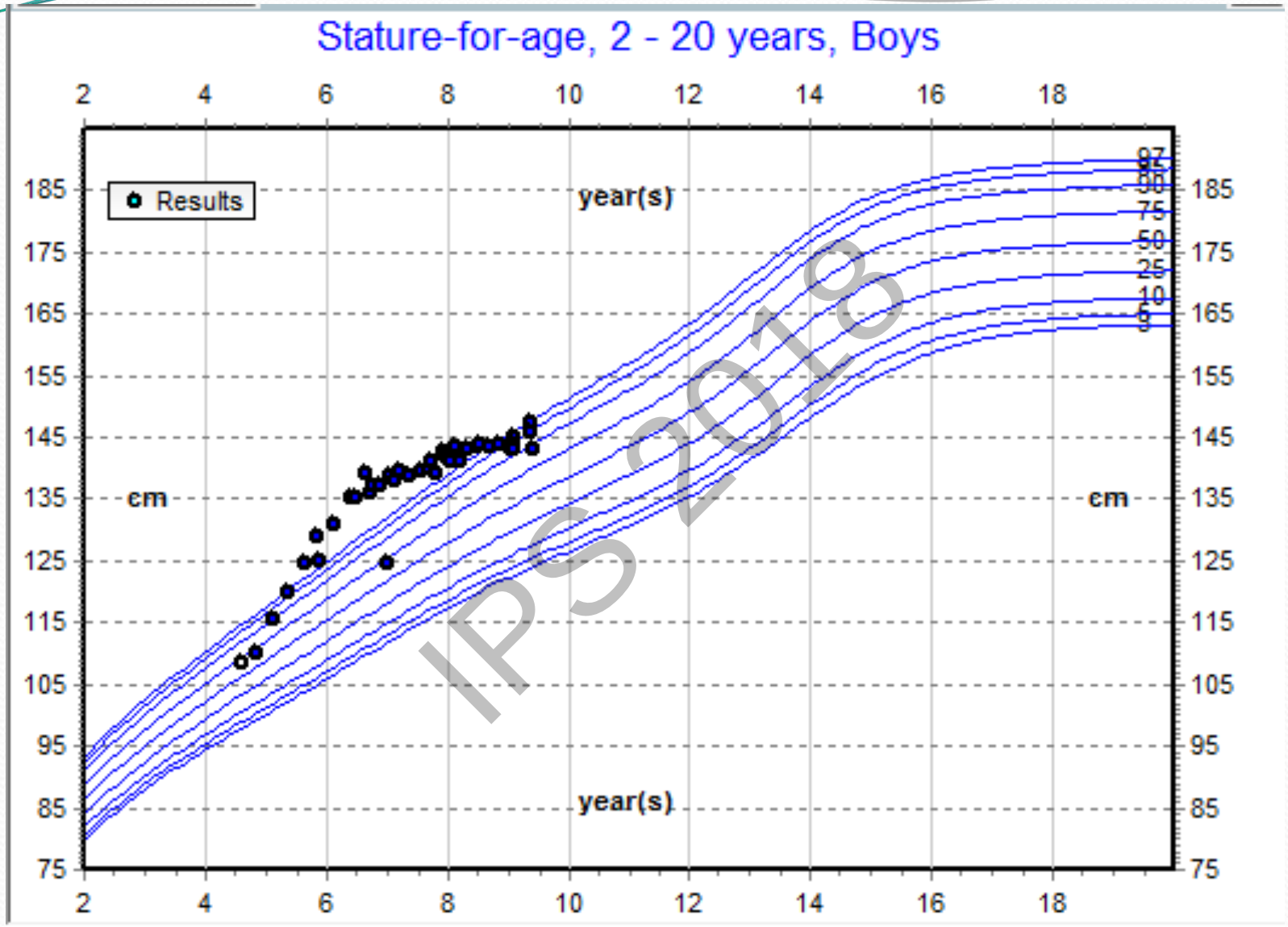
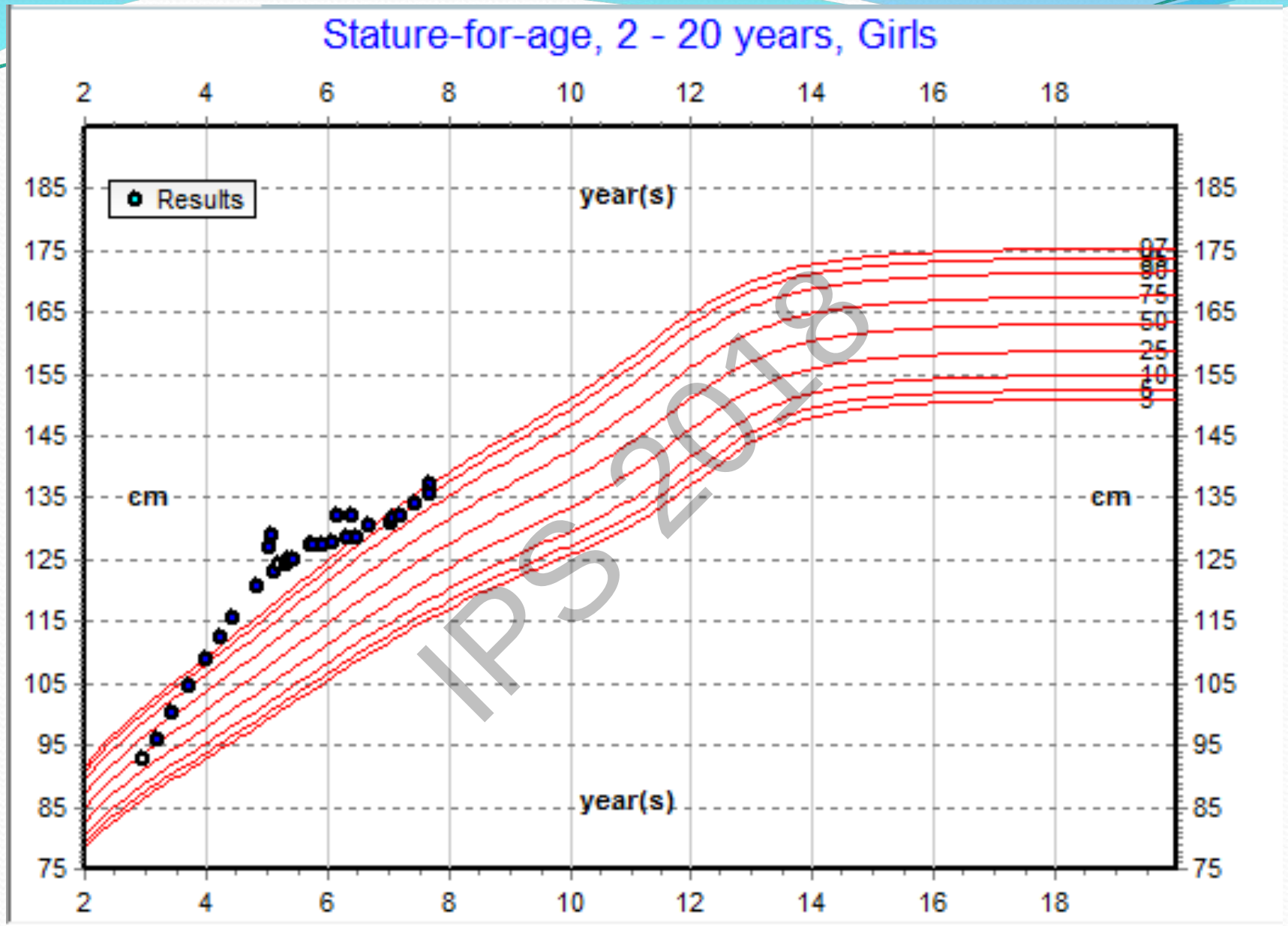

Stature-for-age, 2 - 20 years, Boys
Results
year(s)
cm
year(s)
cm
97
95
90
75
50
25
10
5
3
IPS 2015

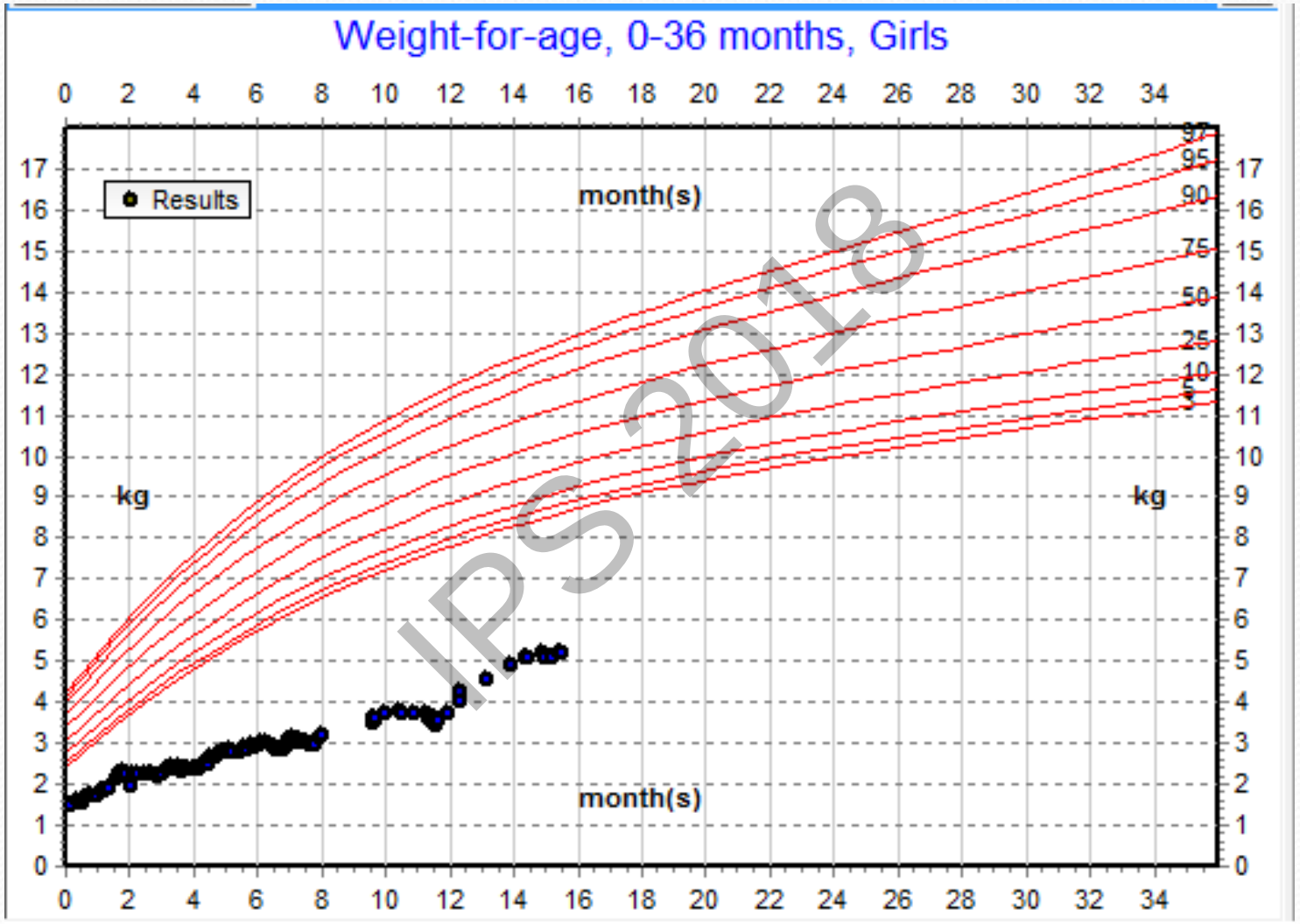
Chart | Calculate GV | Plot All

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
10
5
3
IPS 2018


Stature-for-age, 2 - 20 years, Girls
Results
year(s)
cm
cm
year(s)
97
95
90
75
50
25
10
5
3
IPS 2018


Weight-for-age, 0-36 months, Girls
Results
month(s)
kg
97
95
90
75
50
25
10
5
3
IPS 2018
month(s)
kg

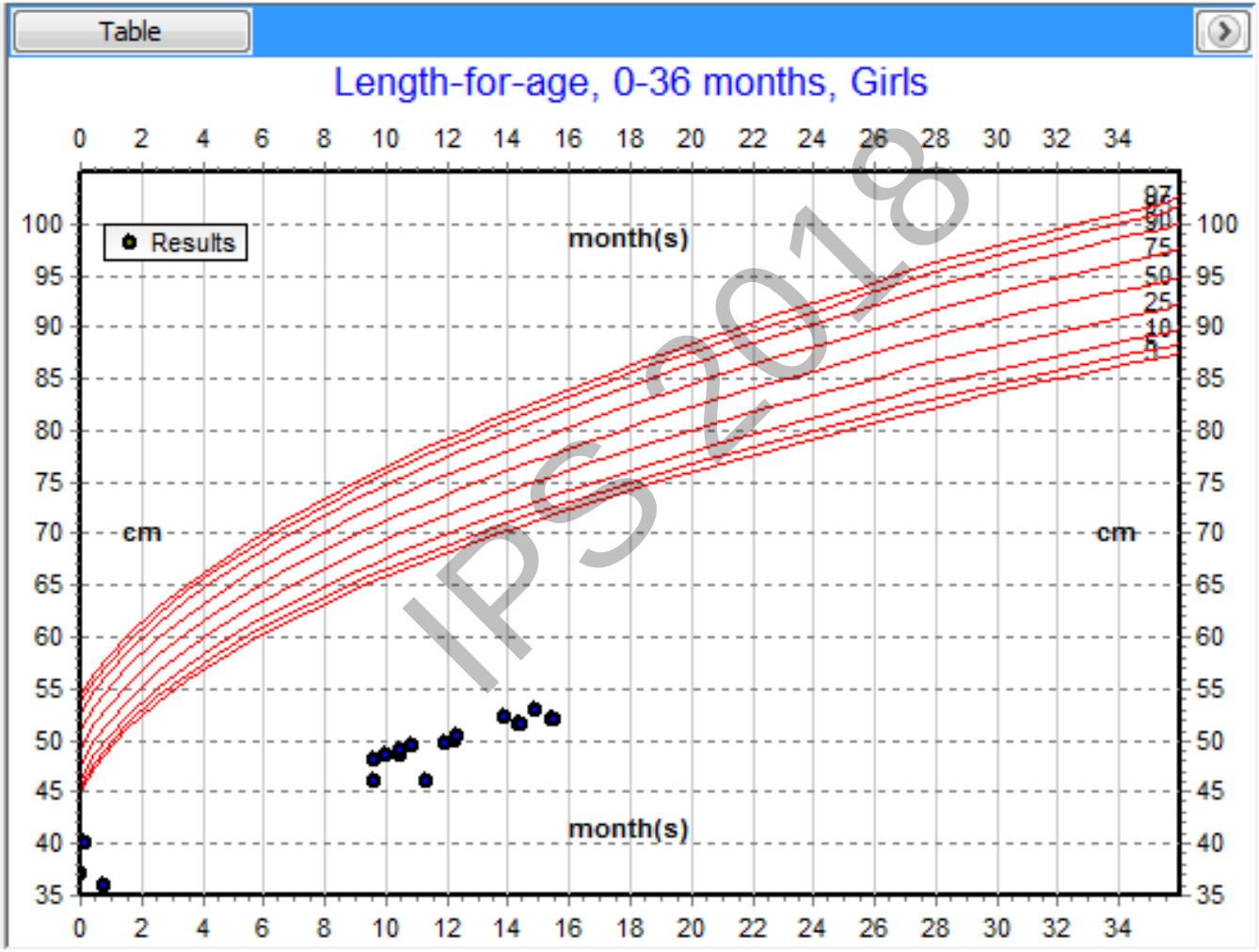
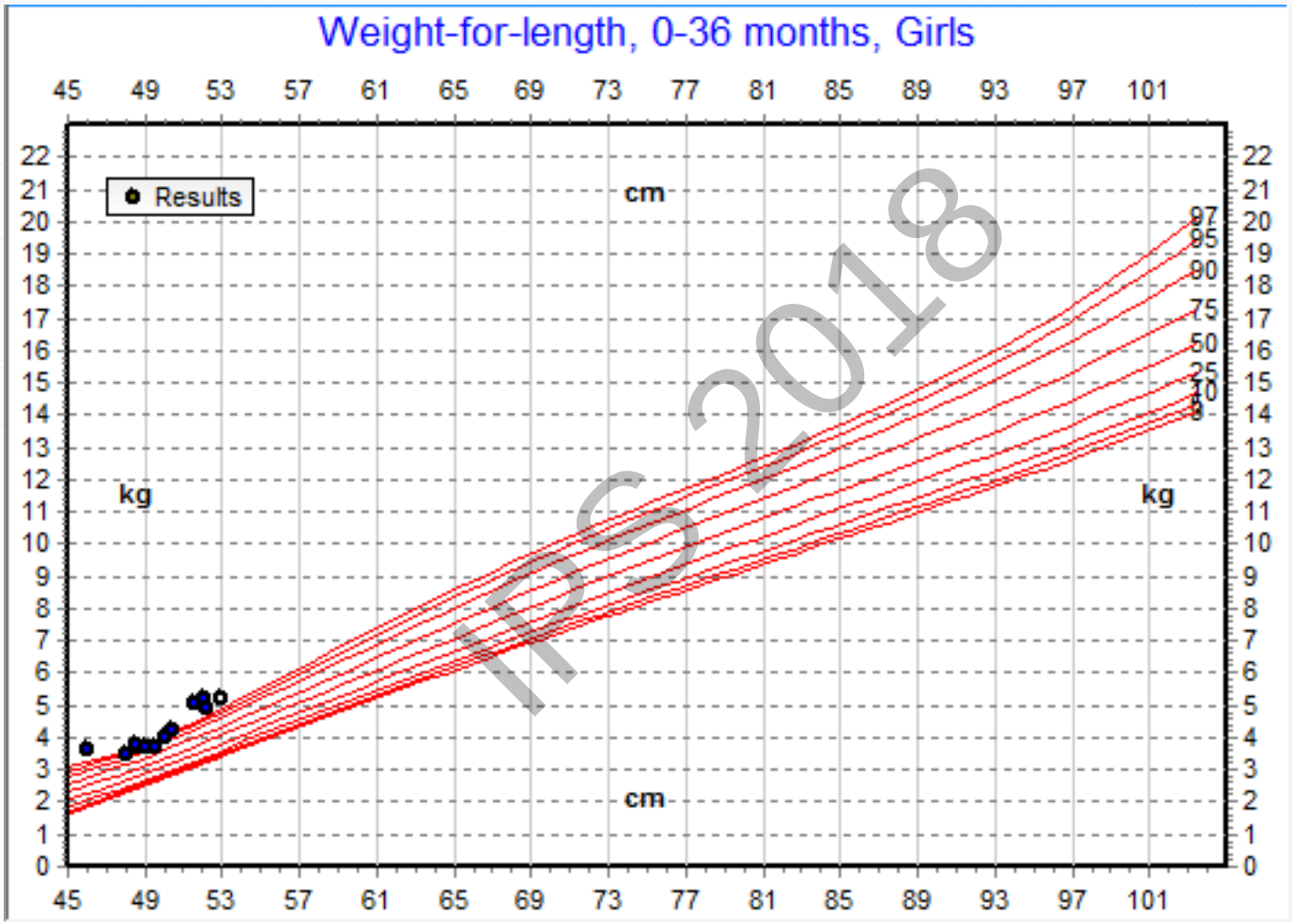


Table
Length-for-age, 0-36 months, Girls
Results
month(s)
cm
cm
month(s)
97
90
75
50
25
10
5
IPS 2018


Weight-for-length, 0-36 months, Girls
Results
cm
kg
97
95
90
75
50
25
10
5
3
IPG 2018

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

- Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency
  - Horm Res Paediatr 2016;86:361–397
- Short Stature in Childhood — Challenges and Choices
  - n engl j med 368;13 nejm.1220 org march 28, 2013
- GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults
  - European Journal of Endocrinology (2016) 174, P1–P9