Diagnosing Growth Disorders

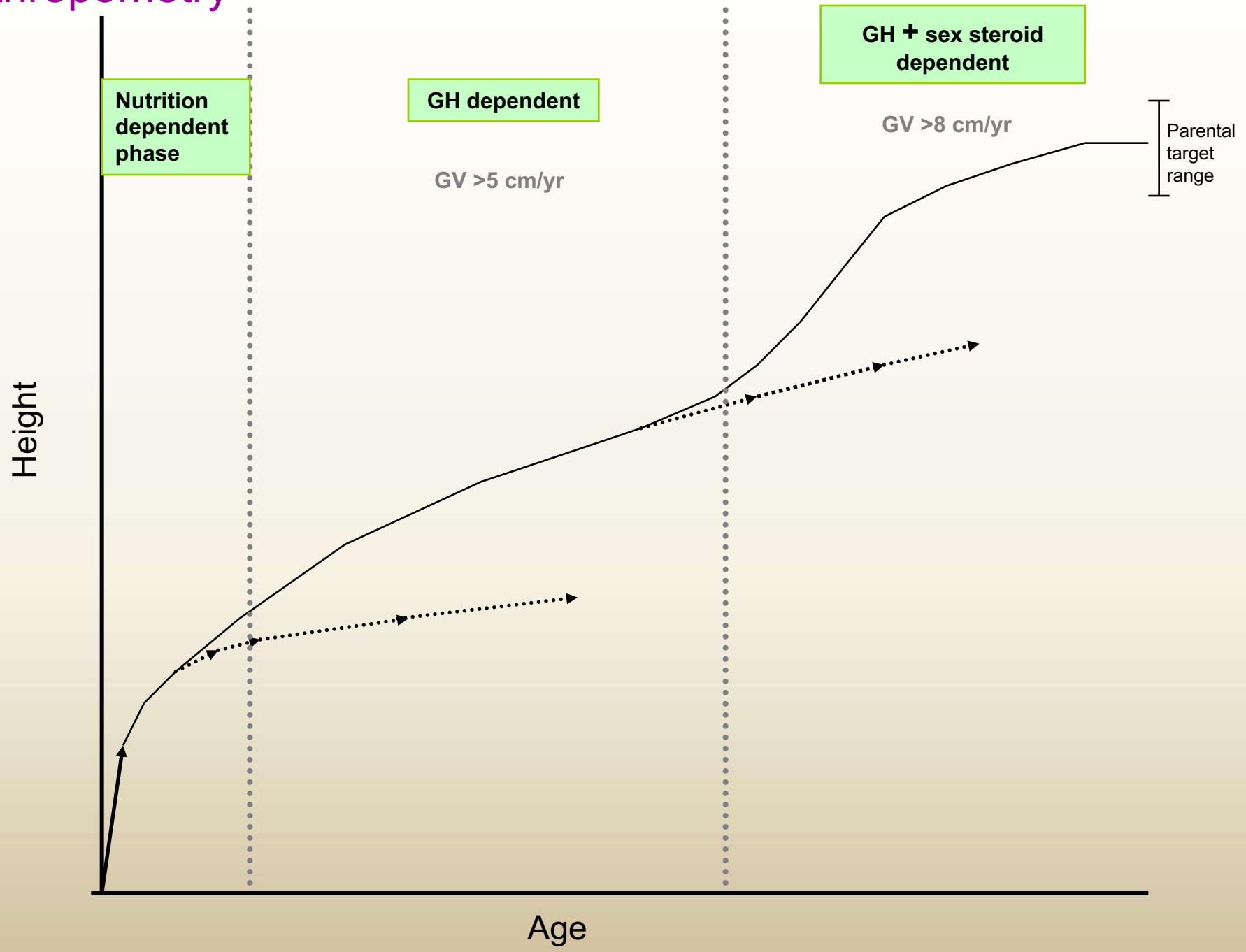
PE Clayton

School of Medical Sciences, Faculty of Biology, Medicine & Health

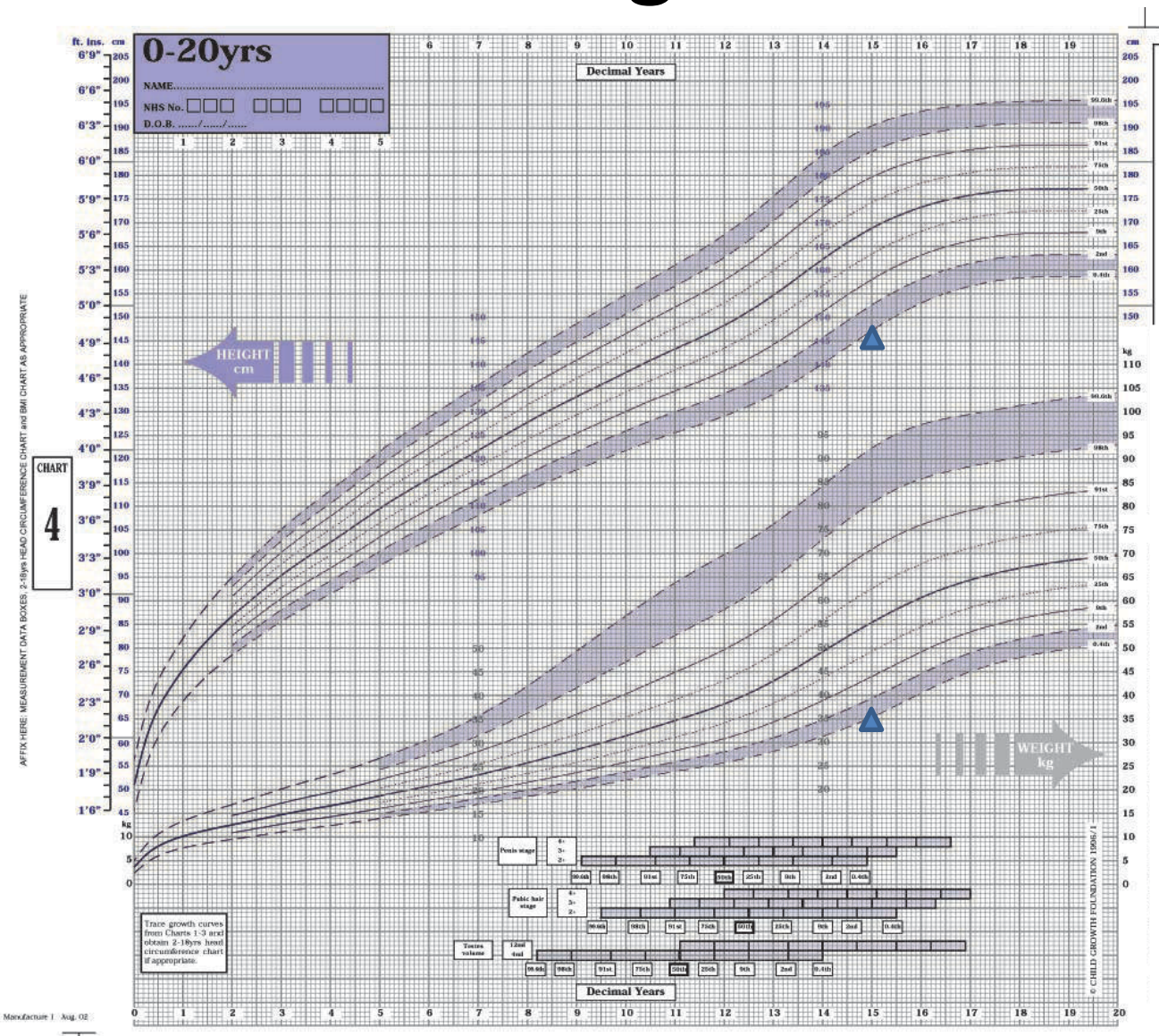
Content

- Normal pattern of growth and its variation
  - Using growth charts
  - Interpreting auxological measures
- Recognising an abnormal growth pattern
  - Clues in the history
  - Triggers to the decision to undertake investigation
    - Types of investigation
- Making a diagnosis

Anthropometry



Plotting Growth Data



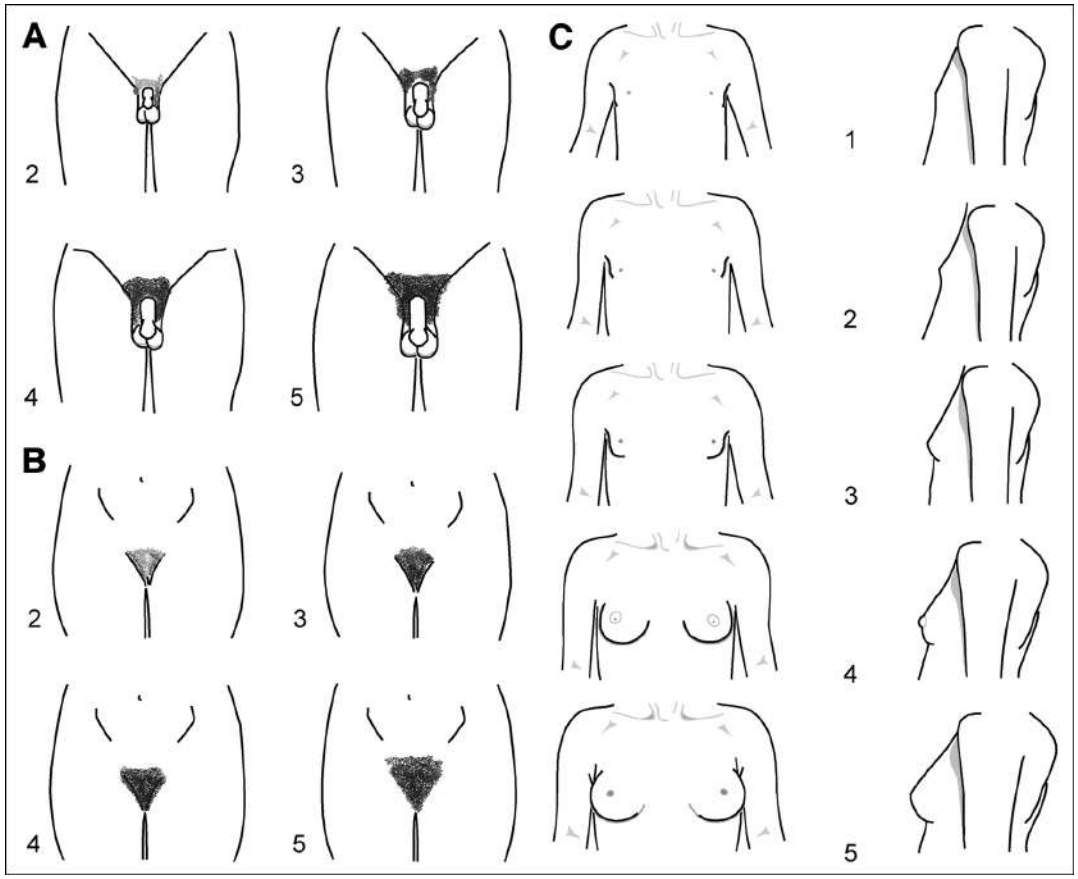
Mid-parental height from Mother's & Father's heights

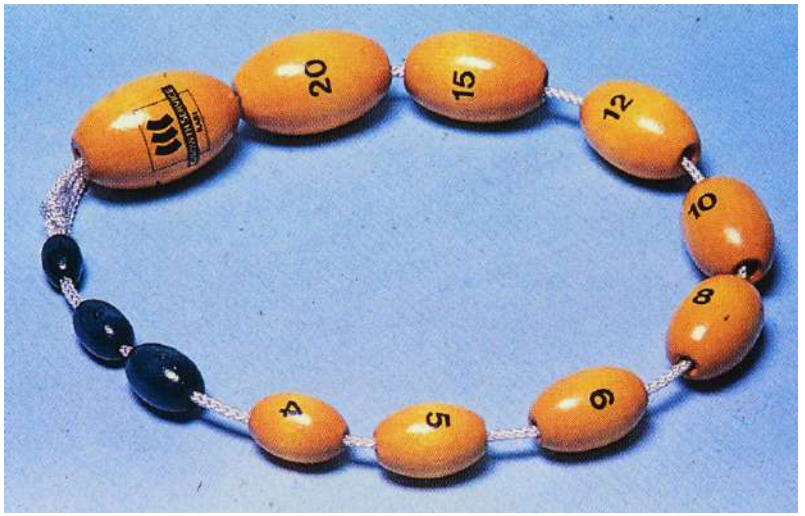
Parental target

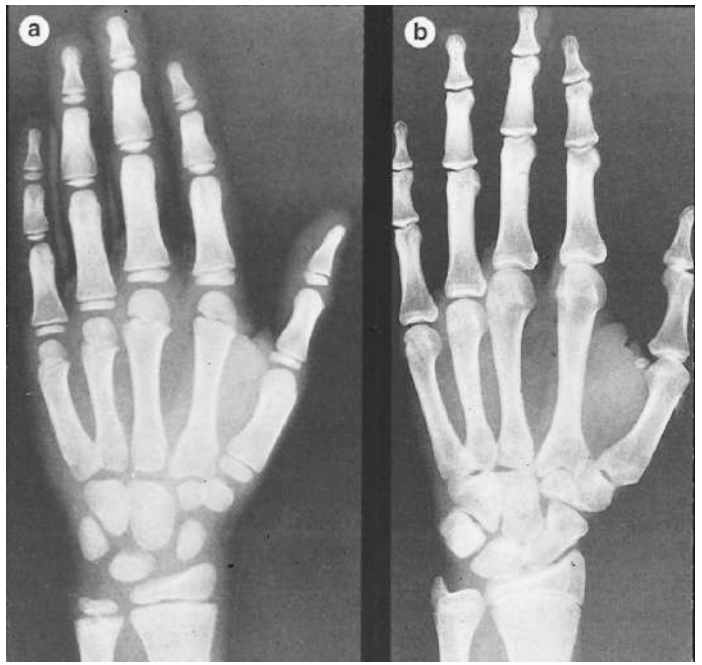
Target height in relation to parental heights (cms)

Boys $\frac{FH + MH + 7}{2}$

Girls $\frac{FH + MH - 7}{2}$







Pubertal Staging:

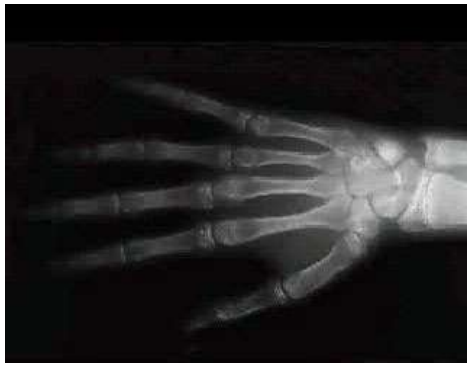
A. Genital & Pubic Hair development in Boys

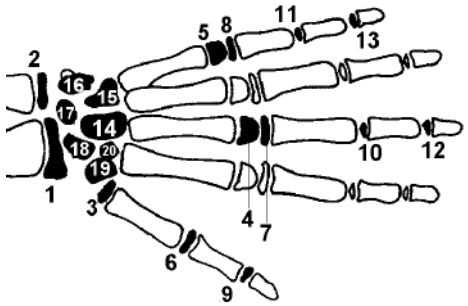
B. Pubic Hair development in Girls

C. Breast development in Girls

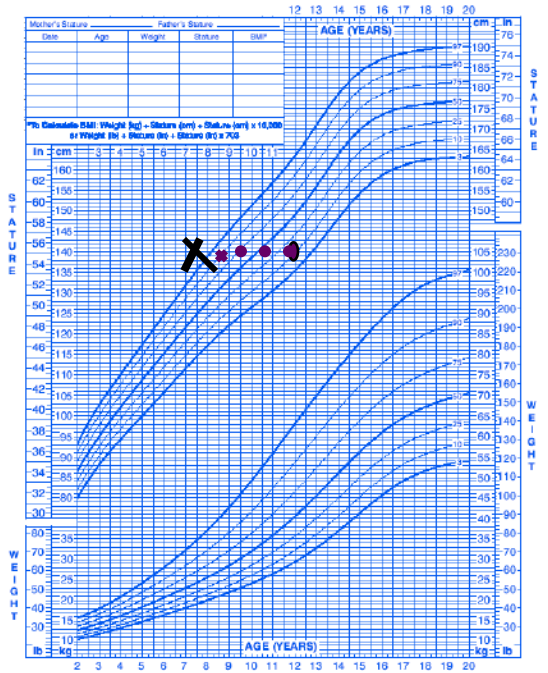
Bone Age

If delayed compared to chronological age – suggestive of chronic underlying problem, but not necessarily endocrine.

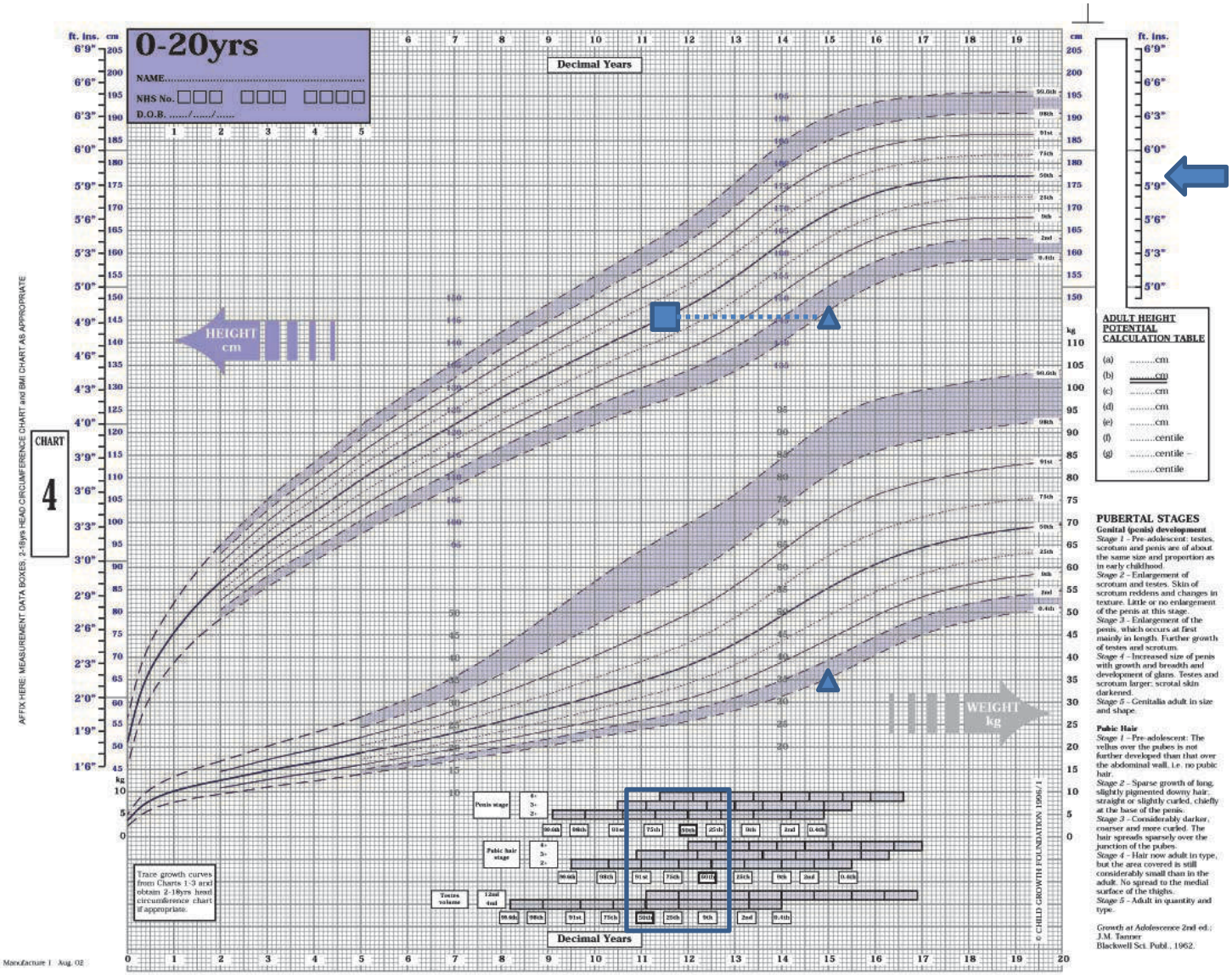




Normal BA = CA +/- 1 year



Growth & Puberty are inextricably linked



Mid-parental height from Mother's & Father's heights

+ details on parental, sibling puberty

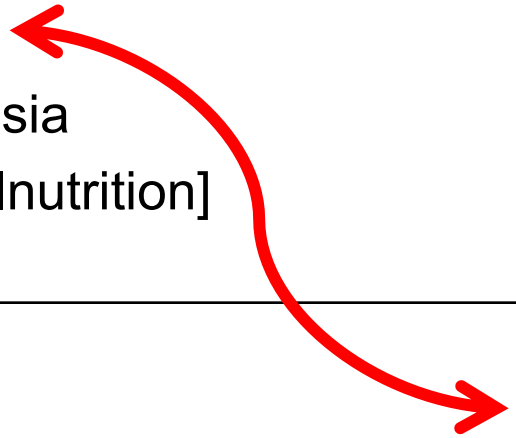
Process to Follow:

- History
  - Medical clues
    - System screen
  - Impact on life
  - Internet exploration*
- Physical Examination
  - System screen
  - Growth & puberty assessment
- Explore expectations*
- Formulate a differential diagnosis
- [Order tests]
- [Evaluate tests]
- Reach a diagnosis or reformulate differential diagnosis

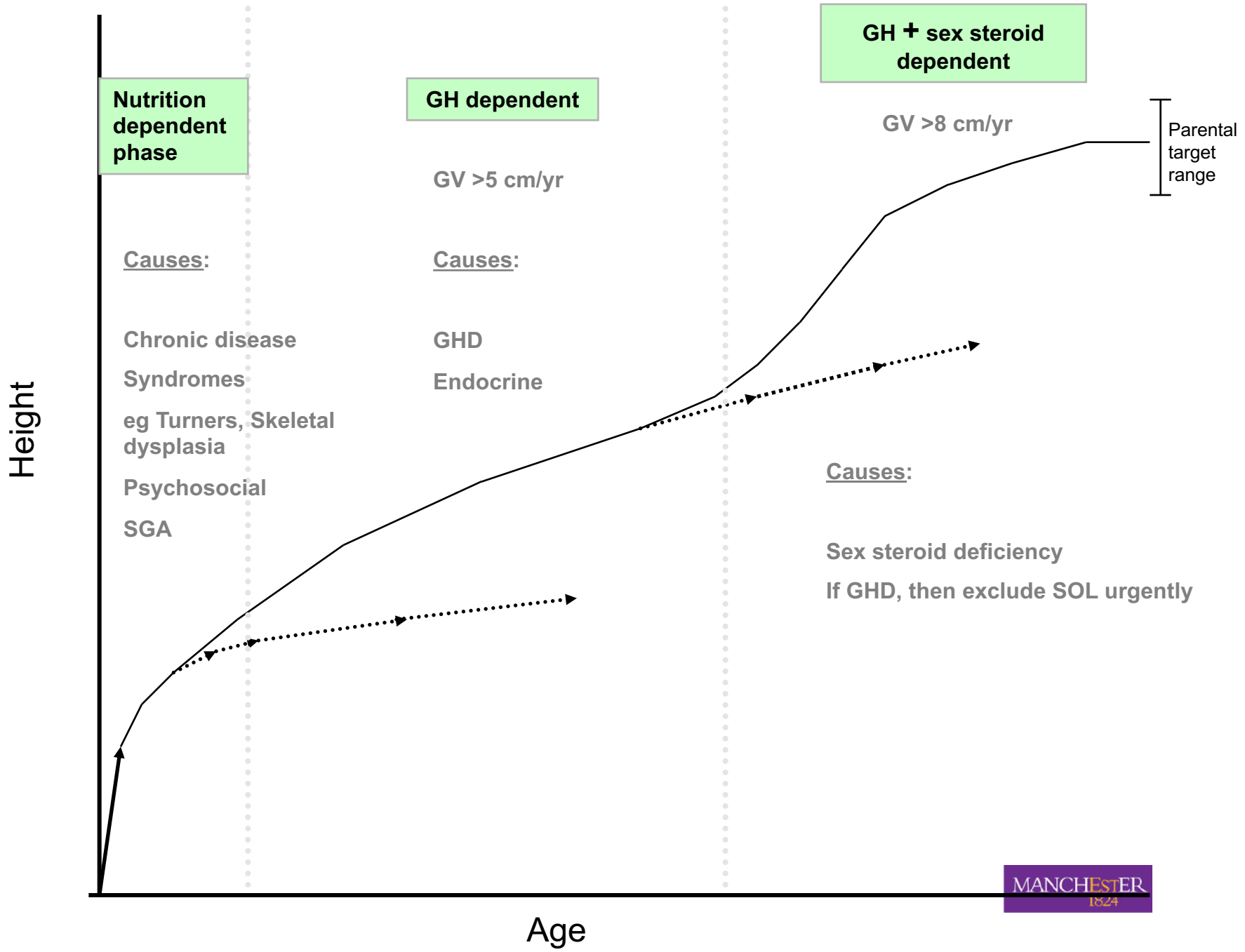
Causes of Short Stature:

- Idiopathic short stature, including
  - Constitutional delay of growth & puberty
  - Genetic / Familial SS
- Associated with systemic disease
- Born small with failure of catch-up
- Chromosomal / Genetic syndrome [monogenic]
- Psychosocial
- Endocrine
- Bone dysplasia
- [Primary malnutrition]

Three specific growth therapies:
r-hGH
r-hIGF-I
Sex steroids



- GH Deficiency / Hypopituitarism
  - Primary
  - Secondary
- Hypothyroidism


Nutrition dependent phase
GH dependent
GH + sex steroid dependent
GV >8 cm/yr
Parental target range
GV >5 cm/yr
Causes:
Causes:
Chronic disease
Syndromes
eg Turners, Skeletal dysplasia
Psychosocial
SGA
GHD
Endocrine
Causes:
Sex steroid deficiency
If GHD, then exclude SOL urgently
Height
Age
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Skeletal dysplasias

Achondroplasia

Causes:

Chronic disease

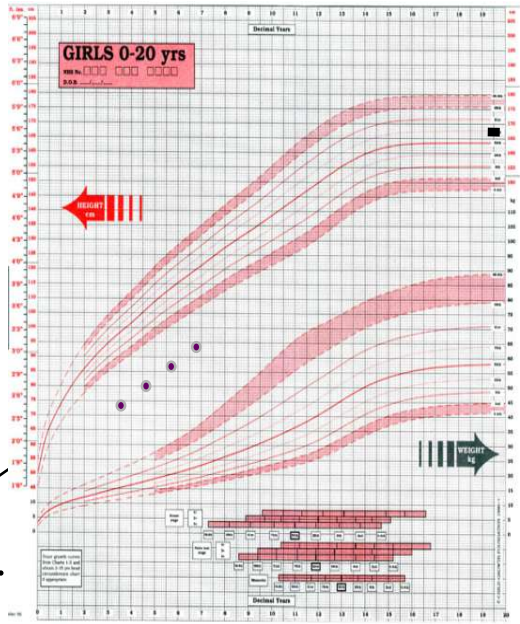
Syndromes

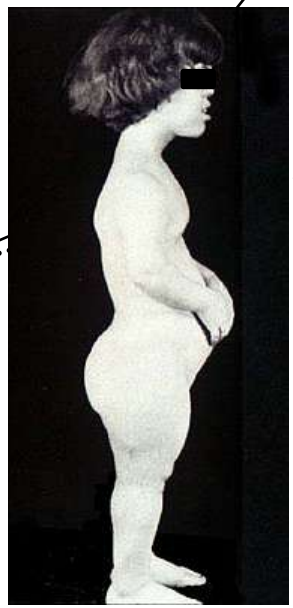
eg Turners,

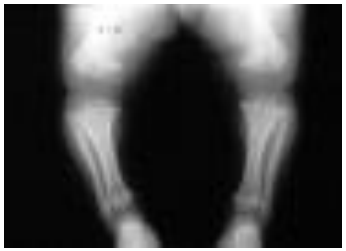
Skeletal dysplasia

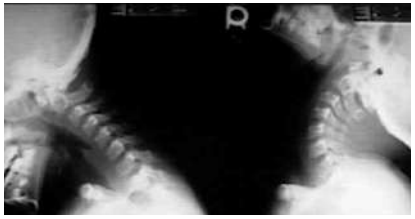
Psychosocial

SGA









Height

Age

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Russell Silver Syndrome

Height

Causes:

Chronic disease

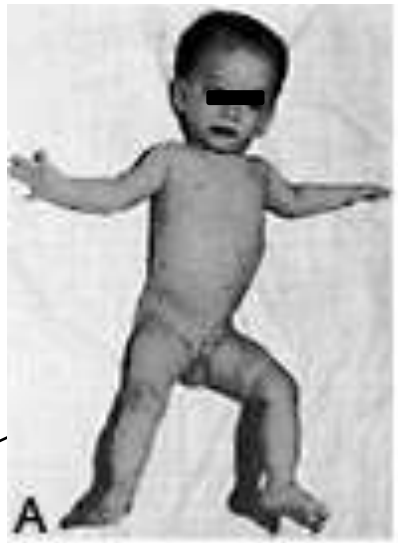
Syndromes

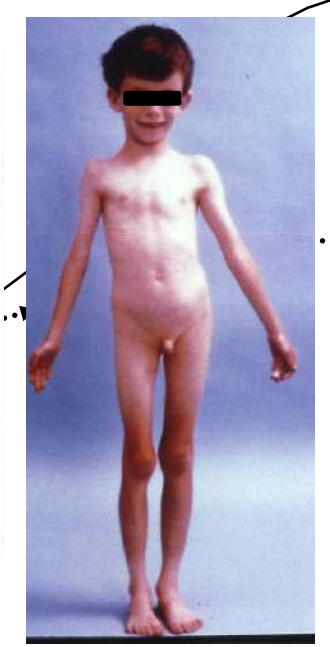
eg Turners,

Skeletal dysplasia

Psychosocial

SGA





SGA

Tendency toward hypoglycaemia

Methylation abnormaities on Chr 11

UPD maternal Chr 7

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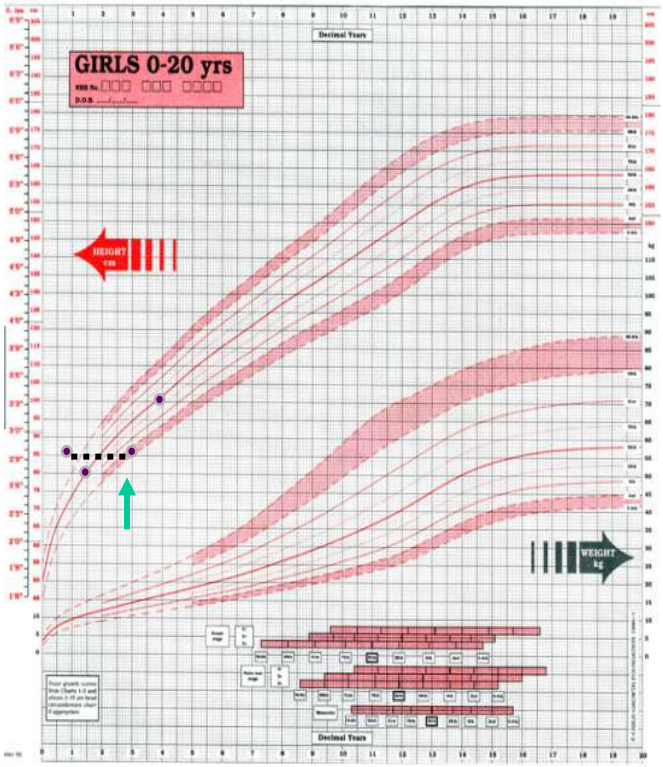
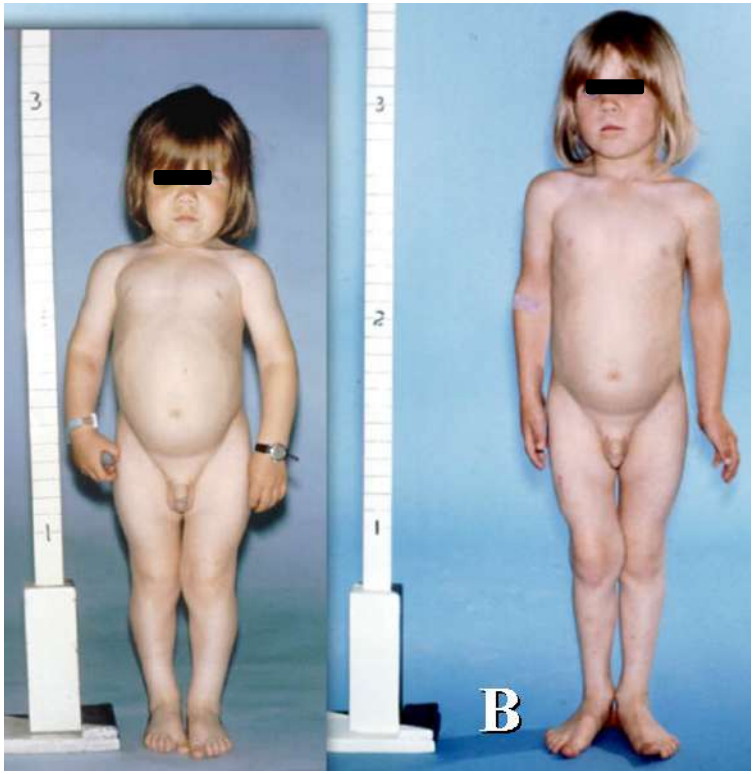
Hypothyroidism





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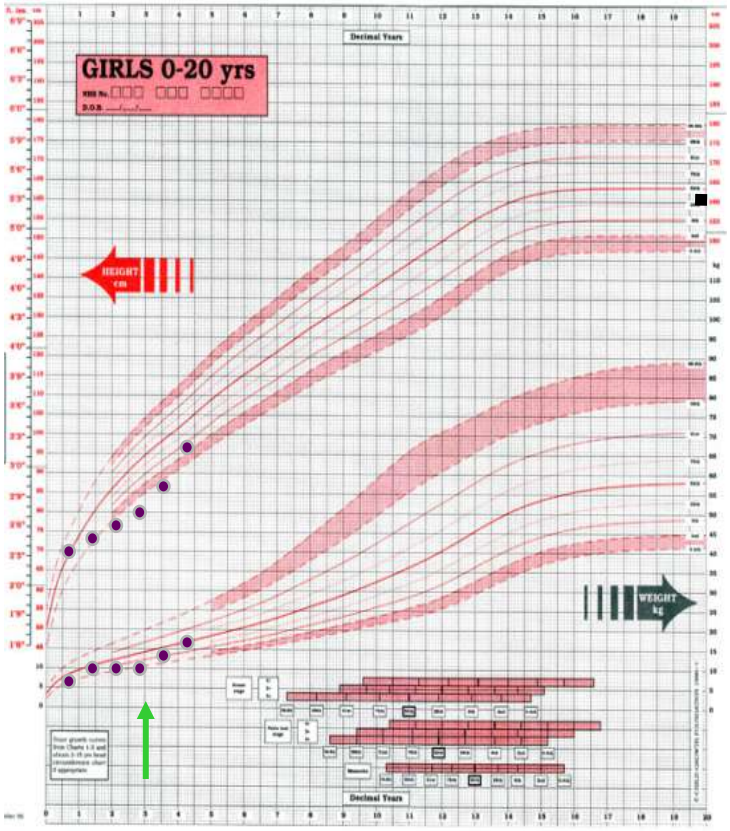
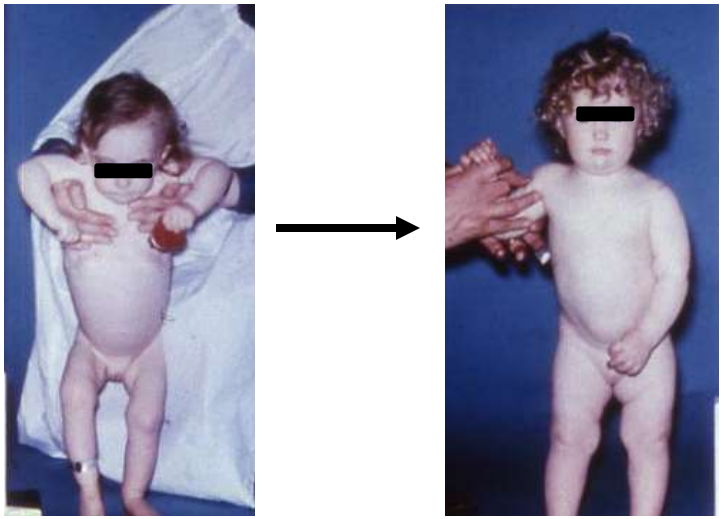
Coeliac disease





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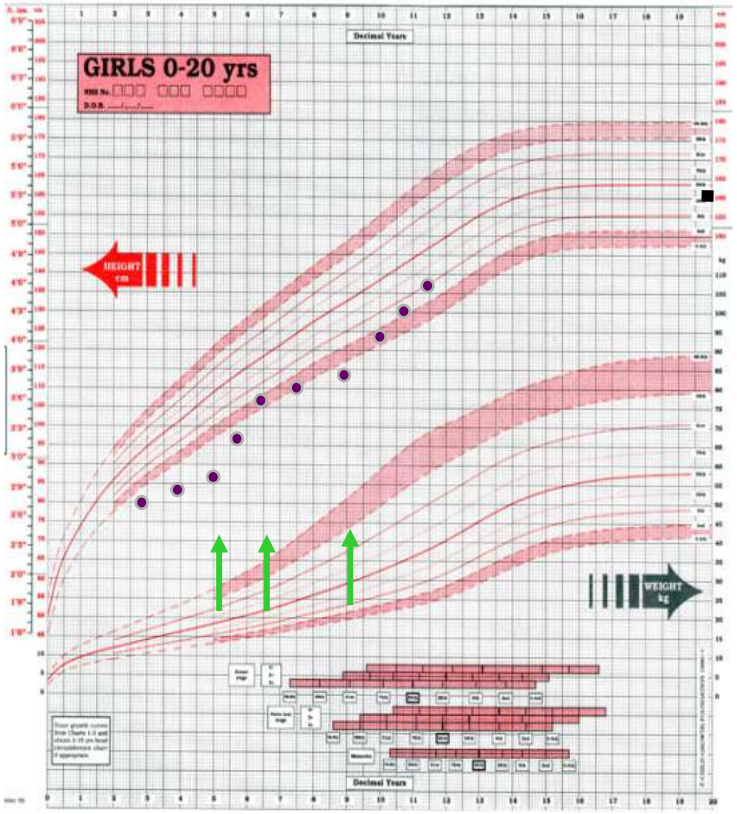
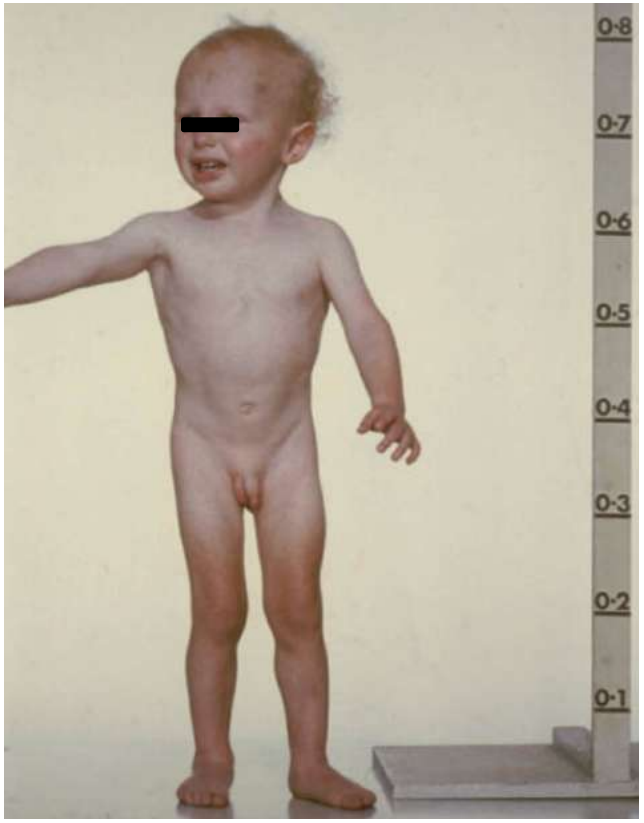
Psycho-social deprivation





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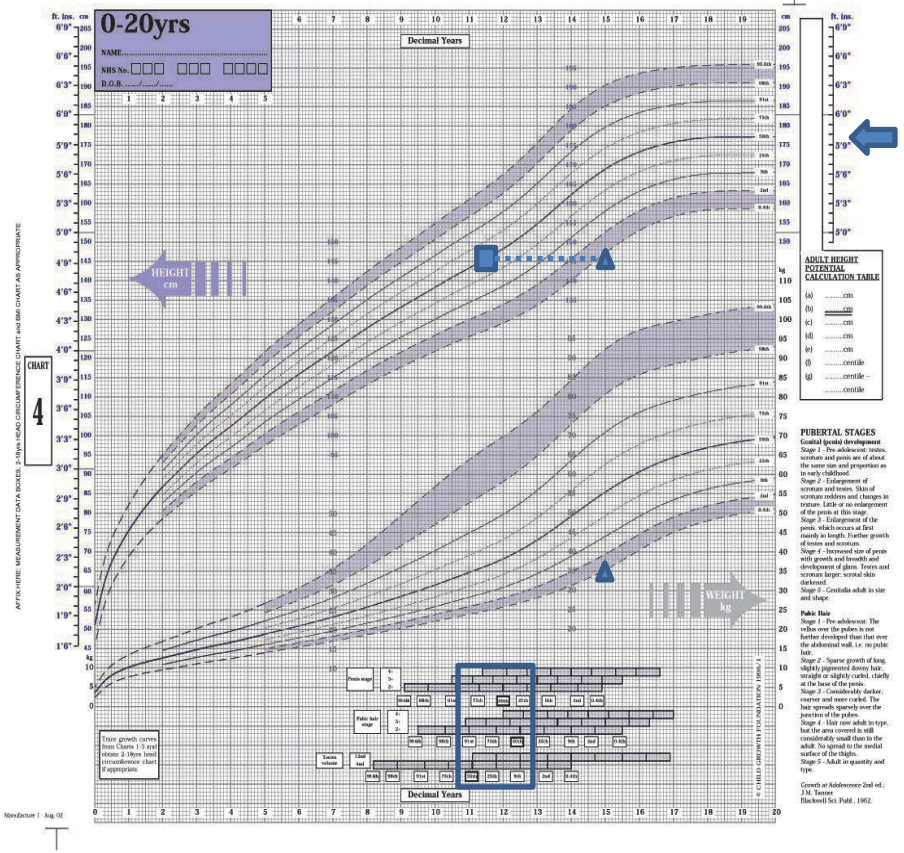
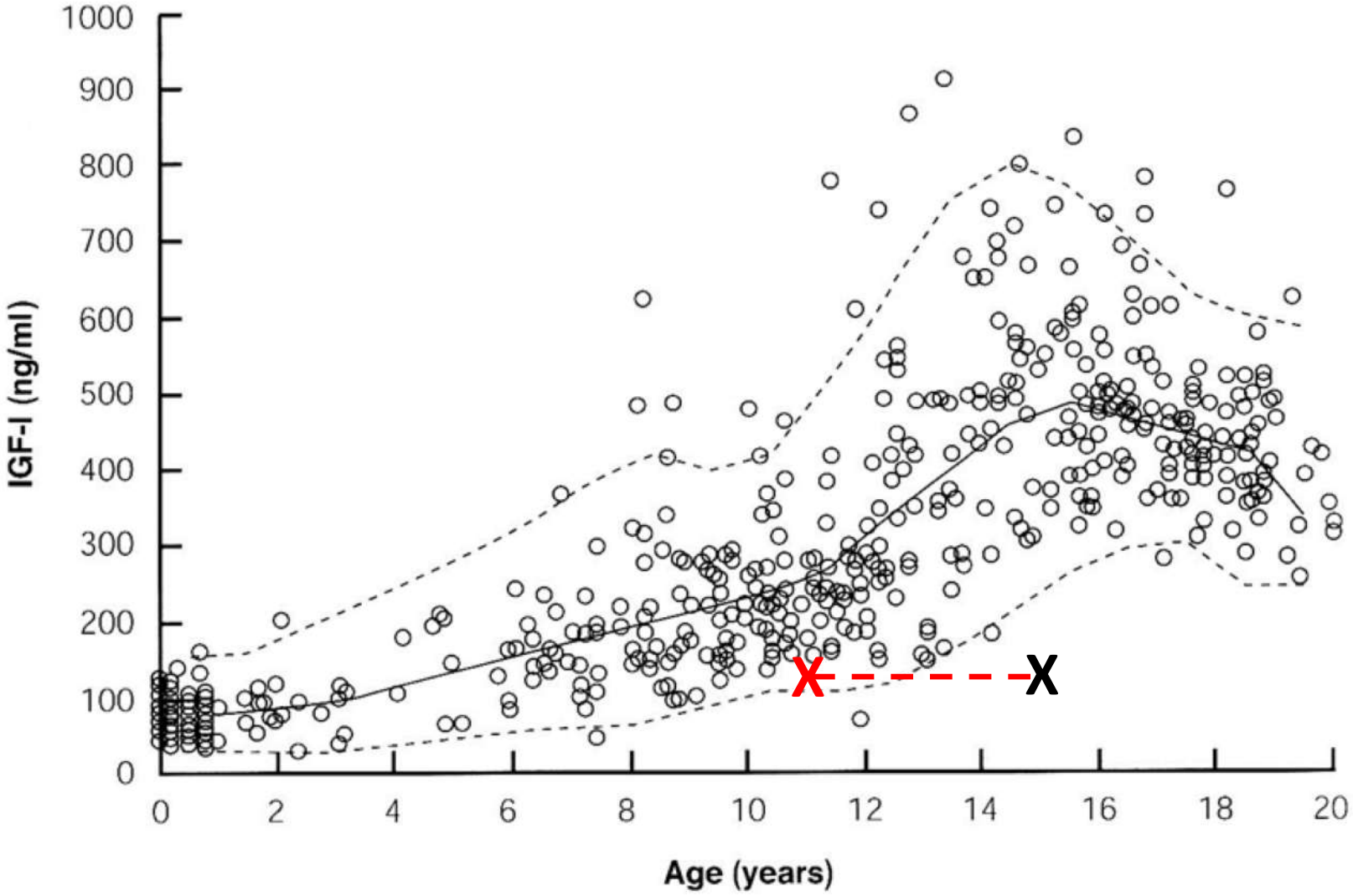
‘Screening’ Investigations in a Short child:

System disorder, Endocrine



Hormone	Subject	**Normal range** (15yr old male)
Free T4 (Thyroxine)	18 pmol/l	9-24 pmol/l
TSH (Thyroid Stimulating Hormone)	2.1 mU/l	0.3-3.0 mU/l
IGF-I (Insulin-like growth factor 1)	110 µg/L	168-859 µg/L

Concentrations of IGF-I in blood versus Age



Juul et al JCEM 1994

Identifying GH Deficiency:

- History, phenotype & anthropometry
- Defining the status of the GH-IGF axis
- MR imaging with specific views of the hypothalamic-pituitary axis
- Genetic analysis

Infant : Early - Late Childhood : Teens

Tips in the History

- Neonatal
  - Hypoglycaemia, prolonged jaundice, microphallus, traumatic delivery
- Prior pituitary ‘insult’
  - Cranial irradiation
  - Tumour, infiltration, infection
  - Trauma
- Family history
  - Consanguinity
- Persistent decrease in growth rate

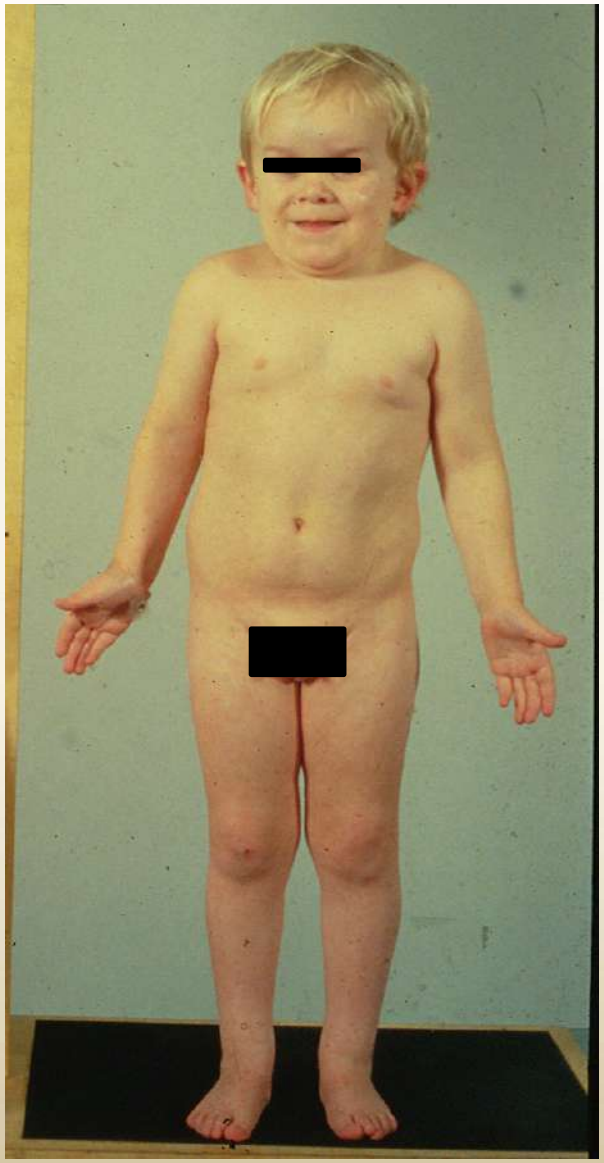
Case1

- Term Female with Hypoglycaemia & prolonged jaundice
- Basal TFT – TSH 9.5u/L, fT_4 9pmol/L
- TRH – TSH 9-20-22u/L
- LDST – Cortisol Peak 300nmol/L
- GH stimulation – Peak GH 15µg/L
- IGF-I sds -4

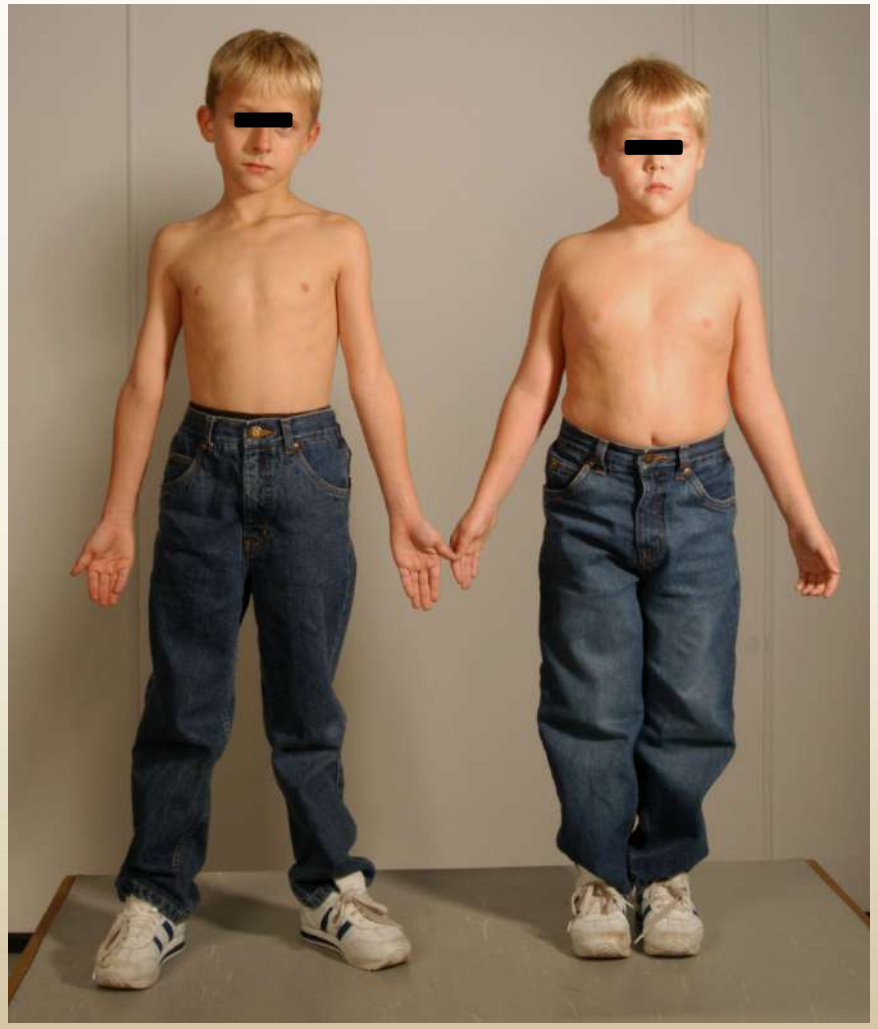
- Treatment started with T_4, Hydrocortisone & GH
- MRI – Small Ant Pit, Ectopic PP, Stalk visible, midline intact
- Diagnosis: Congenital Hypopituitarism

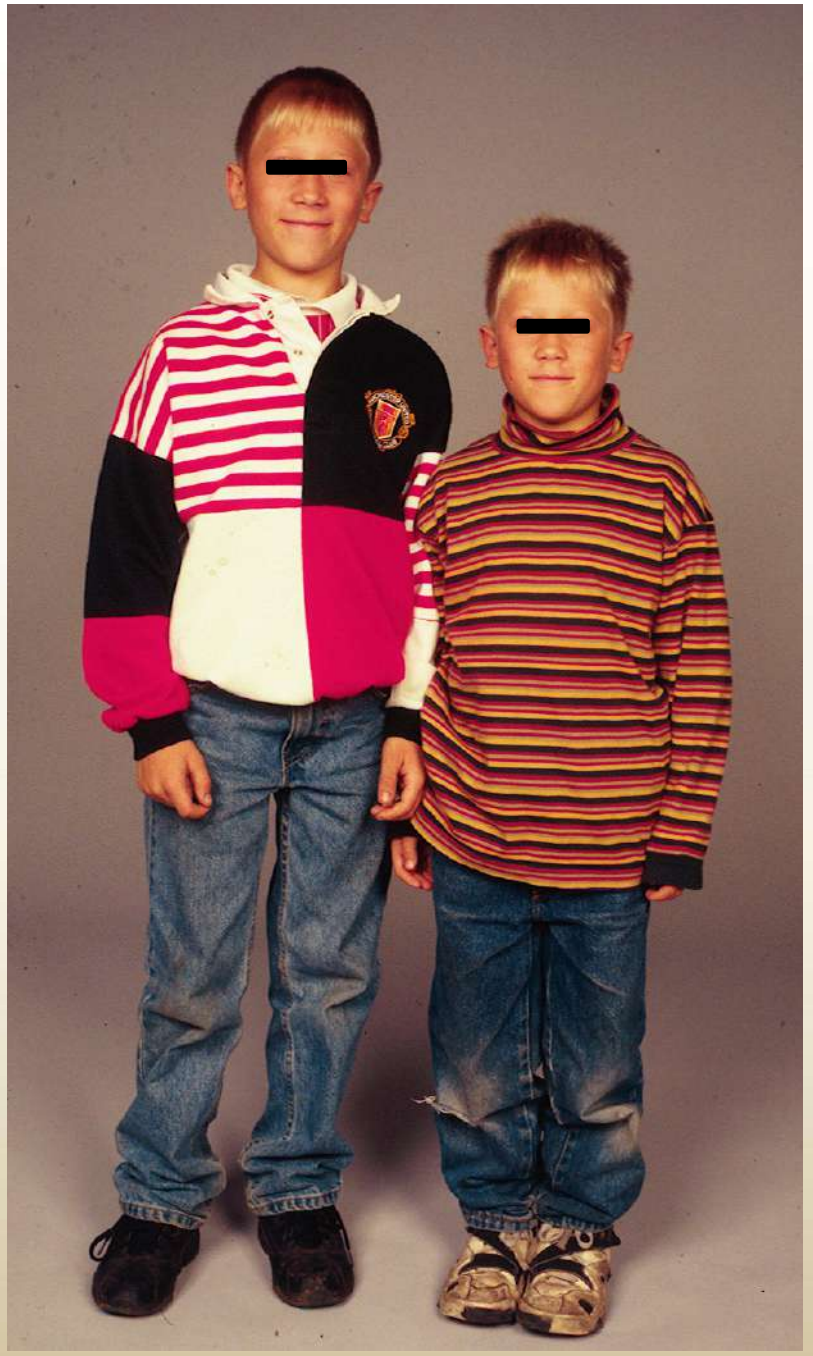
Age 6-8 weeks – Not fixing consistently, “eye wobble” noted.
Ophthalmic review – Small Optic Discs

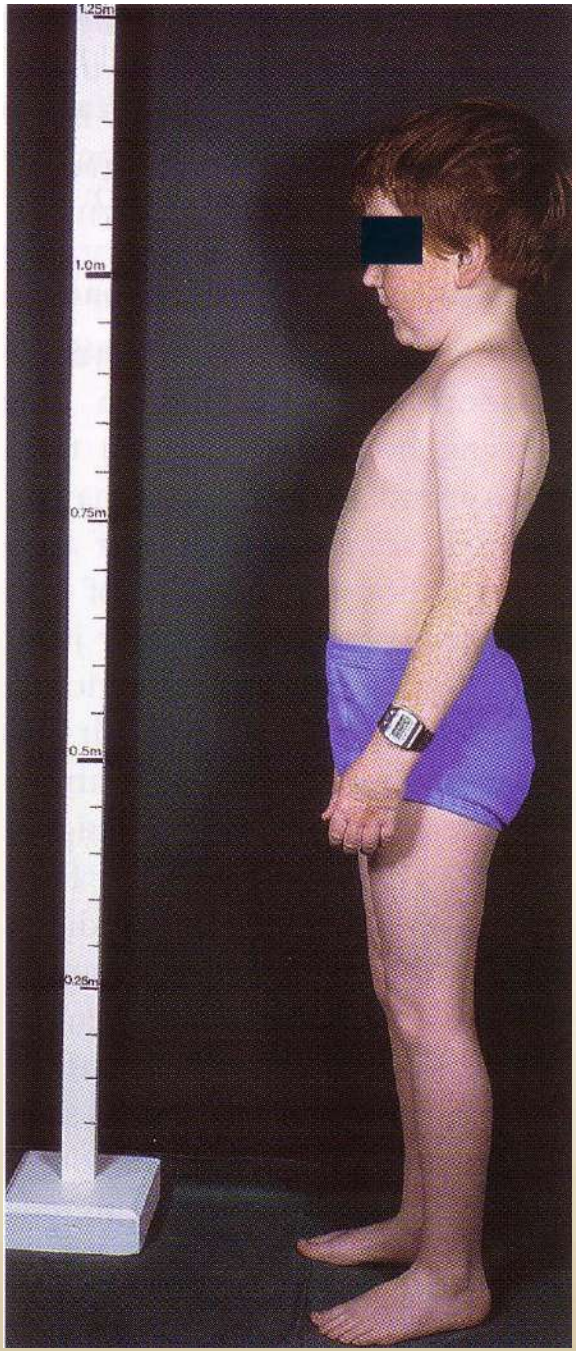
Phenotype: GH Deficiency

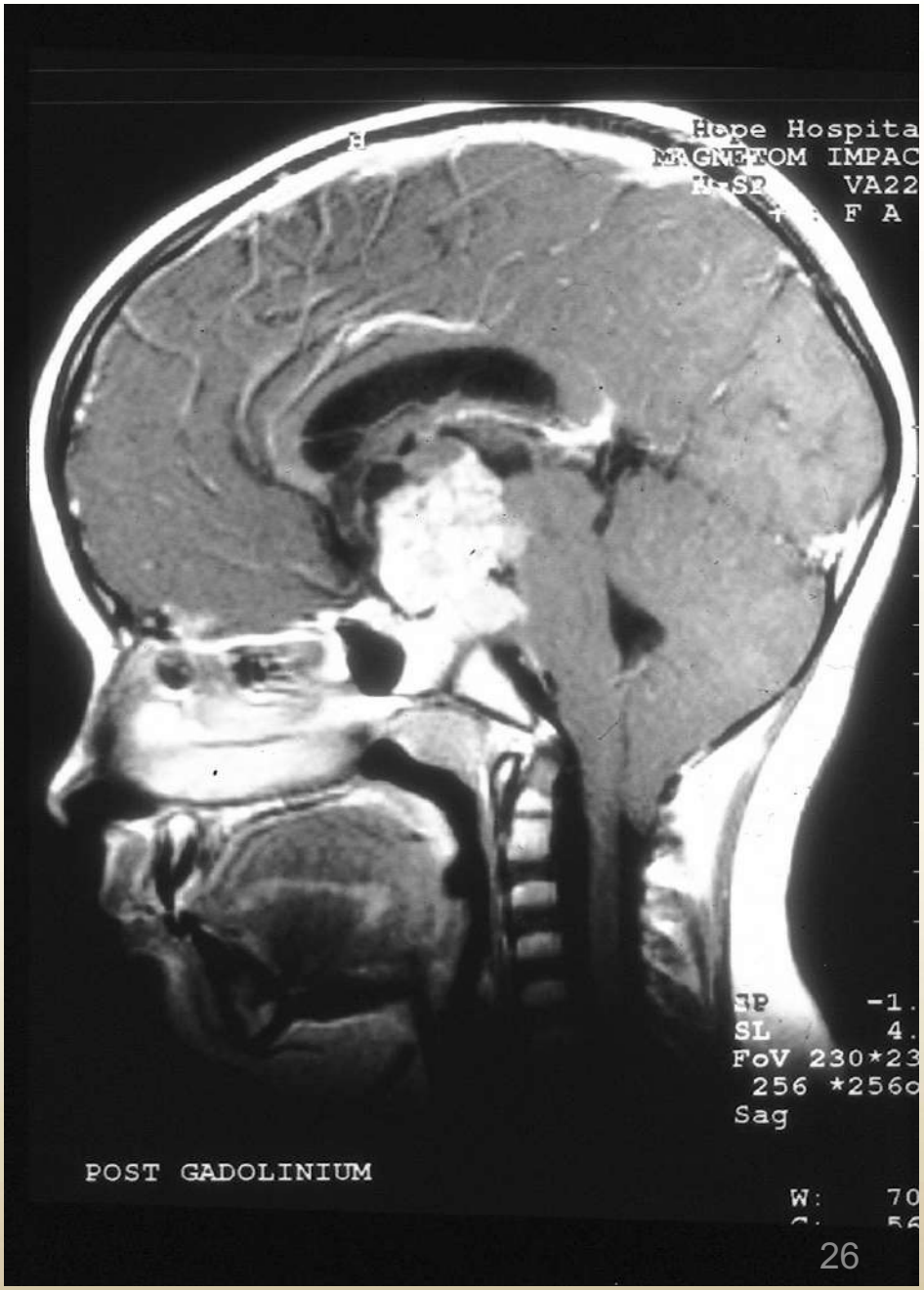


Isolated, ‘idiopathic’ GHD ± MR hypothalamic-pituitary abnormalities






1.25m
1.0m
0.75m
0.5m
0.25m


Hope Hospita
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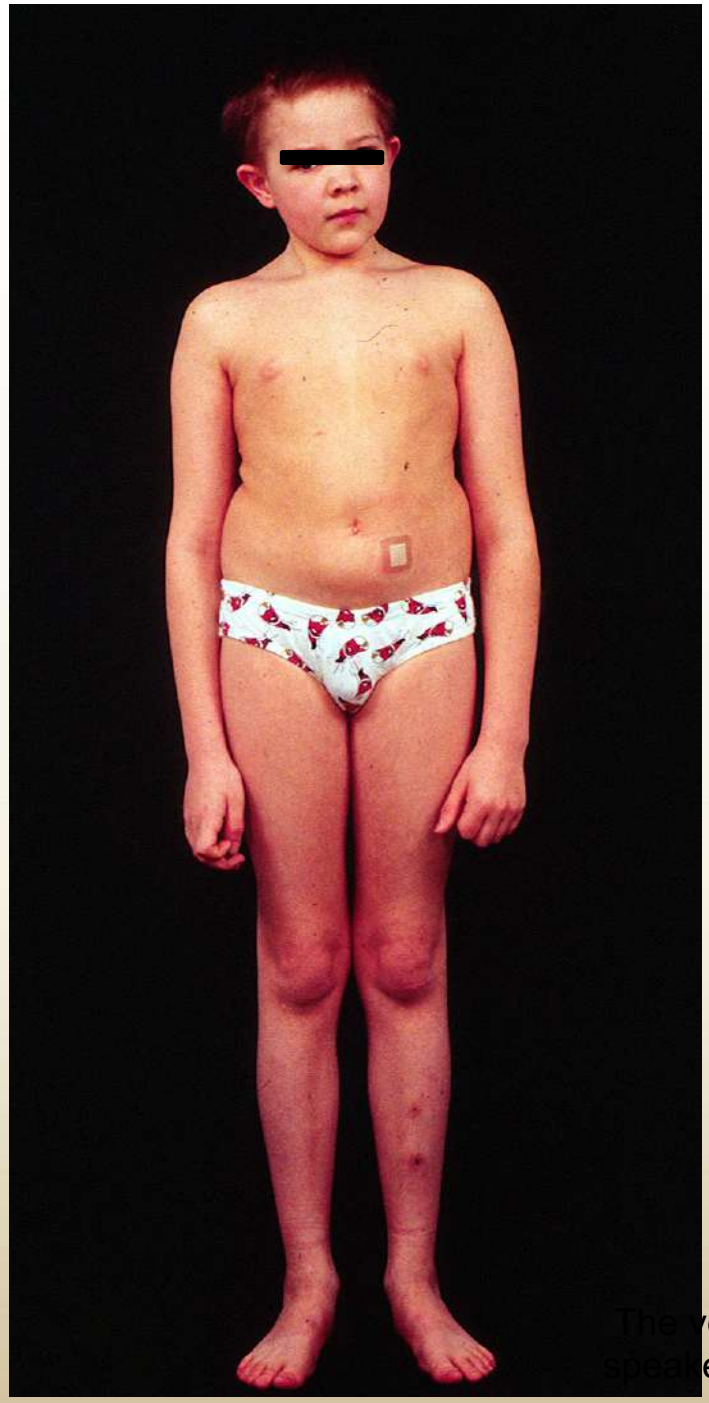
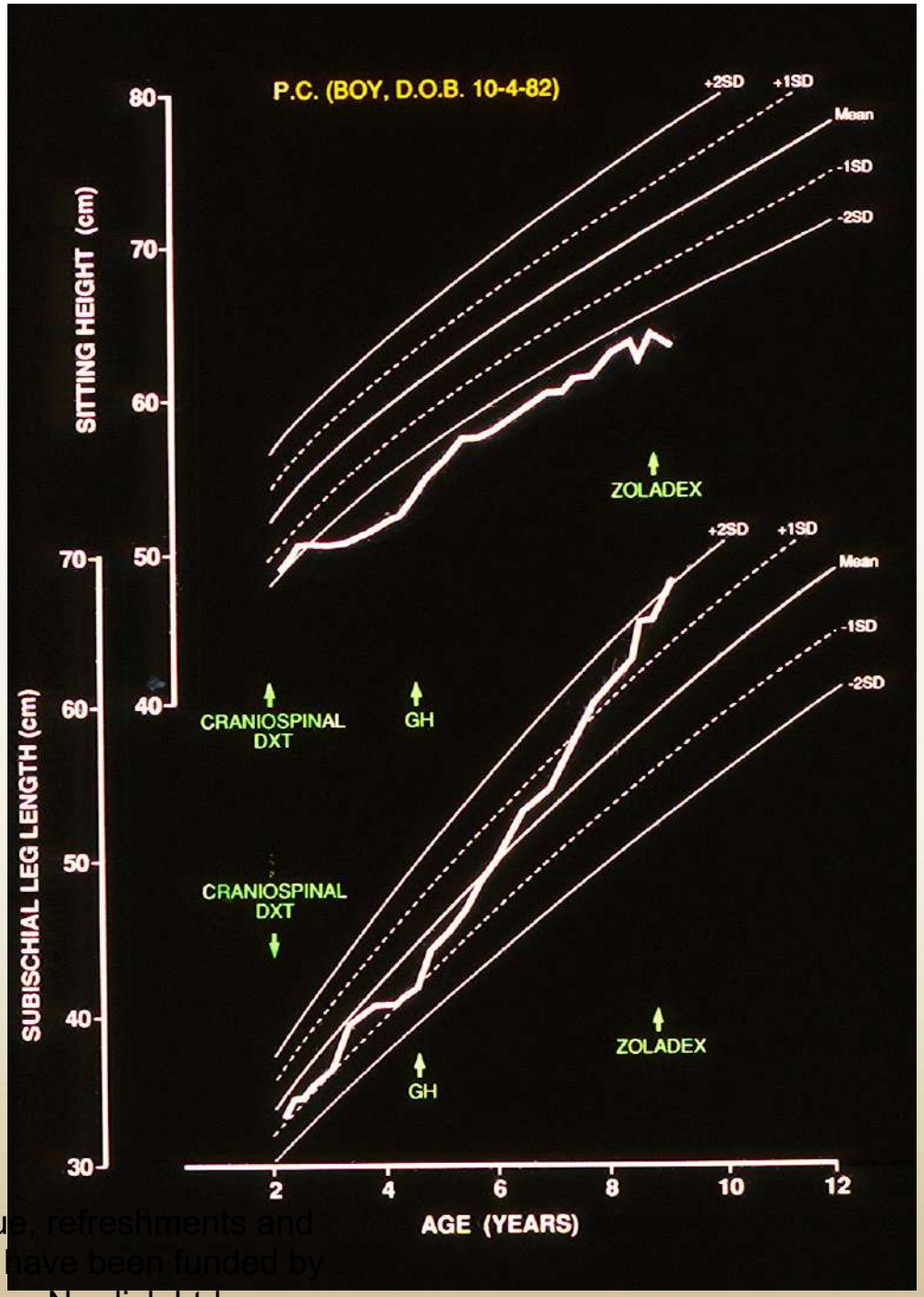
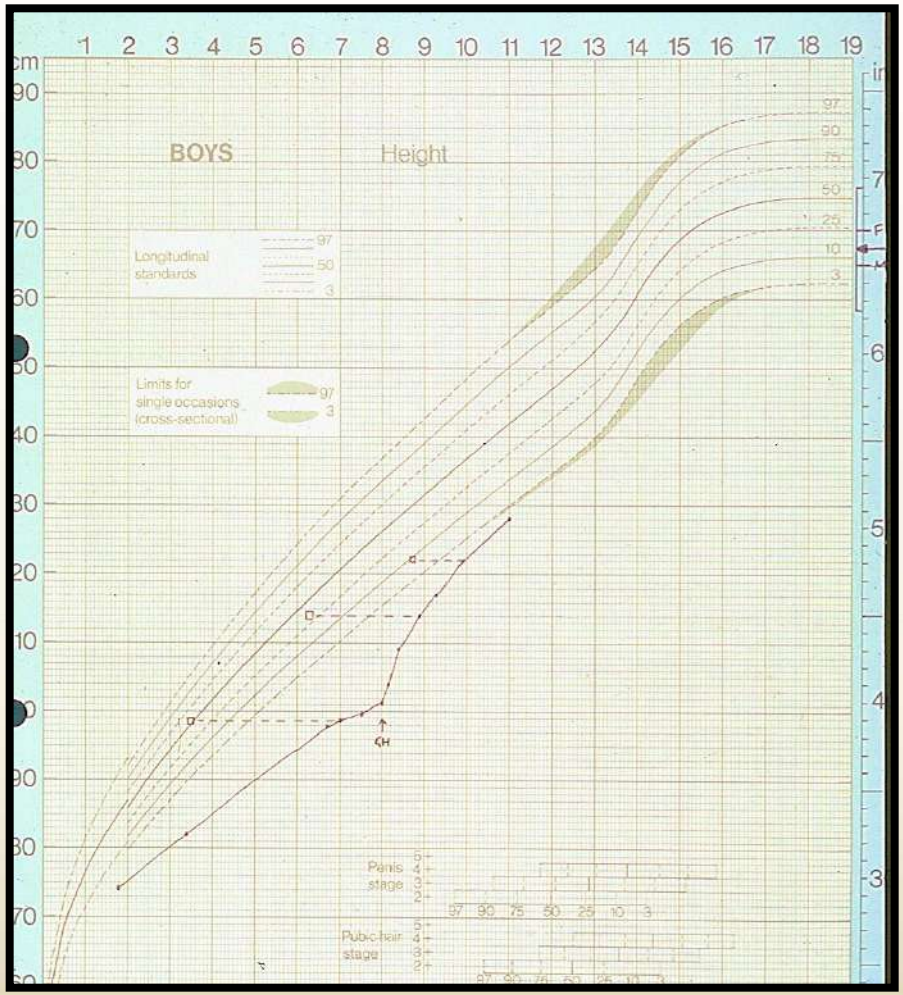
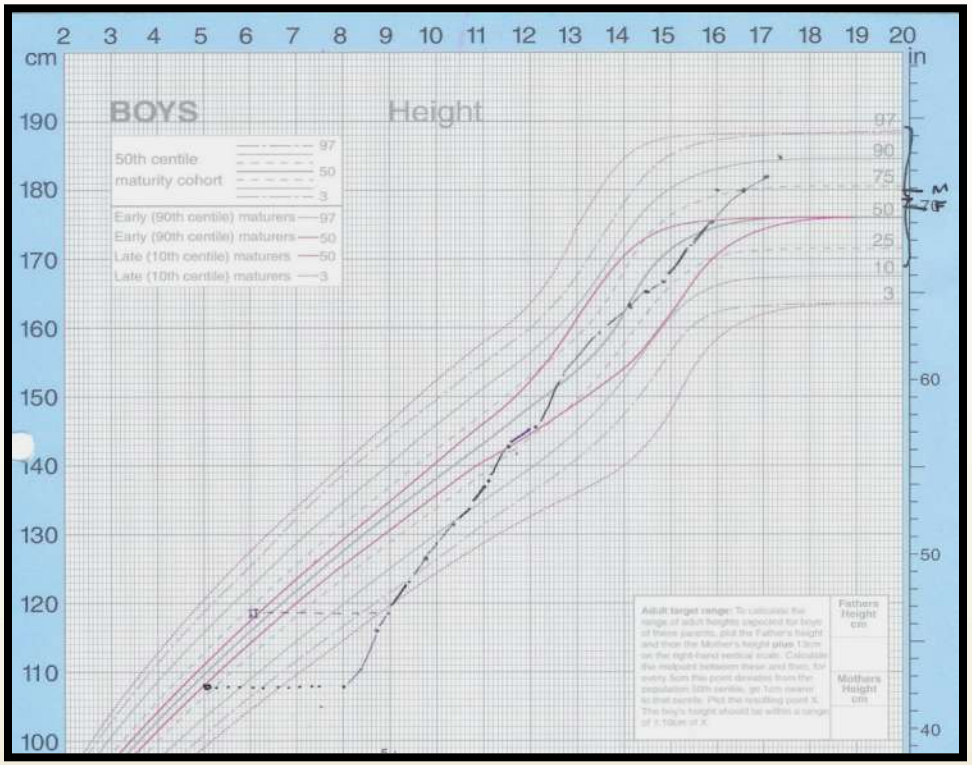




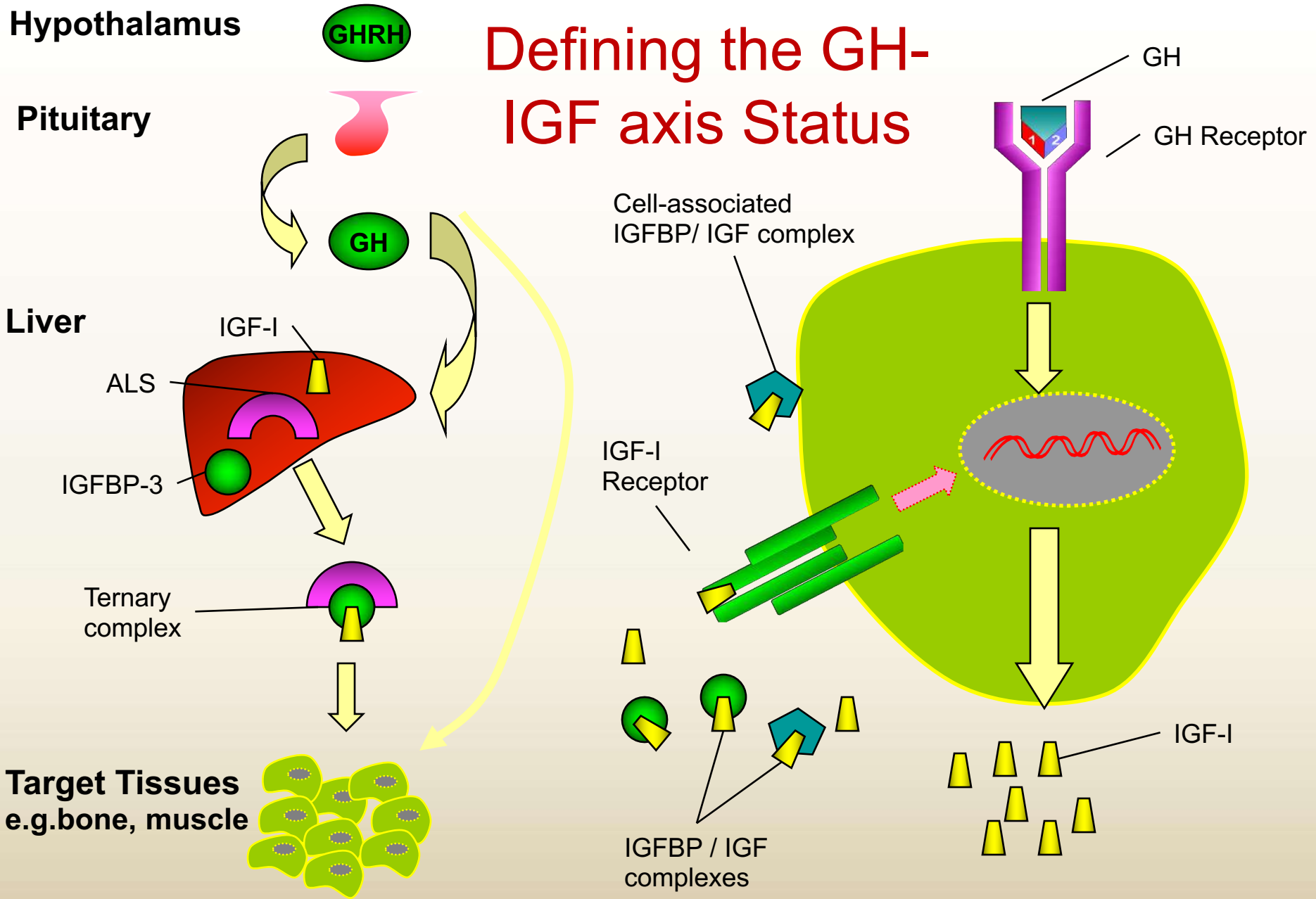
The venue, refreshments and speakers have been funded by Novo Nordisk Ltd

Anthropometry





Defining the GH-IGF axis Status

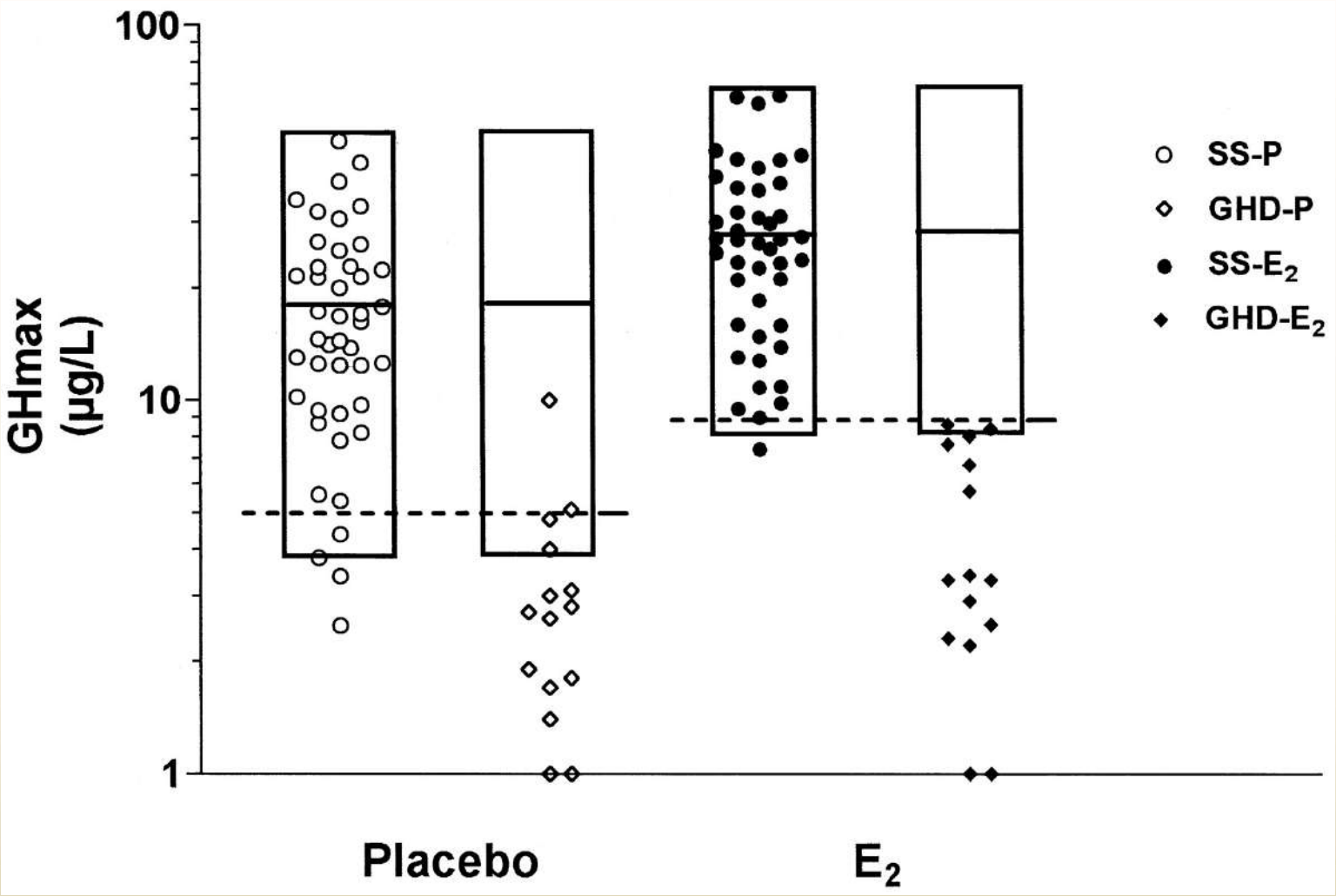


GH Tests

- Insulin Tolerance Test
- Arginine
- Glucagon
- Clonidine
- ‘Sleep’
- GHRH + Arginine
- Profiles – 12hr, 24hr, overnight
- Urinary GH

- Normative data
- Assay issues
- Priming
- Cut-off levels

GH maximal response, under placebo (P) or E2 administration in SS and GHD children.



MartÍnez A S et al. JCEM 2000;85:4168-4172

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GH Assay Issues

Cut-off Levels in GH Stimulation Tests – Wagner et al EJE 2014

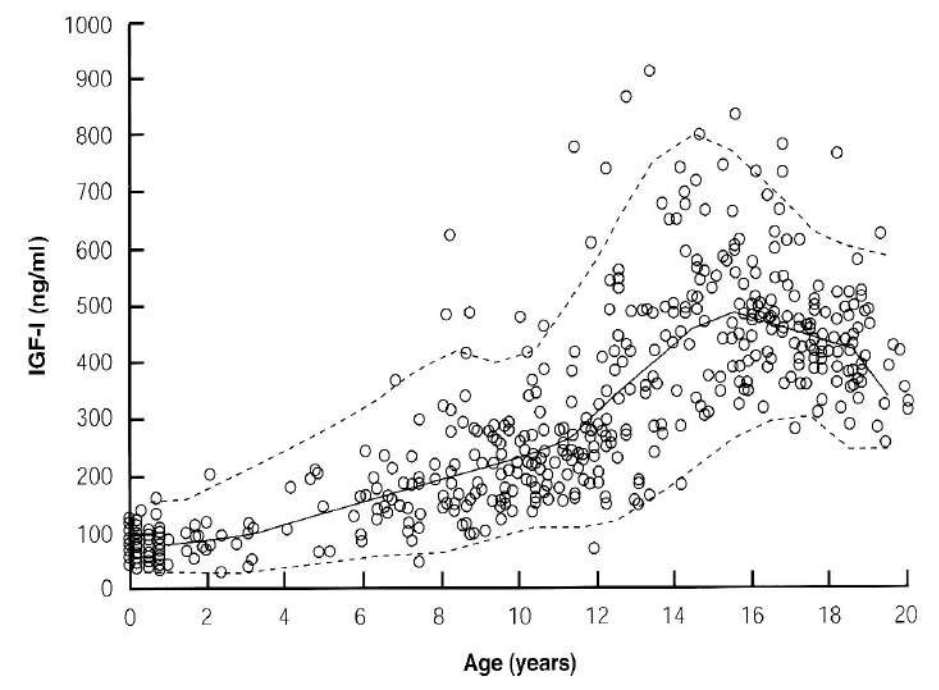
Assay	Regression equation (r)	Cut-off limit (µg/L)
Immulite 2000 (Siemens) [b]	y=1.031x-0.455 (r=0.964)***	7.77
AutoDELFIA (PerkinElmer) [a]	Y=1.004x+0.323 (r=0.922)***	7.44
iSYS (IDS) [b]	N/A	7.09
Liaison (DiaSorin) [b]	Y=0.823x+0.412 (r=0.919)***	6.25
RIA (inhouse Tübingen) [b]	y=0.565+1.271 (r=0.818)***	5.28
DxI (Beckmann-Coulter) [b]	Y=0.689x+0.271 (r=0.880)***	5.15
ELISA (Mediagnost) [b]	y=0.678+0.327 (r=0.869)***	5.14
BC-IRMA (Beckamnn-Coulter) [c]	y=0.622x-0.096 (r=0.927)***	4.32

[a] WHO 1.IS 80/505, [b] WHO 2. IS 98/574, [c] WHO 1. IS 88/624;
*** $p<0.0001$

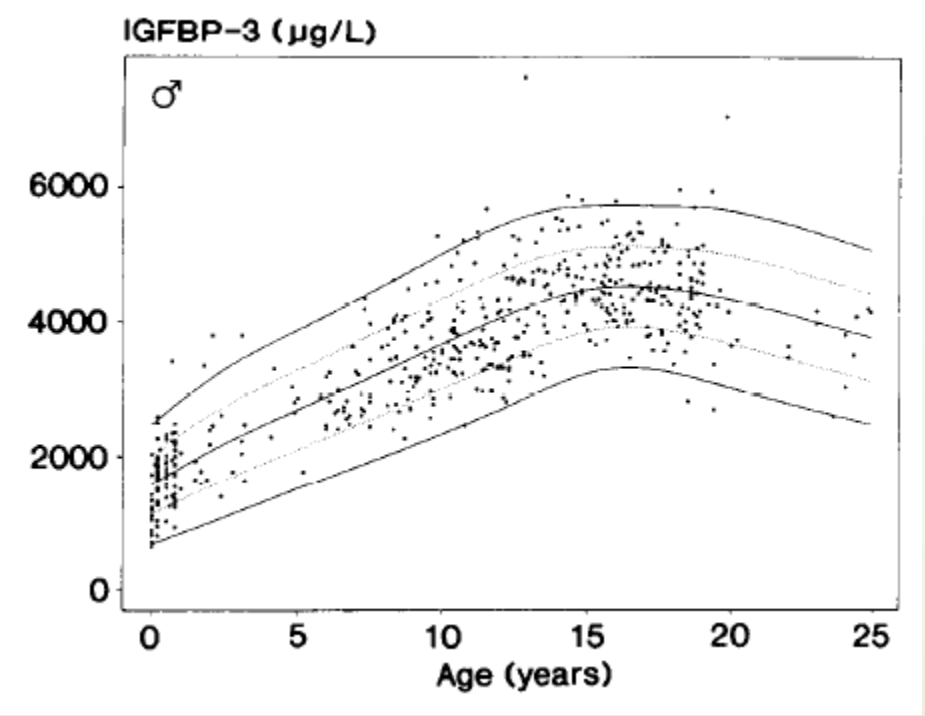
GH Cut-off Levels

- <3 µg/L — Severe childhood GHD: Adult GHD cut-off
- <5 — Transition GHD cut-off
- <6.1 — Transition GHD cut-off
- <6.7 — Childhood GHD cut-off [monoclonal assays]
- <7 — Childhood GHD cut-off
- <10 — Childhood GHD cut-off [older polyclonal assays]

Normative Data for serum IGF-I and IGFBP-3

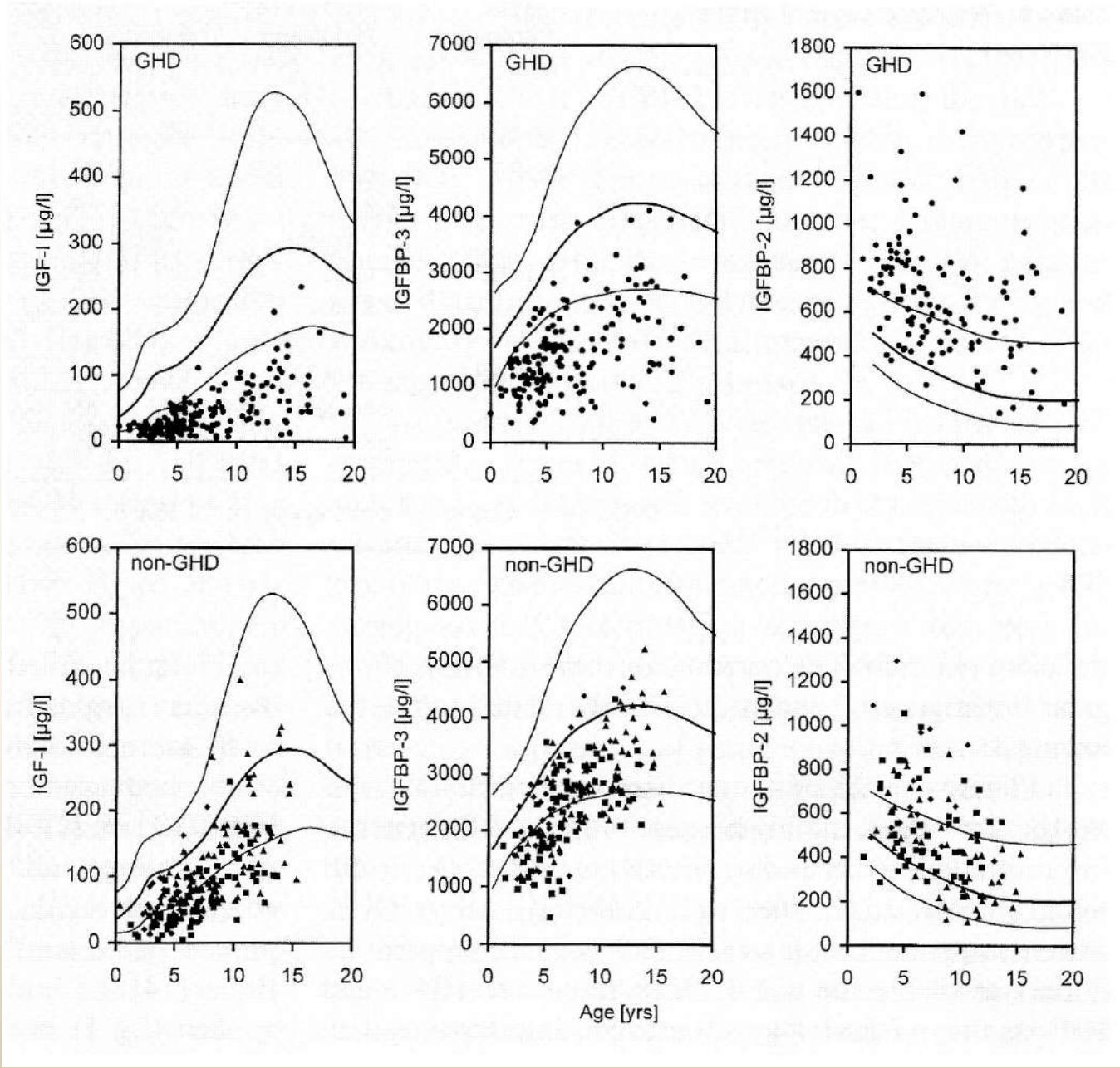


IGF-I levels in Males from Juul et al JCEM 1994



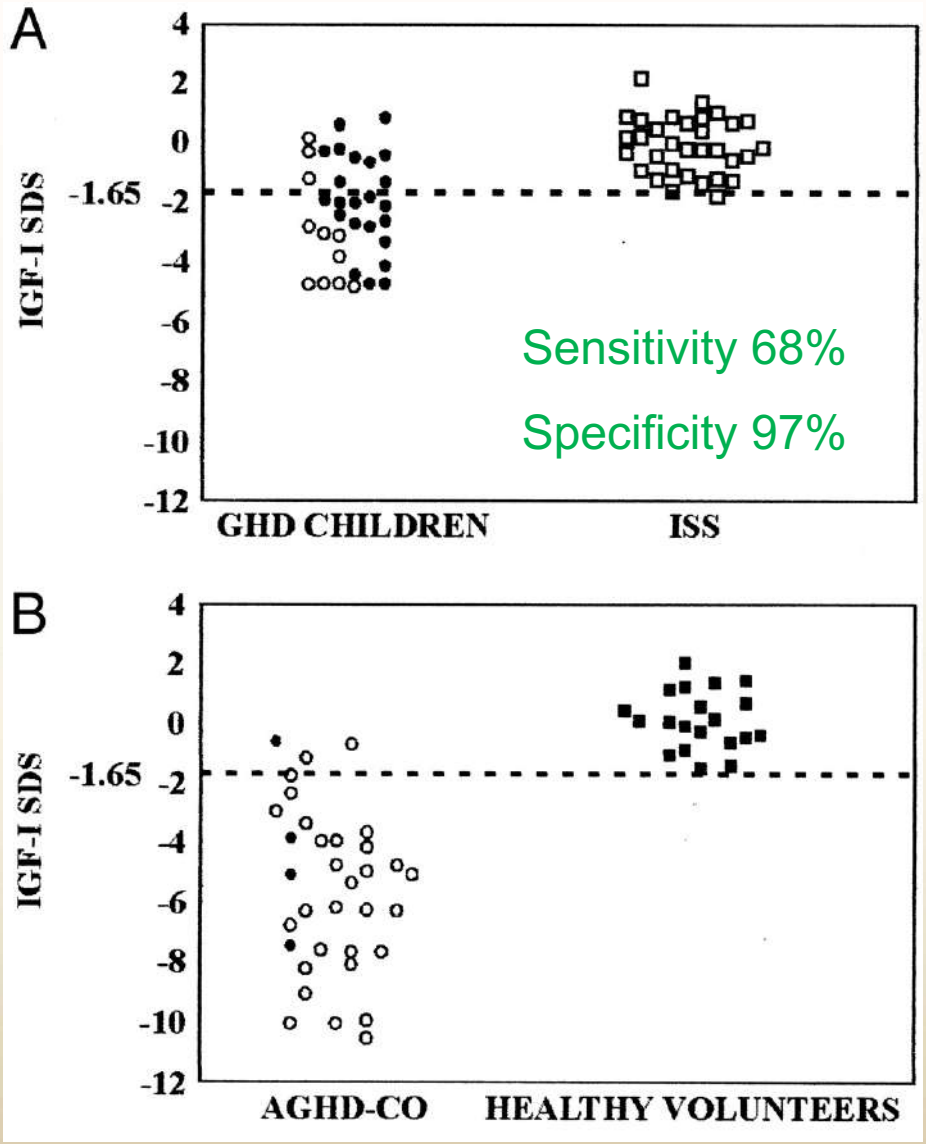
IGFBP-3 levels in Males from Juul et al JCEM 1995

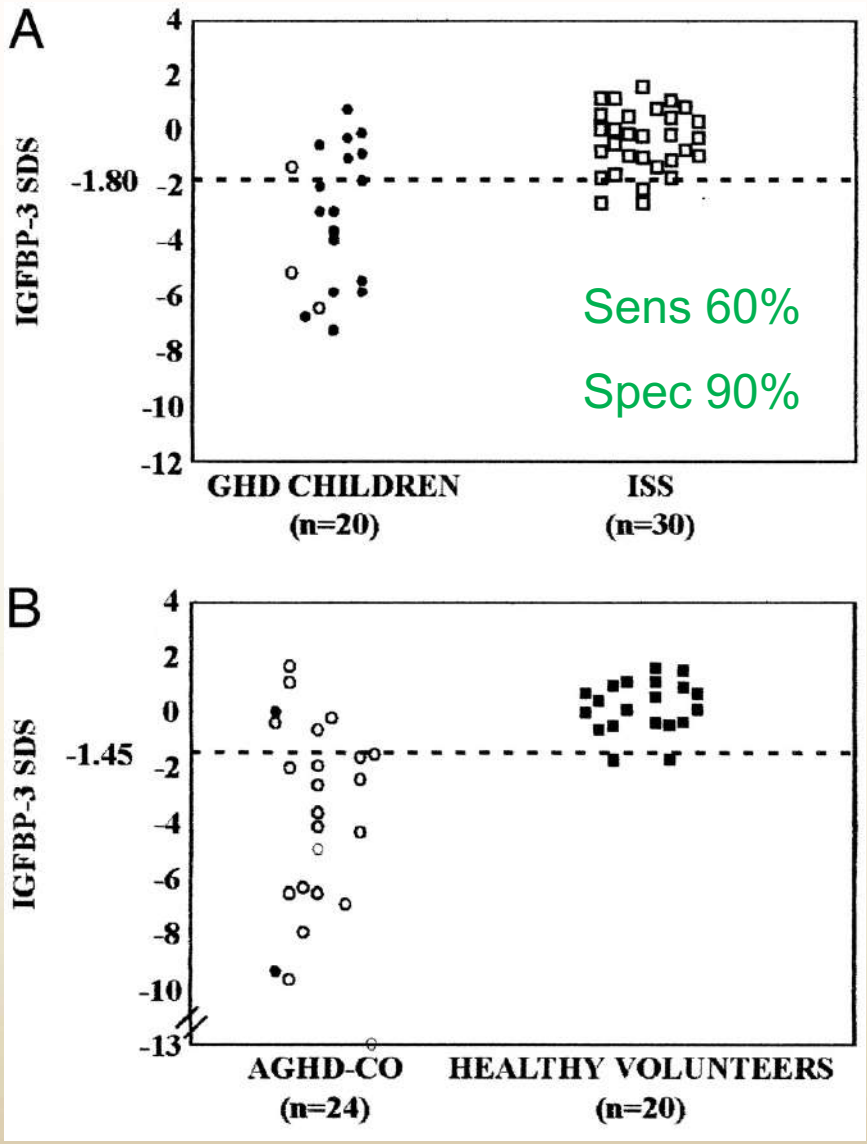
An example of performance of serum IGF-I and IGFBP-3 assessments



Ranke et al Horm Res 2000

Cut-off Values (using ROCs) for IGF-I and IGFBP-3 SDS in the diagnosis of GHD, defined by peak GH level <7μg/L

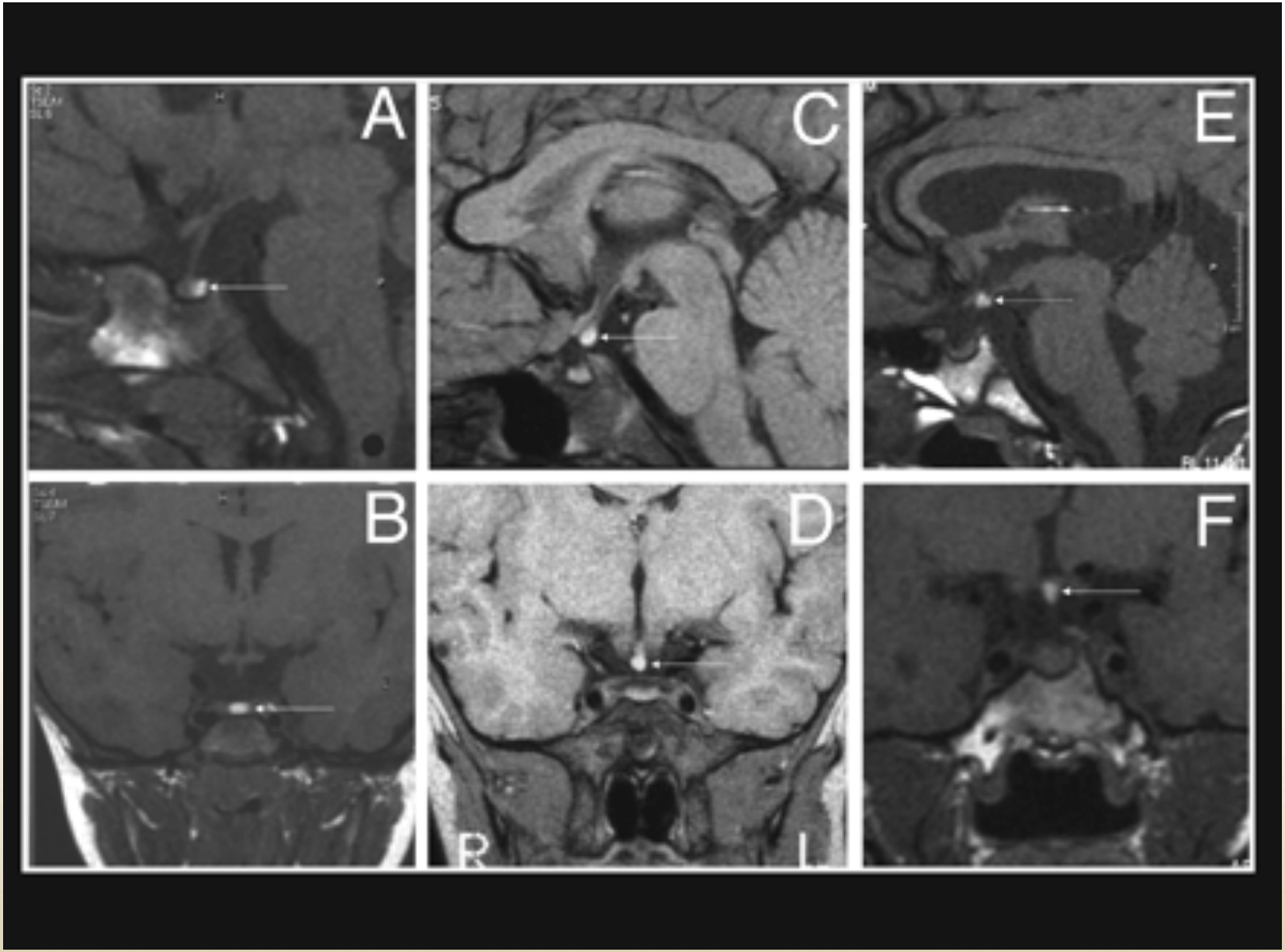




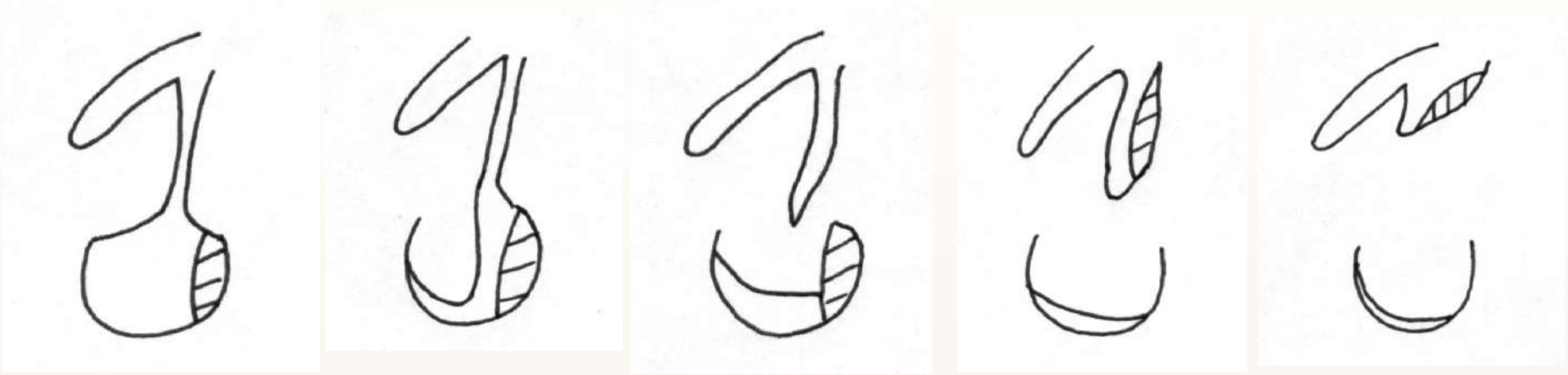
Boquete et al JCEM 2003

The Process (Personal Practice)

- Once a decision is made to undertake GH provocation testing, then other pituitary function needs to be checked
- Single Provocation test (1st choice agent: Arginine) & serum IGF-I
- If there is a test failure (peak GH < cut-off) & background clinical risk factor / recognised associated condition, then accept as GHD, and ensure hp axis MR done
- If there is a test failure with no risk factors, second Provocation test (2nd choice agent: Glucagon) & repeat serum IGF-I
- If both GH tests failed, arrange hp axis MR

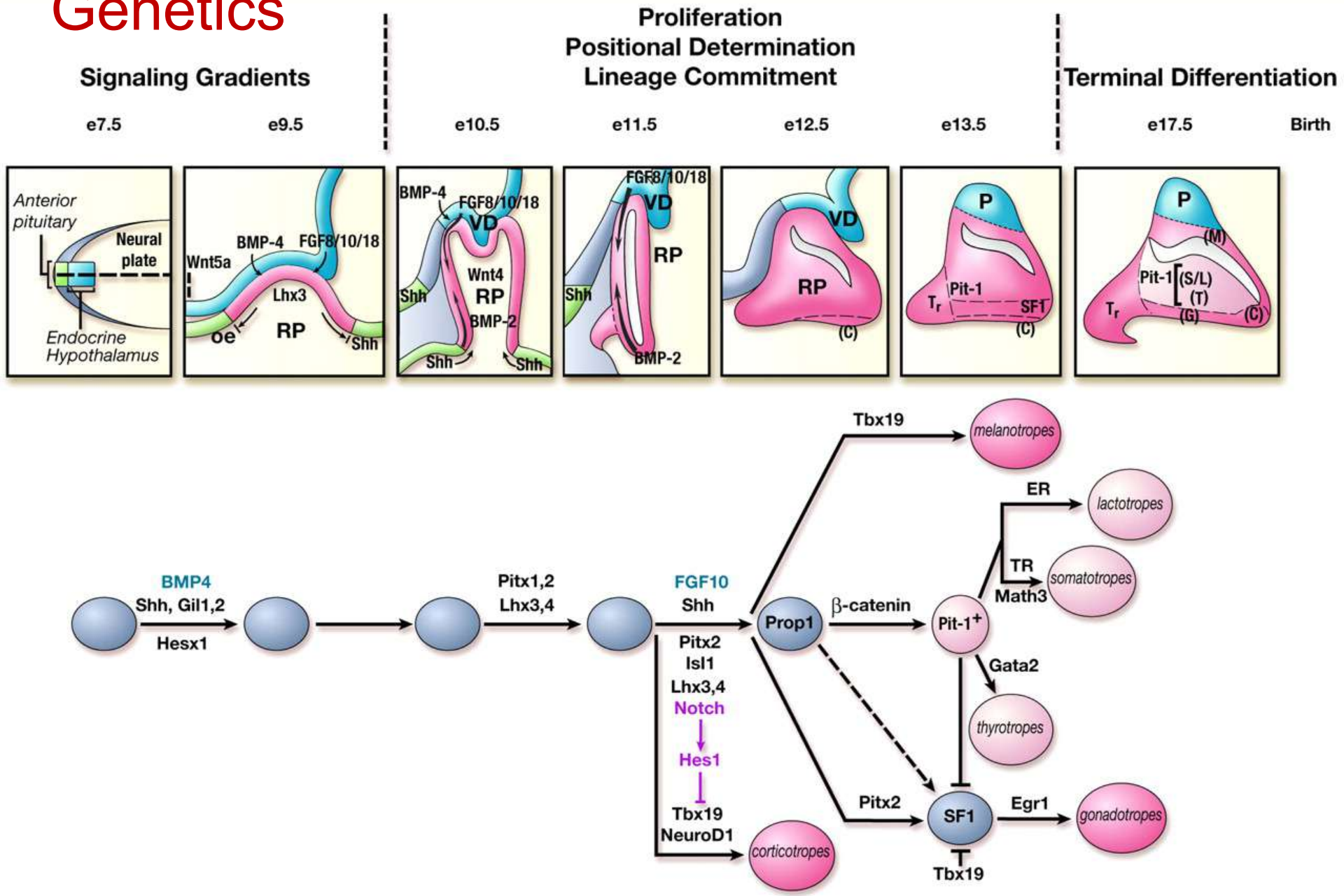


Leger et al JCEM 2005



- We know when we have genuine GHD, but significant uncertainty remains when we have biochemical GHD without MR abnormality, or only minor anomaly

Genetics


Signaling Gradients
Proliferation
Positional Determination
Lineage Commitment
Terminal Differentiation
e7.5
e9.5
e10.5
e11.5
e12.5
e13.5
e17.5
Birth
Anterior pituitary
Neural plate
Endocrine Hypothalamus
Wnt5a
BMP-4
FGF8/10/18
Lhx3
Oe
RP
Shh
Wnt4
BMP-2
VD
P
(M)
Pit-1
(S/L)
(T)
(G)
(C)
Tr
SF1
BMP4
Shh, Gil1,2
Hesx1
Pitx1,2
Lhx3,4
FGF10
Shh
Pitx2
Isl1
Lhx3,4
Notch
Hes1
Tbx19
NeuroD1
Prop1
β-catenin
Pit-1+
Tbx19
melanotropes
ER
lactotropes
TR
Math3
somatotropes
Gata2
thyrotropes
Pitx2
SF1
Egr1
gonadotropes
Tbx19
corticotropes

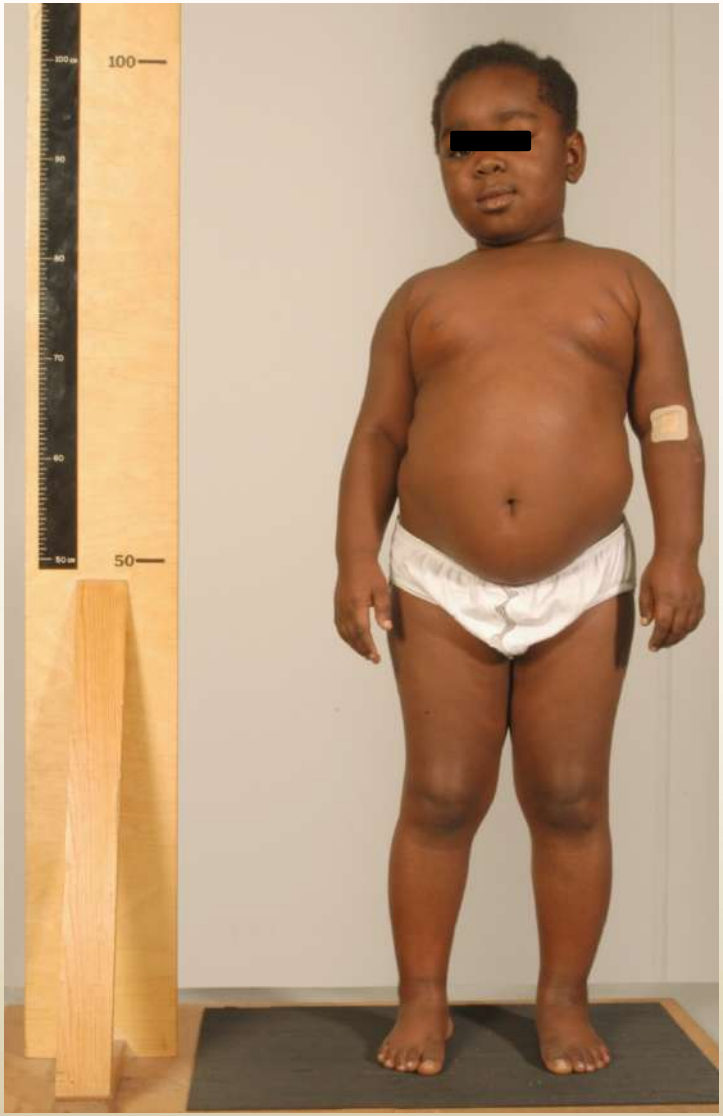
Case 2

- First seen at 2 years with poor growth from birth
- Normal developmental milestones
- Positive history of short stature in paternal grandfather
- By the age of 7 years, she was self-conscious, manipulative and was showing deterioration in her school performance
- Mid-parental height – 25th centile

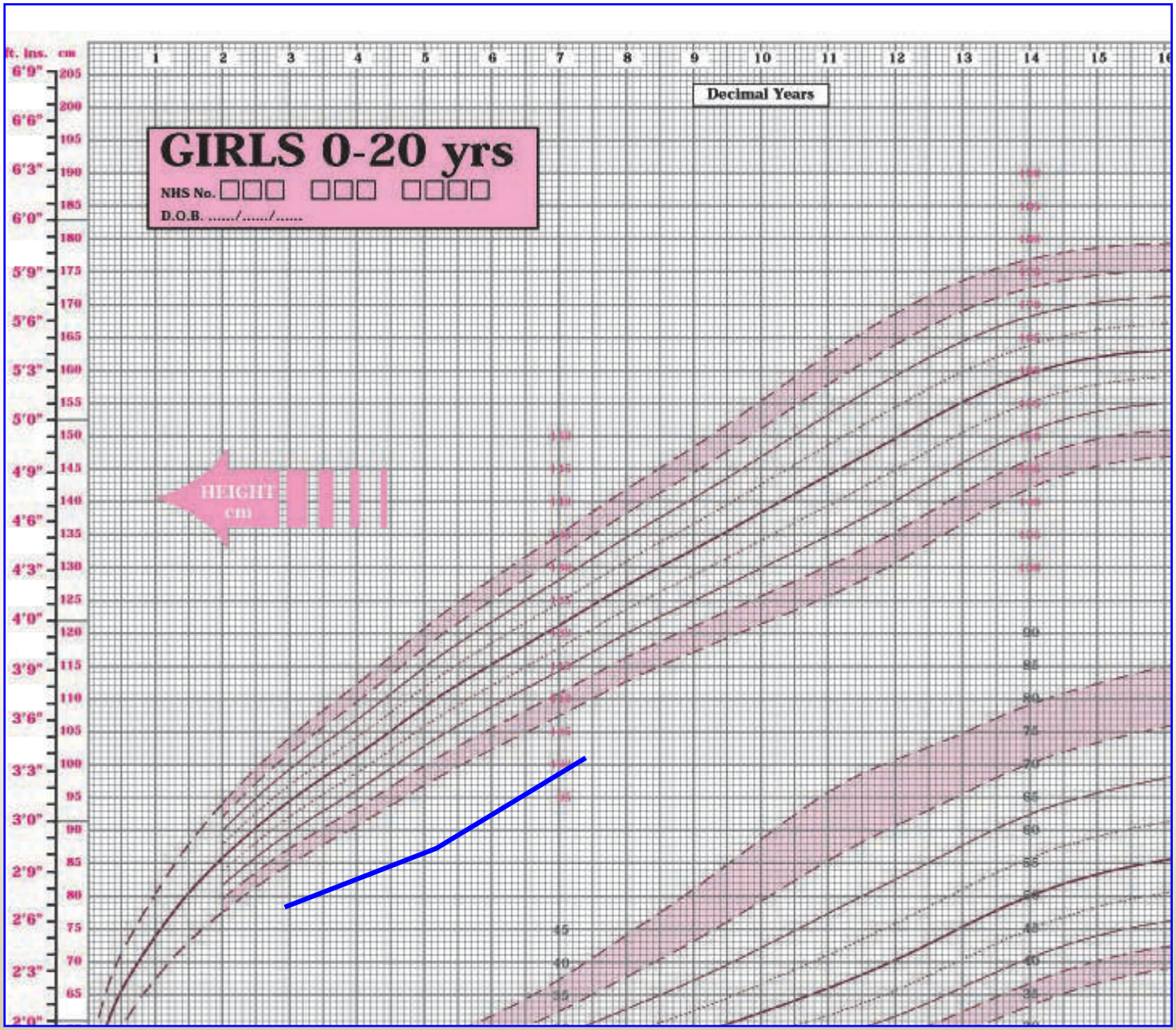
- Initial Investigations: FBC, ECG, Blood sugar, Urinalysis, Urea & Electrolyte, Chest radiograph – Normal

Case 2

- Marked short stature – Cause not defined
- Differential diagnosis:
  - Skeletal dysplasia
  - Storage Disorder (Mucopolysaccharidosis)
  - GH deficiency
- Further investigations required for which facilities were not available in Nigeria



Age 7 years


ft. ins. cm
6'9" 205
6'6" 200
6'3" 195
6'0" 190
5'9" 185
5'6" 180
5'3" 175
5'0" 170
4'9" 165
4'6" 160
4'3" 155
4'0" 150
3'9" 145
3'6" 140
3'3" 135
3'0" 130
2'9" 125
2'6" 120
2'3" 115
2'0" 110
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Decimal Years
GIRLS 0-20 yrs
NHS No. □□□ □□□ □□□□
D.O.B. ...../...../.....
HEIGHT cm

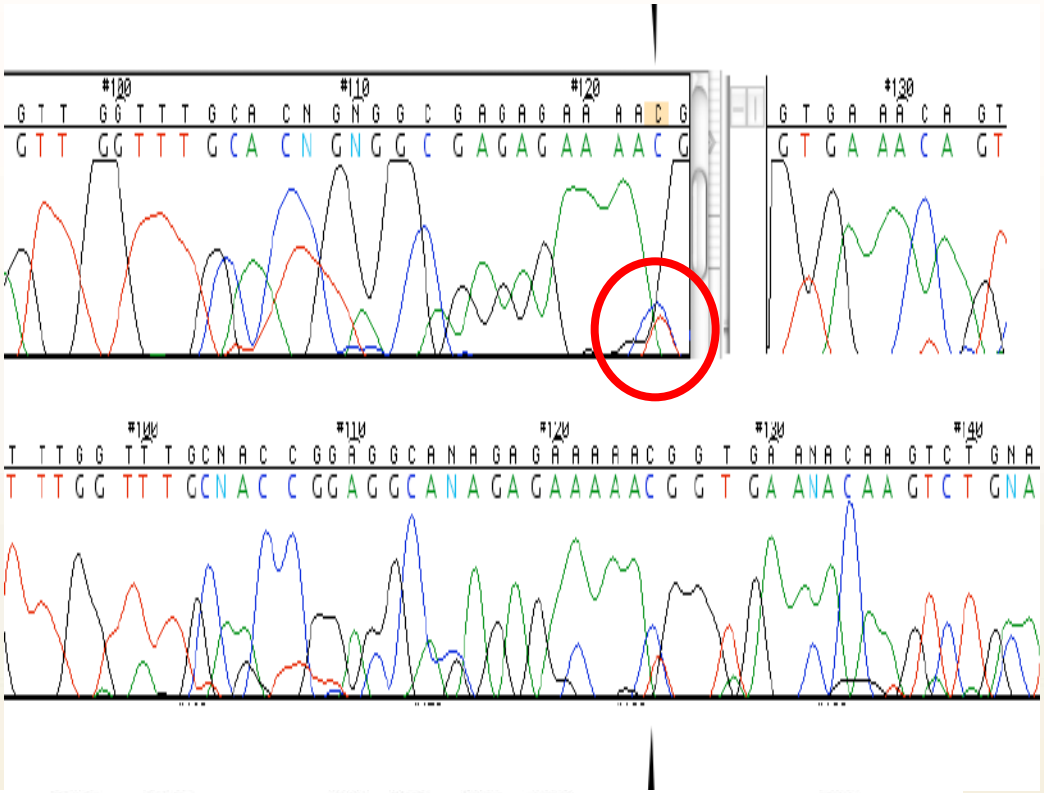
Summary of Pituitary Investigations in the UK

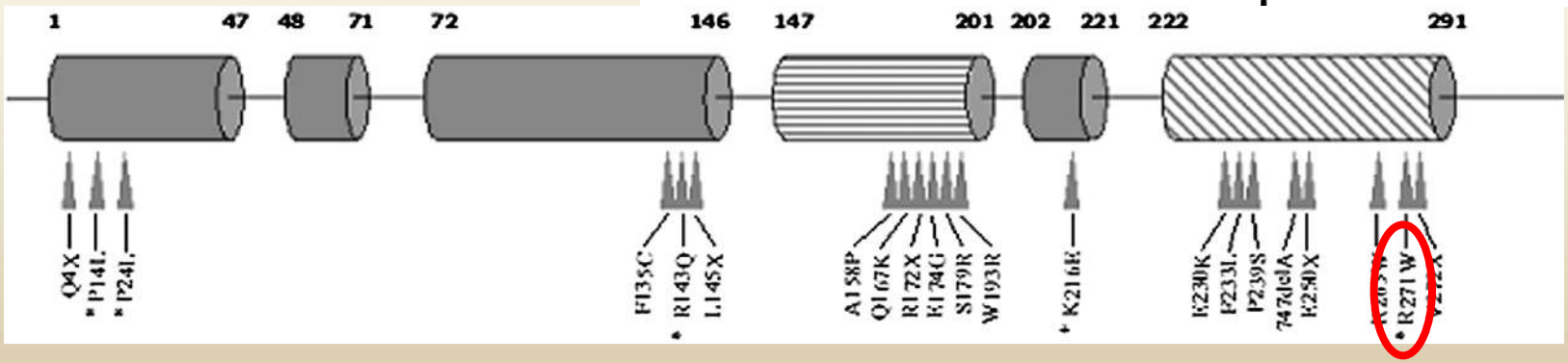
Test	Result	Comment
Arginine Stimulation test - peak GH level	<0.05mcg/l	low
IGF-1	33ng/ml	low
Prolactin	<50mu/l	low
Synacthen Test – Cortisol (nmol/l) Basal 30 minute 60 minute	 161 667 881	 Normal result
GnRH Test Basal 30 minute 60 minute	LH (U/l) FSH (U/l) <0.1 1.1 1.7 10 2.6 14	 Normal result
TRH test Basal TSH 15minute TSH 60minute TSH Free T4	 3.4mu/l 3.6mu/l 3.3mu/l 9pmol/l	 normal normal low

What is the Diagnosis?

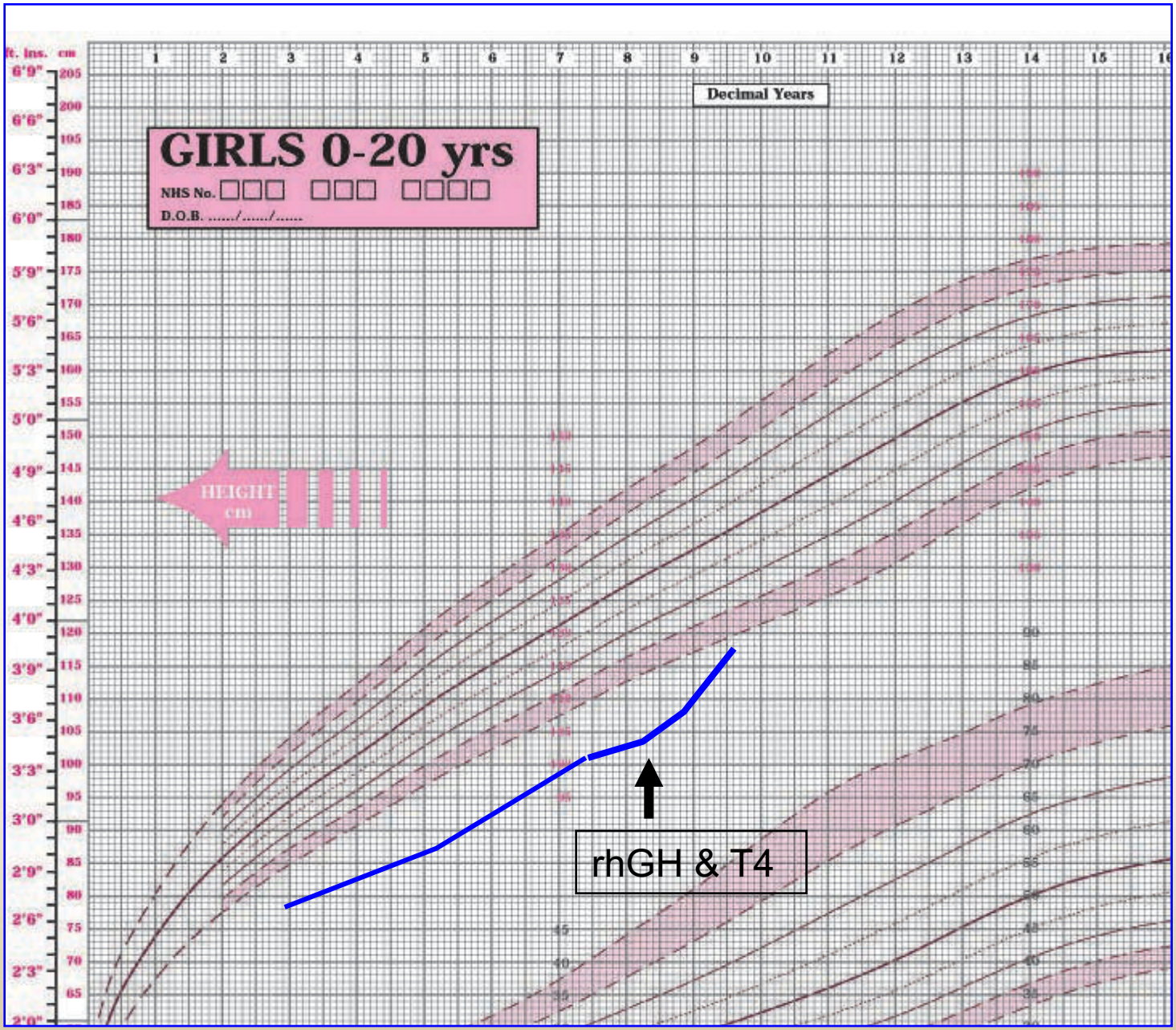
PIT1/R271W mutation in exon 6

- Heterozygous c>t change indicated by circle
- (cgg>tgg, R>W)
- Dominant mutation in POU1F1





Turton, J. P. G. et al. J Clin Endocrinol Metab 2005;90:4762-4770


GIRLS 0-20 yrs
NHS No. □□□ □□□ □□□□
D.O.B. ...../...../.....
Decimal Years
HEIGHT cm
rhGH & T4

Guiding Clinical Practice

- Clinicians should be familiar with the details of the assays used in their local laboratories for GH, IGF-I and IGFBP-3.

- Where local GH assay and test specific data on cut-offs for stimulation tests are not available, we would recommend the use of cut-off values described by Wagner et al.

- Normative data are available for most IGF-I and IGFBP-3 assays. These should be used when interpreting results.

- The diagnosis of GHD remains multifactorial and our practice is based around Consensus Guidelines. MR imaging should include specific views of the hypothalamic-pituitary axis.

- Our practice is to prime all prepubertal patients (aged >8 years for girls or >9 years for boys) prior to GH stimulation testing; oral oestrogen based preparations are used for girls and boys.

- Genetic tests may be required to confirm diagnoses

Conclusions

- Regular plotting of growth data on an appropriate chart
- Recognising an abnormal growth pattern & triggering investigations
  - Hierarchical approach
- Achieving a specific diagnosis