Disorders of Growth

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knowledge changing life

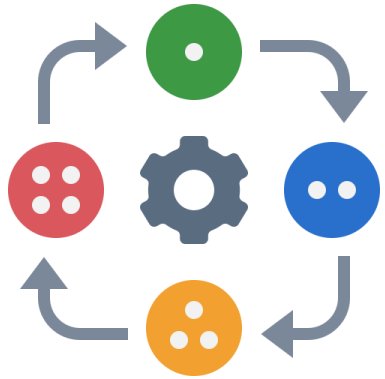
ABP Content Domains

- GH/IGF-1 axis
- Regulation of growth in the fetus, neonate, child, and adolescent
- Short stature
- Congenital and acquired GH deficiency
- Disorders of GH action and GH sensitivity (primary IGF-1 deficiency)
- Idiopathic short stature
- Syndromes associated with short stature
- Growth disorders not related to the GH-IGF axis
- Skeletal dysplasia
- Effects of chronic illness on growth including cancer therapy
- Tall stature
- Overgrowth syndromes

We will also cover previous content specs

Let’s start with normal physiology

Phases of Typical Linear Growth



1. Intrauterine growth

- Most rapid growth during lifetime (100 cm/yr)
- **Nutrition** and **maternal/fetal health** are key drivers
- Paternally expressed **IGF-2** in fetus and placenta is important in fetal growth

2. Infancy (birth to age 2)

- Growth remains rapid (25-50 cm/year)
- **Nutrition** remains key driver 6-9 months of life, then **GH** gains importance
- **Physiological rechanneling** (crossing height percentiles) during transition from prenatal to postnatal growth

3. Childhood

- Slowest and longest period of growth (5 cm/yr)
- **Growth hormone** is primary driver
- Shifting percentiles is *abnormal* in this phase

4. Adolescence

- Final 15% of growth (8-10 cm/year)
- **Girls**: accelerate at 10 years, peak 9 cm/yr at 11.5 years, with average 7.5 cm growth post-menarche
- **Boys**: accelerate at 12 years, peak 10 cm/yr at 13.5 years, with 97% height attained at bone age of 15 years
- **Growth hormone** secretion increased by **sex steroids**

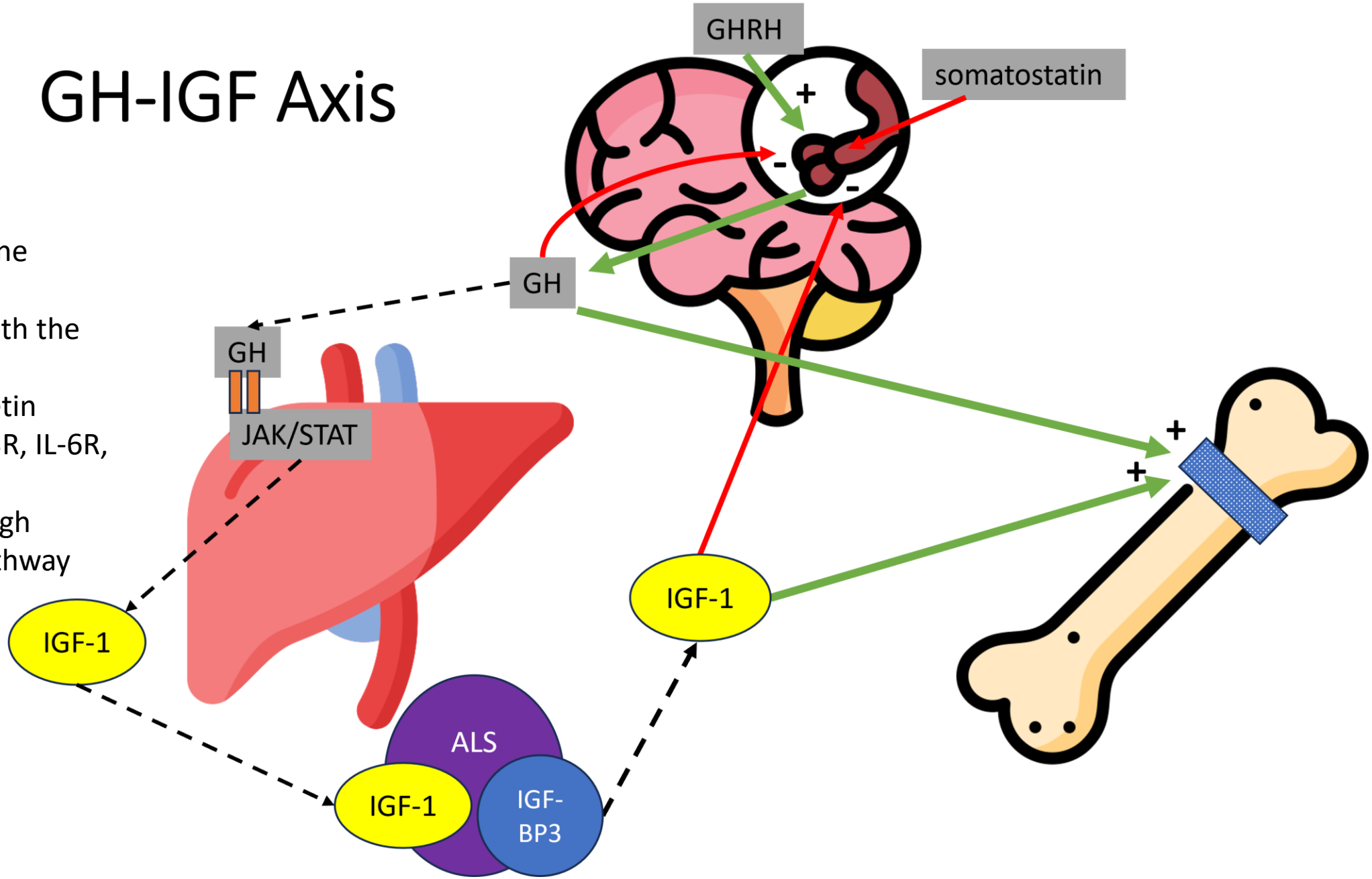
Regulators of Linear Growth

	Variables
Endocrine System	Growth Hormone, IGF-1, Thyroid Hormone, Glucocorticoids, Estrogens, Androgens, Insulin
Nutrition	Undernutrition, Overnutrition
Autocrine/Paracrine at Growth Plate Chondrocytes	Fibroblast Growth Factors (FGF), C-Type Natriuretic Peptide, PTHrP and Indian Hedgehog (IHH), IGF-1 and IGF-2
Pro-inflammatory Cytokines	TNF-α, IL-1β, IL-6
Cartilage Matrix	Collagen type I, Collagen type II, Collagen type III, Aggrecan
Intracellular Signaling	*SHOX* encoded transcription factor, RAS-mitogen-activated protein kinase (MAPK) pathway
Growth Plate Senescence 	Intrinsic developmental program of growth plate. Decrease of chondrocyte proliferation → involution of growth plate → inert cartilage remodeled into bone → epiphyseal fusion

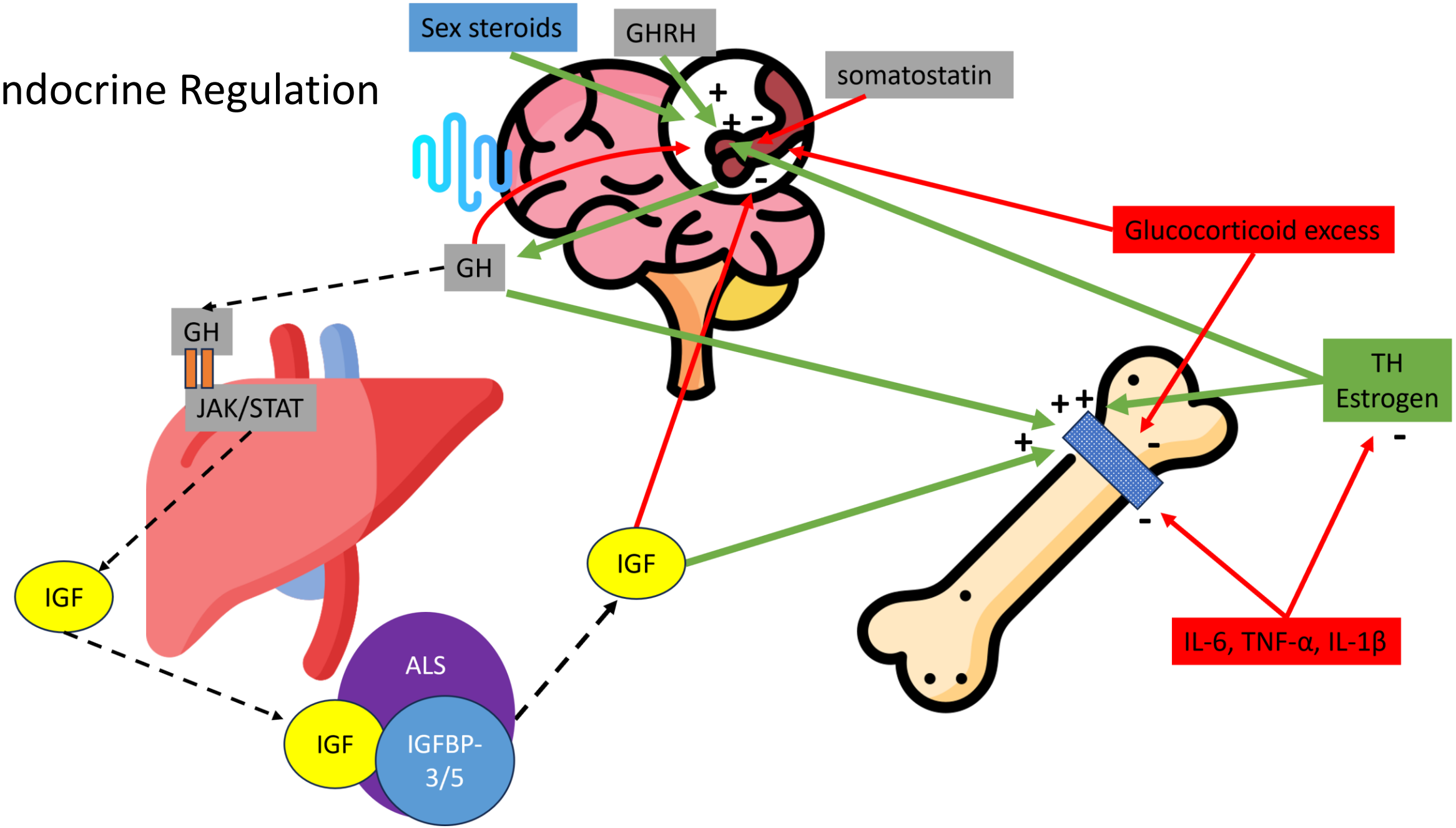
GH-IGF Axis

GHR

- Class I cytokine receptor
- Homology with the PRLR, EPOR, thrombopoietin receptor, IL-3R, IL-6R, IL-7R
- Signals through **JAK/STAT** pathway

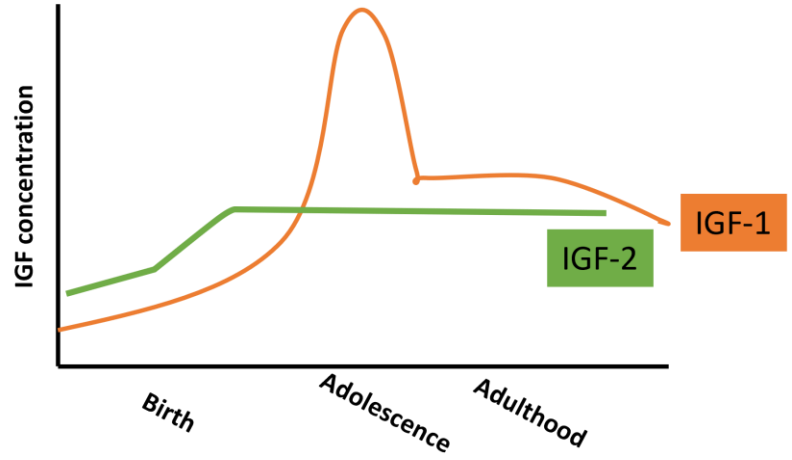


Endocrine Regulation



Insulin-like growth factors

- Polypeptides with homology to insulin
- **IGF-1**: Primarily produced in liver and acts in an *endocrine* manner as the major mediator of GH-stimulated somatic growth.
  - Produced in growth plates and acts as *paracrine* factor. Acts in an *autocrine* manner in muscle and adipocytes
- **IGF-2**: Primarily a *paracrine* factor, expressed at high levels in fetal tissues; IGF-2 is maternally imprinted

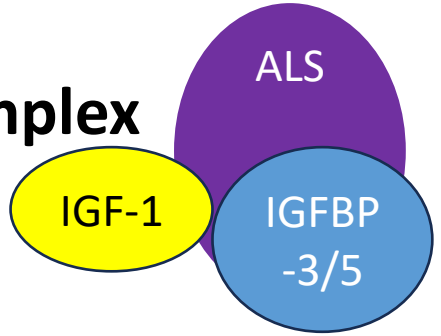


Note: IGF-2 and IGF-1 levels not to scale

- Bind and activate the **IGF1 receptor**, a class II tyrosine kinase receptor
  - Heterotetrameric glycoprotein with 2 alpha and 2 beta subunits
  - Similar structure to insulin receptor
  - High affinity for IGF-1 and IGF-2
  - 100-fold lower affinity for insulin
  - Stimulate cell growth and proliferation
  - Inhibit apoptosis via activation of **PI3K/AKT** pathway
- **IGF2/mannose-6-phosphate receptor** inhibits IGF-1 and IGF-2 activities by sequestering and degrading these hormones

IGF Binding Protein Superfamily

- Family of bioactive binding proteins that bind IGFs with higher affinity than IGF1R
  - Extend half life of IGFs
  - Transport IGFs to target cells
  - Modulate interaction of IGFs with surface membrane receptors
  - Six IGFBPs have been identified
- IGFBPs mostly act to *inhibit IGF action* by competing with IGFRs
- IGFBP-1: stimulated by prolonged fasting; suppressed by insulin
- **IGFBP-3**: major IGFBP in human serum; primarily stimulated by GH
  - Testosterone, estrogen, and thyroxine also promote IGFBP-3 synthesis
- IGFBP-3 and IGFBP-5 unique in that they circulate as a **ternary complex**

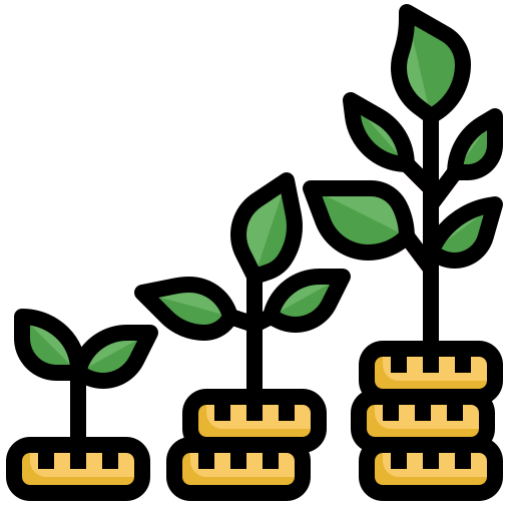


Evaluation of Growth

Clinical Evaluation of Growth

- **Measurement**
  - Wall-mounted stadiometer for standing height
  - Recumbent length board for recumbent length
- **Growth Charts**
  - CDC and WHO curves for height, weight, BMI
  - Velocity charts
  - Growth charts for certain genetic syndromes (Turner Syndrome, Down Syndrome)

Growth Charts



CDC (2000)

- 2-19 years
- Standing height (> 2 years)
- Cross-sectional data across U.S.
- Reference population from national surveys from 1963-1980
- ~50% ever breastfed and only 1/3 breastfed at 3 months
- Observationally describe how children in the population grow

WHO (2006)

- Birth to 2 years
- Recumbent length (≤ 2 years)
- Longitudinal data across 6 diverse countries
- Children predominantly breastfed for at least 4 months and still at 12 months
- Identify how children **should** grow when provided optimal conditions (ideal growth)
- Better description of physiological growth in infancy

Clinical Evaluation: Body Proportions

Body Proportion Measure	Technique	Diagnostic clues
Upper to lower segment ratio	LS: pubis symphysis to floor (legs) US: standing height – LS (head + trunk)	Normal: U/L 1.7 at birth; 1.0 by age 10 yrs Early growth cessation: ↑ U/L Late growth cessation: ↓ U/L
Arm span to height	Arm span (AS) – distance from end of middle fingers with outstretched arms versus standing height	AS < height until age 8 yrs AS = height at 8-12 years AS > height once > 12 years
Sitting height index	Sitting height / standing height (Reference data by age and sex from NHANES III)	Elevated sitting height index: SHOX deficiency, hypochondroplasia
Limb segment proportions	Proximal limbs: humerus & femur Middle limbs: radius/ulna & tibia/fibula Distal limbs: hands & feet	Rhizomelia – proximal shortening Mezomelia – middle shortening Acromelia – distal shortening

Clinical Evaluation of Growth

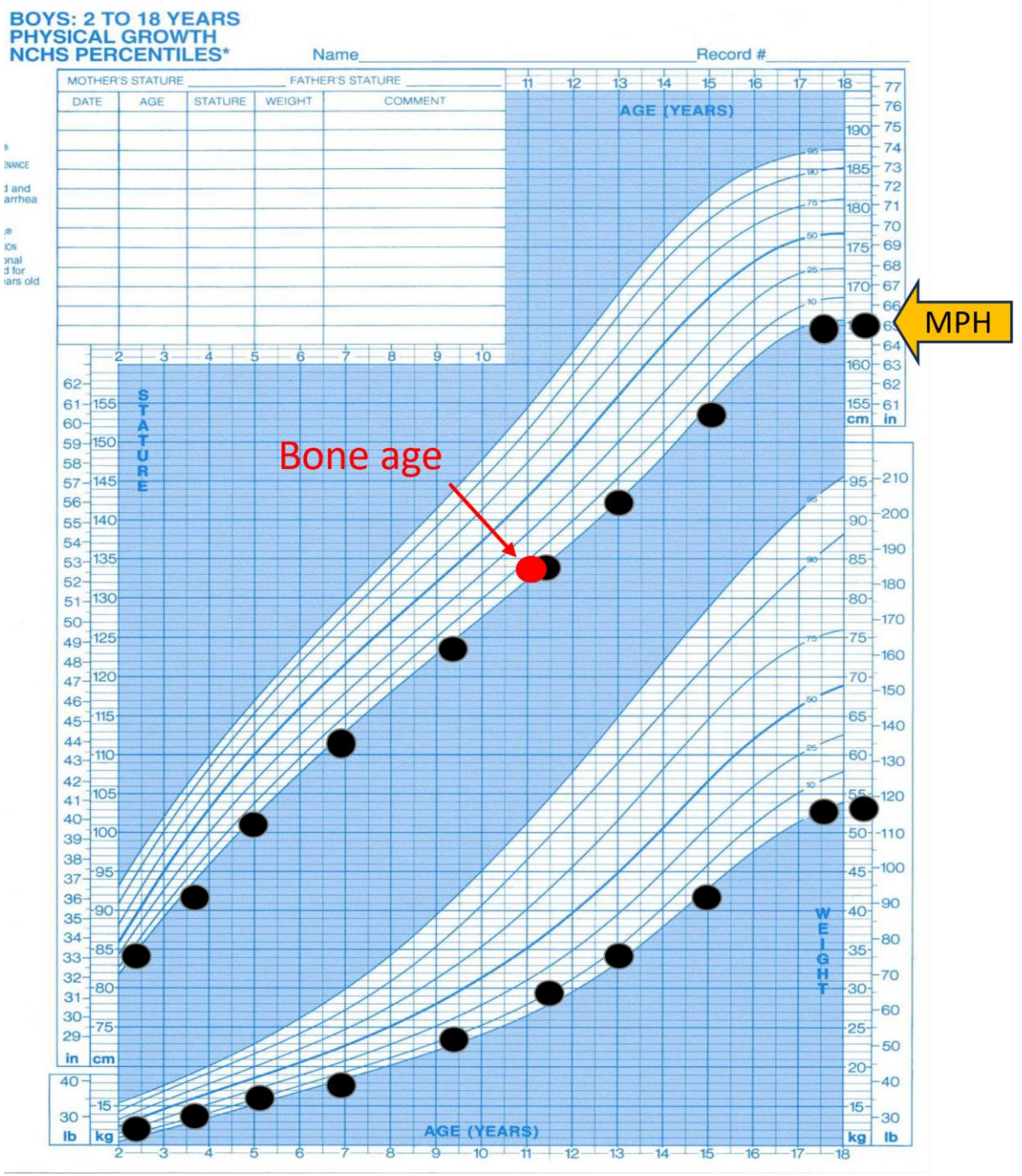
- **Skeletal Maturation**
  - Bone age radiograph, compared to published standards (Greulich and Pyle or Tanner-Whitehouse), to assess degree of skeletal ossification
  - Mirrors physical development tempo, indicates remaining growth potential
  - Factors that drive growth (TH, GH, E2, nutrition) positively regulate skeletal maturation
  - Dental maturation correlates with skeletal maturation
- **Prediction of Adult Height (humility needed!)**
  - Simplest/least accurate: child follows constant height centile until adulthood
  - Mid-parental height (MPH): [Note - assumes height inherited in polygenic fashion!]
    - For boys: [mother's height + 5 inches] + father's height / 2
    - For girls: [father's height – 5 inches] + mother's height / 2

    } **~70% of kids within ± 2-2.5 inches**
  - **Bayley-Pinneau** prediction: adult height predicted by combining child's bone age with height measured at time of the radiograph (Greulich and Pyle Atlas)

Physiologic Short Stature

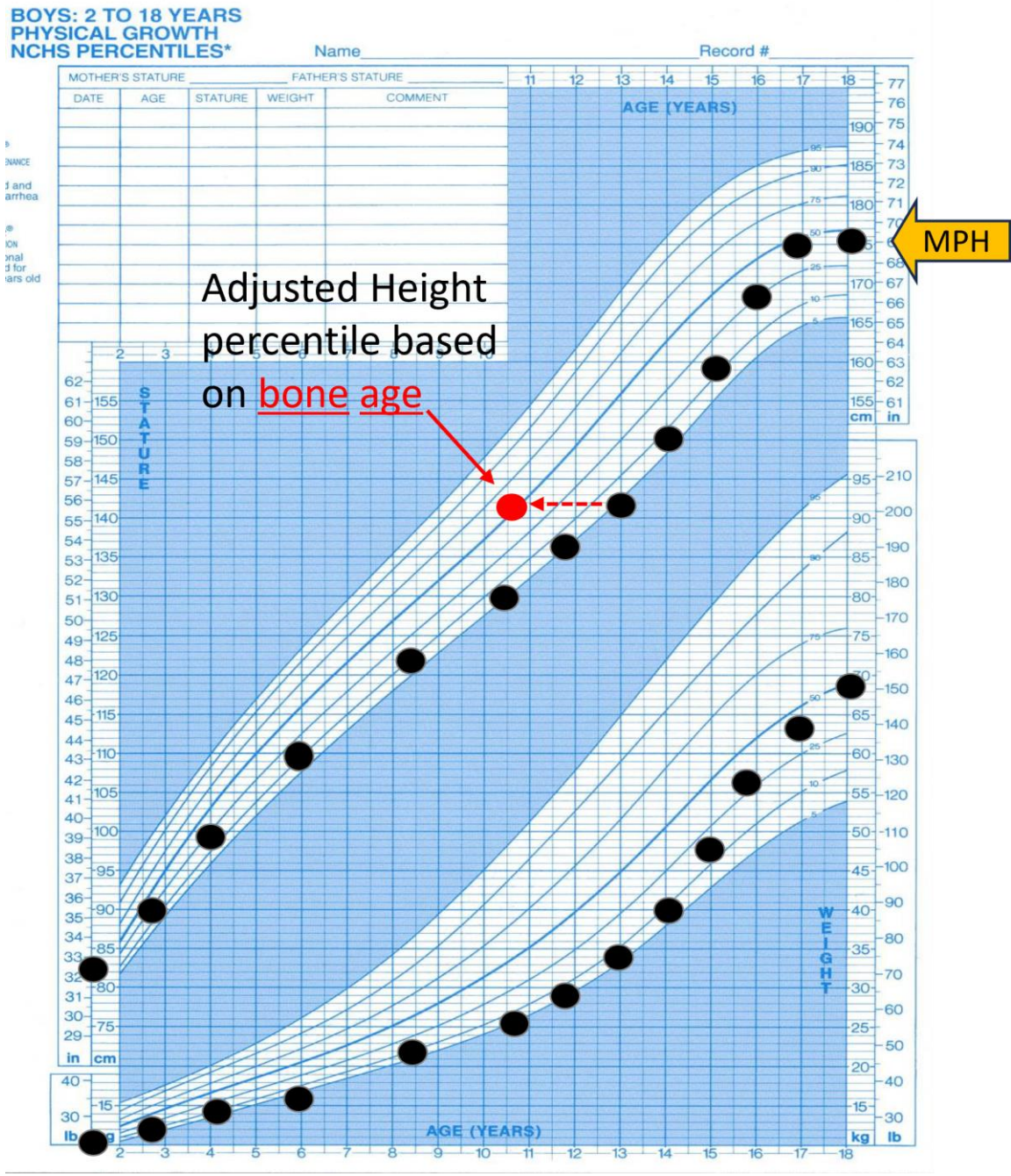
Normal variant: Familial Short Stature

- Height velocity (HV) and bone age are within normal range for familial potential (MPH)
- One or both parents are short
- Rx: reassurance



Normal variant: CDGP

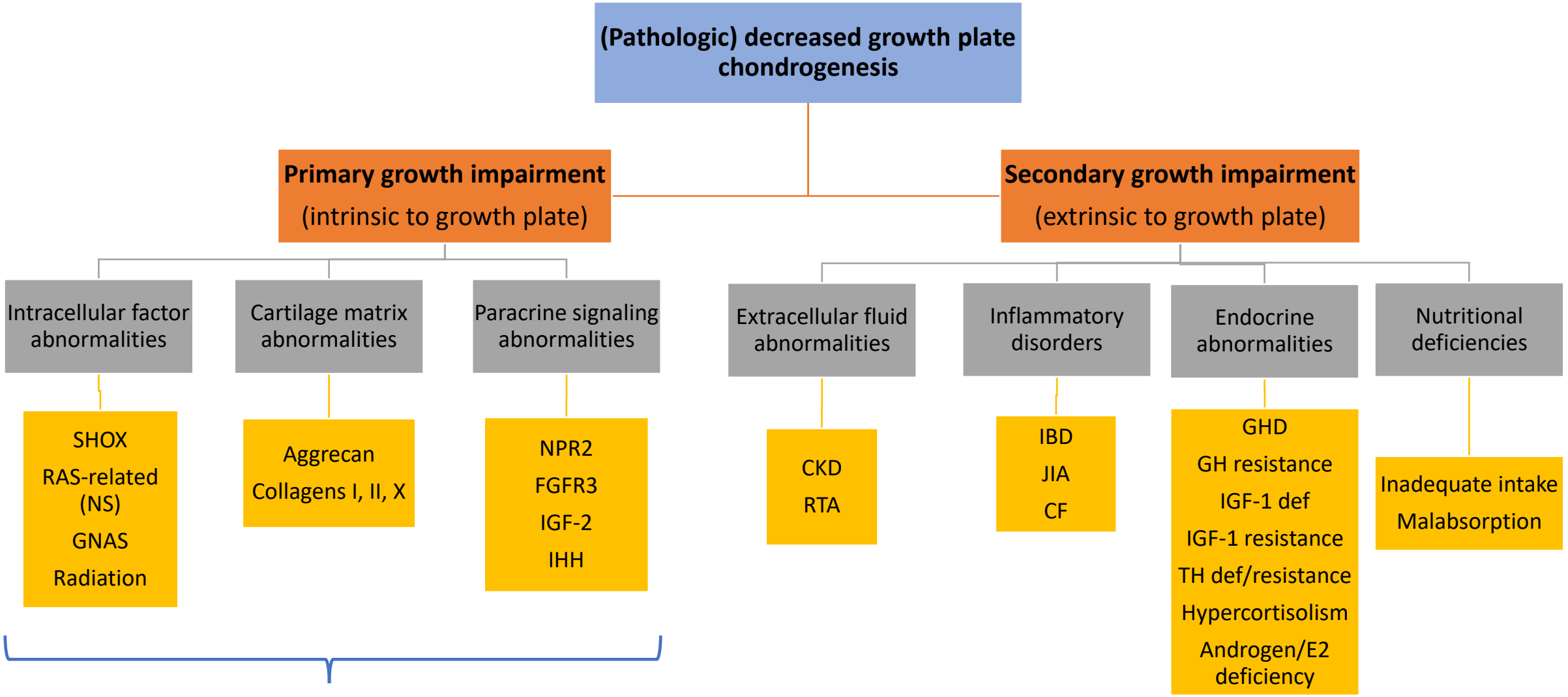
- Constitutional Delay of Growth and Puberty (CDGP)
- Growth is appropriate for bone age, which is delayed relative to chronological age
- Predicted height by bone age aligns with MPH and is within normal range for population
- Often a positive family history for CDGP
- Rx: reassurance and observation
- Consider course of testosterone or estrogen if puberty is delayed and there is increased psychosocial stress



When to suspect pathologic short stature

1. Disproportionate growth (suggests skeletal dysplasia)
2. Downward crossing of height percentile after 2 years of age
3. Growth velocity below the 3rd percentile (-2 SDS) for at least 1 year
4. Height percentile less than the 3rd percentile (-2 SDS)
   - Especially if height centile is less than mid-parental height calculation

- Differential diagnosis very broad, driven by medical history and physical examination



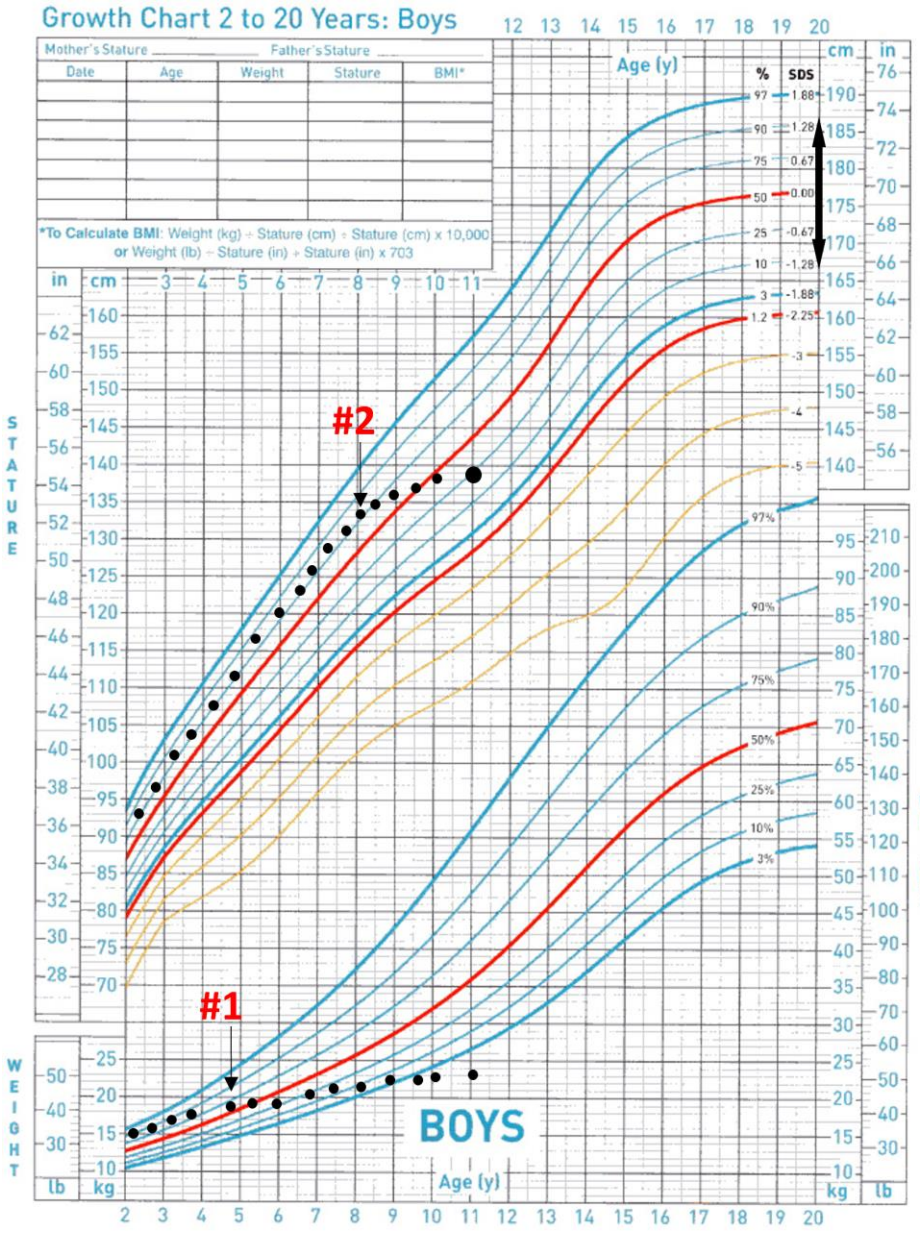
- Skeletal dysplasias and chondroplasias (short/malformed bones)
- Genetic defect affects growth plate and other tissues → syndromes with short stature and other congenital abnormalities

- Primary issue is in extra-skeleton organ system (kidneys, thyroid, immune system), causing abnormal concentration of molecules needed for growth (steroids, inflammatory cytokines, phosphate)

Short Stature: Secondary Growth Impairment

Short Stature: Nutritional Deficiencies

- Most common cause of poor growth globally
- Energy needs exceed intake (EDOs, picky eating) or due to malabsorption (celiac, IBD, CF)
- Malnutrition decreases GH sensitivity and downregulates GHR → decreased IGF-1
- Weight failure precedes height failure
- Bone age and puberty are delayed
- Assess dietary intake and for S/Sx of malabsorption (celiac disease can present as isolated growth failure +/- weight loss)
- **Remember**: short stature genetic conditions can include low BMI in their phenotype (RSS, Noonan)



Compliments of P. Wolfgram

GH Deficiency

- 1:4000 prevalence during childhood
- Isolated or multiple pituitary hormone deficiency (MPHD)
- Congenital or acquired
- Must exclude other causes

GH Research Society recommendations for diagnosis of GHD in childhood and adolescence (2000):

1. Severe short stature (height less than -3 SDS)
2. Height less than 1.5 SD below MPH
3. Height less than 2 SDS and GV less than 1 SDS for CA or a decrease in height SD of less than -1.5 SD sustained over 2 years
4. S/Sx worrisome for intracranial lesion
5. S/Sx suggestive of MPHD
6. Neonatal S/Sx of GHD

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GHD: Congenital

- Neonatal presentation:
  - Hypoglycemia
  - Congenital hyperbilirubinemia (associated with ACTH def)
  - Micropenis
- Typically, AGA with decreased GV in first year of life, falling to a height SDS below -2 SD
- Phenotype affected by ± MPHD
- "Cherub-like" phenotype: midface hypoplasia, frontal bossing, hypotonia, truncal adiposity, delayed dentition, high-pitched voice

Causes of Congenital GHD
Genetic • Isolated: GH1, GHRHR • Bio-inactive GH (d/t defect in GH1) • MPHD: LHX3, LHX4, PROP1, POU1F1
Congenital malformations of brain, hypothalamus, or pituitary gland (structural brain abnormality) • Small anterior pituitary, ectopic posterior pituitary Holoprosencephaly or anencephaly • Optic nerve hypoplasia/septo-optic dysplasia
Midline Facial Defects • Cleft lip/cleft palate • Single central incisor
Idiopathic

GHD: Acquired

- Presents with growth failure, delayed bone age, and increased weight to height ratio
- Somatotrophs vulnerable to disruptions in blood supply (trauma, infarction) as they only receive blood from portal vessels, not the anterior pituitary artery

Causes of Acquired GHD
Pituitary/Midline Tumors • Midline brain tumors: germinomas, meningiomas • Optic gliomas (*50% associated with NF1*)
Cystic Lesions • Rathke's cleft cysts, arachnoidal cysts • Craniopharnygiomas (*GHD is most common hormone deficiency, in 75-100% cases before Rx*)
Radiotherapy
Chemotherapy
Trauma (TBI)
Infiltration (Langerhan cell histiocytosis with pituitary involvement – DI nearly 100%; *GHD in 40%)*
Inflammation or Infection (neurosarcoidosis, meningitis, hypophysitis)
Pituitary Infarction
Psychosocial (emotional) deprivation (growth arrest lines with recovery when circumstances improve)

GH Insensitivity/Resistance

- Group of inherited disorders with reduction or absence of biologic effects of GH, many related to loss-of-function *GHR* mutations
- **Laron Syndrome**
  - Homozygous or compound heterozygous mutations in *GHR*
  - Severe **post**natal short stature
  - Dysmorphic features: small face, hypoplastic "saddle" nasal bridge, high-pitched voice, truncal adiposity, micropenis
  - Hypoglycemic episodes in infancy; hyperlipidemia
- ***STAT5B*** missense mutation
  - Severe postnatal growth failure and immune dysregulation
- Milder phenotypes exist (partial GHI) d/t heterozygosity for dominant-negative GHR mutations

Lab evaluation

- ↓↓ IGF-1, IGFBP-3, and ALS
- ↑ basal and stimulated GH levels
- With classic GHI: **↓↓ GHBP levels**
- With less common GHI: nl/↑GHBP

Treatment

- Trial of rhGH (preferred; better safety profile and more convenient)
- If no response, recombinant human IGF-1 (mecasermin) in those aged > 2 yrs. Dosed BID, after meals. May cause hypoglycemia.

IGF-1 Deficiency/Resistance

Primary IGF-1 Deficiency/Resistance

- *IGF-1* defects
  - Prenatal growth failure, microcephaly, severe neurocognitive deficits, sensorineural hearing loss
- *IGF-1R* defects
  - Partial loss-of-function
  - **SGA** without catch-up growth
  - Variable degree of growth restriction and delays in psychomotor/mental development
  - Delayed bone age
  - Dx: Nl/↑IGF-1, IGFBP-3, GH
  - May be misdiagnosed as ISS; requires molecular genetic diagnosis

Acid-Labile Subunit Deficiency

- ALS is essential for stabilization of the IGF-1/IGFBP-3 complex as part of the ternary complex
- Defects in *IGFALS*
  - Delayed pubertal onset, slow pubertal progression, but only mild to moderate growth failure
  - ↓↓ ALS, IGF-1, IGFBP-3 (IGFBP-3 lower than IGF-1)

Treatment:

- Trial of rhGH
- If no response, rhIGF-1 therapy
- No effective Rx for IGF-1R defects.

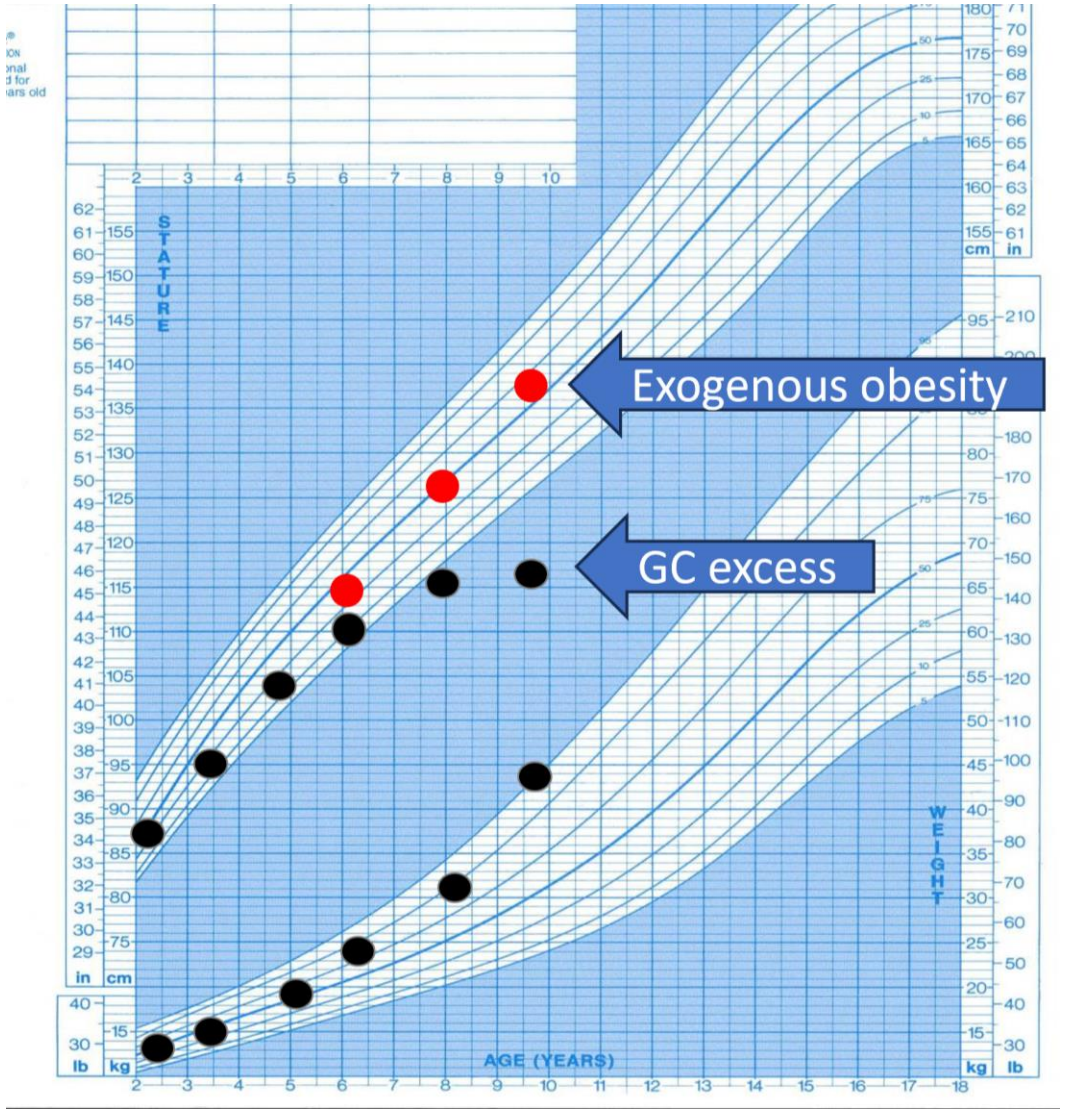
Thyroid Hormone Deficiency or Resistance

- Thyroid hormone (TH) promotes skeletal maturation
  - Directly and indirectly increases IGF-1, IGBP-3, and GH
  - Stimulates key growth factor signaling pathways (IGF1, FGF, PTHrP, Wnt)
  - Stimulates osteoblast activity
- **Hypothyroidism**
  - Most common manifestation in children is declining height velocity, resulting in short stature
  - Initiation with L-T4 associated with period of rapid catch-up growth, frequently without restoration of full growth potential

- **Thyroid Hormone Resistance**
  - **TRβ resistance** (85% cases)
    - Labs: ↑ FT4 and FT3 with unsuppressed TSH level
    - Growth failure, tachycardia, ADHD/hyperactivity, **goiter**
  - **TRα resistance**
    - Labs: low T4, borderline high T3, normal/slightly increased TSH
    - **Prominent growth failure**, delayed dentition, neurocognitive deficits
    - Radiographs: Wormian bones, epiphyseal dysgenesis

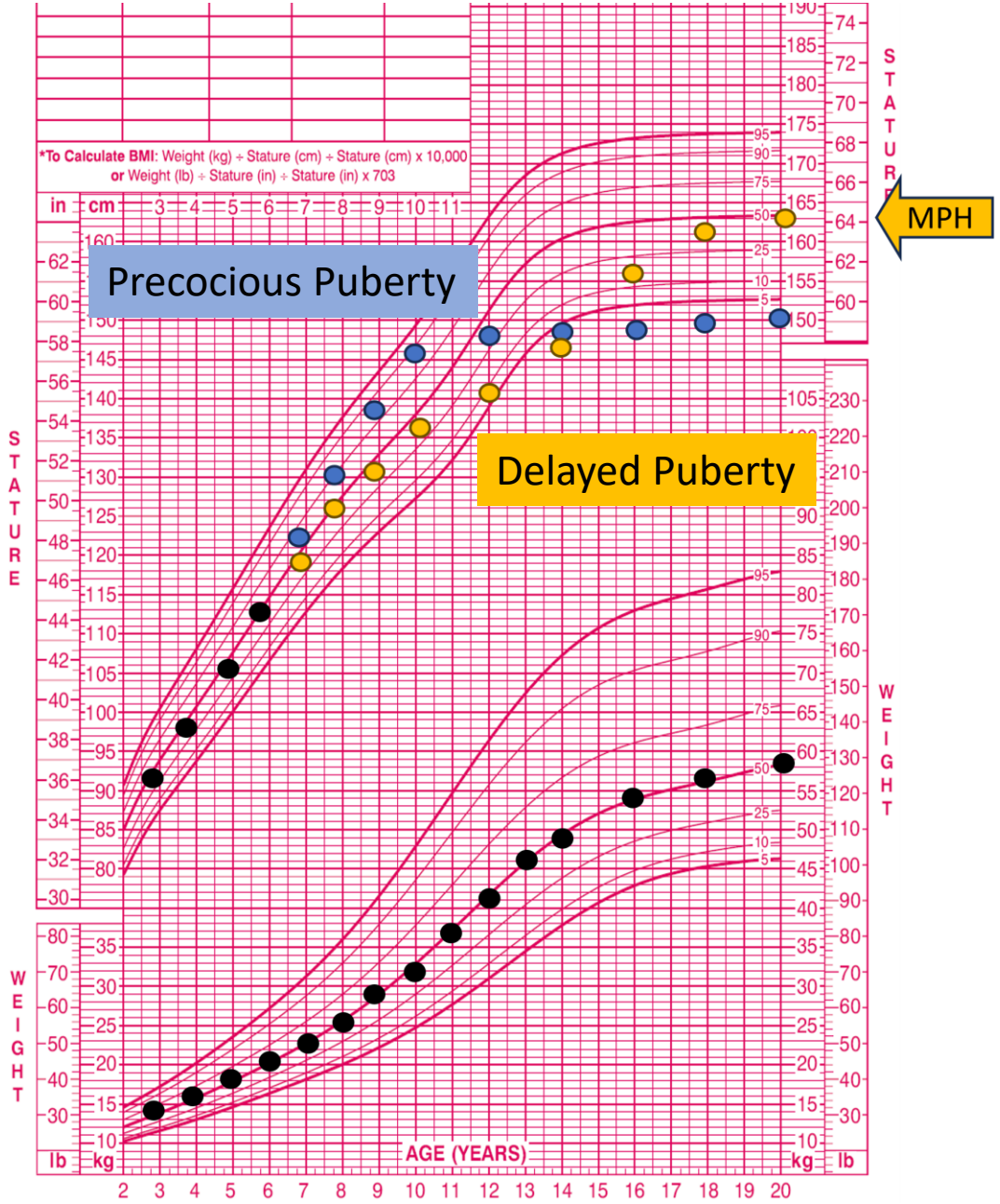
Glucocorticoid Excess

- GCs (exogenous or endogenous) primarily slow growth by *direct action* at the growth plate; also interfere with bone and collagen formation
- Growth impact of GC therapy worse with longer duration of action, duration of use
- GH secretion is normal; IGF1 and IGFBP concentrations are normal
  - rhGH Rx not very effective
- Children with GC excess may present primarily with linear growth deceleration with weight acceleration and lack the “classic” Cushingoid features



Premature Sex Steroid Exposure

- Estrogen accelerates linear growth by stimulating GH secretion and acting directly on chondrocytes
- Estrogen acts on growth plate to accelerate growth plate senescence, decreasing remaining growth potential
- Androgens, aromatized to E2, act on growth plate



Effects of Chronic Illness on Growth

- Chronic inflammatory disorders negatively impact growth by multiple mechanisms
  1. TNF α, IL-1β, IL-6 act inhibit chondrocytes
  2. Malnutrition → reduced IGF-1 levels
  3. Required glucocorticoid therapy
  4. **Relative GH resistance**, possibly due to downregulation of STAT5/JAK2 signaling
- **IBD (Crohn disease)**
  - Poor growth and/or delayed puberty may be the presenting manifestation
  - **50% kids with Crohn Disease have decreased height velocity prior to GI symptoms**
  - Nutritional deficiencies, inflammation, and glucocorticoid therapy.
  - IGF-1 and GH may be decreased
- Conditions that affect content of the extracellular fluid slow linear growth directly at chondrocytes and indirectly through endocrine and nutritional factors
- **CKD:**
  - 1/3 have growth failure, more common with younger age of onset and greater severity
  - Disturbances of GH metabolism and IGF-1 (GH insensitivity, decreased IGF bioavailability due to increased IGFBP concentrations (decreased renal clearance))
  - Metabolic acidosis, uremia, malnutrition, calcium and phosphate imbalance
- **Hypophosphatemia:**
  - low phosphate in extracellular fluid directly impairs growth plate chondrocyte differentiation

Effects of Cancer Therapy on Growth: Radiation

- **Childhood cancer survivors are at increased risk of growth failure**
- Radiation arrests growth plate chondrogenesis, disrupts metaphyseal bone and cartilage absorption, and alters diaphyseal periosteal activity
- Cranial Radiation Therapy (CRT)
  - Greatest growth risk with highest RT doses, younger age, female gender, and prepubertal status
  - GHD most common endocrine late effect of those with h/o CRT with risk highest if the tumor, surgery, or RT > 18 Gy occurs in the hypothalamus-pit region
- Spinal Radiation directly injuries vertebral bodies → disproportionate short stature (↓ U/L ratio, arm span > height)
- *Craniospinal Radiation* has most significant impact on growth of all pediatric cancer radiation treatments
- Total Body Irradiation → ↑ risk GHD and disproportionate short stature
- Cumulative impact of multiple RT courses/types on growth

Effects of Cancer Therapy on Growth: Chemo

- Tyrosine kinase inhibitors
  - Imatinib, sorafenib, sunitinib, used in CML
  - Decreased signal transduction through IGF-1 receptor (a tyrosine kinase receptor) or disrupted growth plate chondrocyte recruitment
- Anti-CTLA-4 monoclonal antibodies (ipilimumab)
  - Risk of immune hypophysitis with resultant GHD and other anterior pituitary deficiencies
- Retinoic acid (neuroblastoma)
  - Irreversible growth plate damage, causing growth failure
- Prolonged systemic glucocorticoid treatment

Short Stature: Primary Growth Impairment

Condition intrinsic to the growth plate

Russell Silver Syndrome

- DNA hypomethylation in *IGF2,* resulting in reduced paternal IGF2 expression
- Pre- (IUGR) and post-natal growth restriction (AH -4 SDS)
- Phenotype: SGA with relative macrocephaly, triangular face, micrognathia, asymmetry
- Labs: ↓ IGF-2, nl/↑ IGF-1, IGFBP-3, GH

Netchine-Harbison Clinical Scoring System (≥4/6)

- ❑ **SGA**: birth weight &/or length ≤ -2 SDS
- ❑ **Postnatal growth failure**: Height at 24 mos ≤ -2 SDS ***OR*** height ≤ -2 SDS from mid-parental target height
- ❑ **Relative macrocephaly at birth**: Head circumference at birth ≥ 1.5 SDS above birth weight &/or length SDS
- ❑ **Protruding forehead**: forehead projecting beyond the facial plane on side view as a toddler
- ❑ **Body asymmetry**: leg length discrepancy (LLD) of ≥ 0.5cm or arm asymmetry ***OR*** LLD < 0.5cm with at least 2 other asymmetrical non-facial body parts
- ❑ **Feeding difficulties &/or low BMI**: BMI ≤ -2 SDS at 24 mos ***OR*** use of a feeding tube or cyproheptadine for appetite stimulation

Molecular Testing:

11p15 LOM (30-60%) and mUPD7 (5-10%)

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Albright Hereditary Osteodystrophy (AHO)

- Pseudohypoparathyroidism type 1a
- Autosomal dominant inheritance of loss-of-function mutation of the maternal allele of *GNAS1*, the gene encoding Gs-alpha
- Short stature, subcutaneous calcifications, brachydactyly (3rd, 4th and 5th metacarpals and metatarsals)
- Round facies, obesity, developmental delay
- Resistance to PTH, gonadotropins, TSH, and GHRH
- If paternally transmission of mutated *GNAS1*: AHO phenotype ONLY with no hormonal resistance

When to Suspect an Osteochondrodysplasia

Prenatal Onset	Postnatal Onset
IUGR Bowing/shortening of long bones, vertebral defects Shortening of ribs; abnormal calvaria ossification Fractures/decreased bone density	Short stature/growth failure; bone deformities Recurrent/pathologic fractures Abnormal radiographs

Diagnostic Evaluation

Clinical Assessment	Radiologic Evaluation
Head circumference, length, height Body segment proportions (↓ arm span; ↑ sitting ht index) Scoliosis or spinal/chest deformities Brachydactyly; Madelung deformity	Skeletal radiographs for appearance of epiphyses, metaphyses, vertebral bodies (enchondromas, vertebral segmentation defects, scoliosis)

Disorders of FGF3 Signaling (gain-of-function mutations)

- Impaired endochondral bone formation

Achondroplasia: most common	AD but most cases are sporadic; rhizomelic dwarfism, large head, midface hypoplasia, lumbar lordosis Motor delays common; IQ normal
Hypochondroplasia: milder phenotype	Short stature typically recognized in early-mid childhood, brachydactyly, large head, ↓ elbow extension

SHOX Deficiency Syndromes

- Skeletal manifestations associated with areas with intrauterine expression of SHOX, affecting chondrocyte proliferation and apoptosis

Leri-Weil dyschondrosteosis (LWD)	SHOX haploinsufficiency; mesomelic dwarfism; Madelung deformity
Turner Syndrome	SHOX haploinsufficiency
Langer's mesomelic dwarfism	homozygous defect (complete SHOX deficiency)

Turner Syndrome

- Dx: 1 X chromosome with complete or partial absence of the 2nd X chromosome, associated with ≥ 1 typical clinical TS manifestations
- Significant phenotypic variability by karyotype
- Short stature is MOST common feature
- Intrinsic growth failure due to absence of *SHOX* in the pseudo-autosomal region of the 2nd X chromosome
- *Prenatal growth restriction*: mild IUGR, average BW 1-2 cm below mean values
- Skeletal anomalies: scoliosis, kyphosis, cubitus valgus, genu valgum, Madelung deformity, short 4th and 5th metacarpals and metatarsals

When to consider TS genetic testing

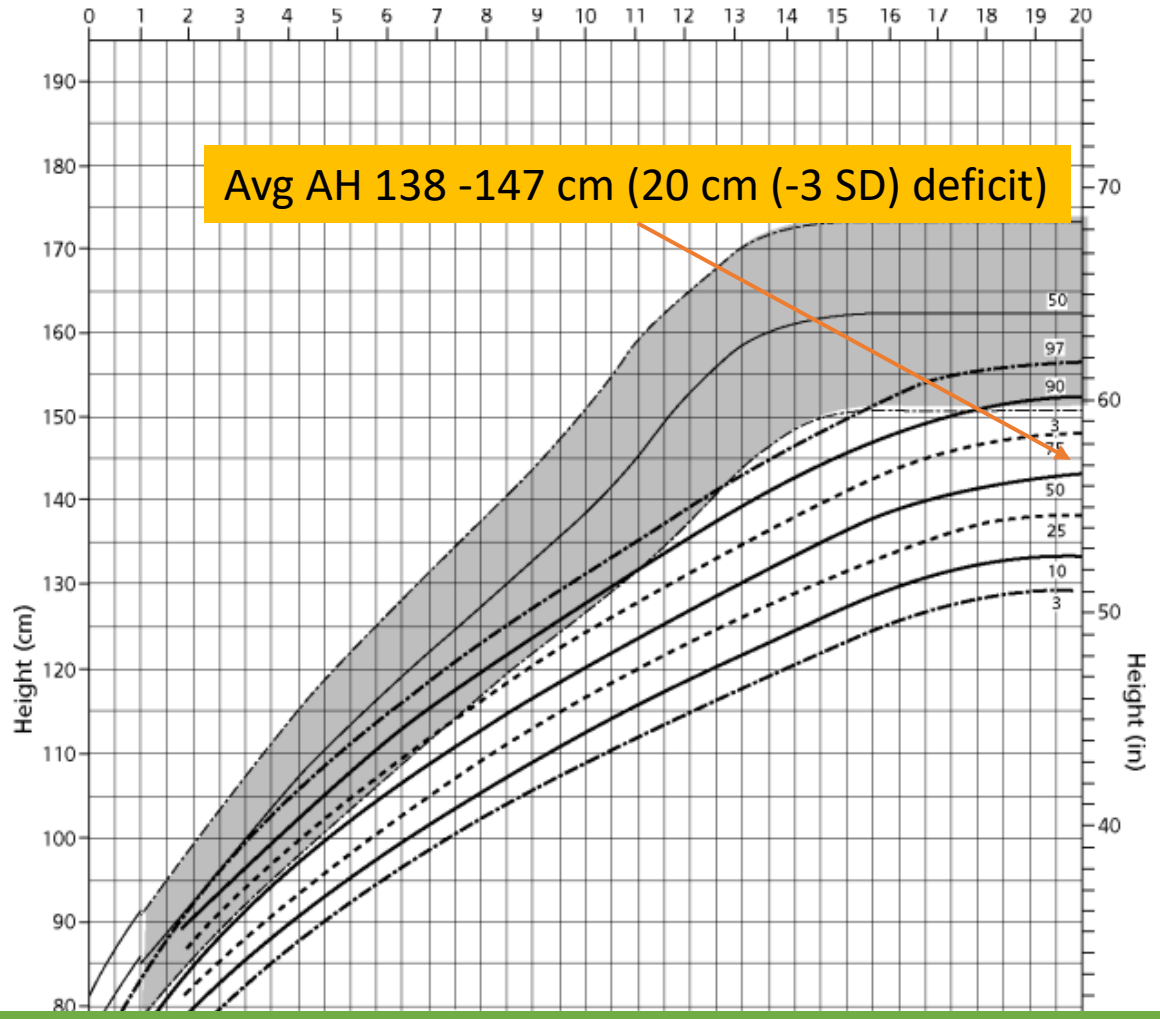
ONE of the following:

- Fetal cystic hygroma or hydrops
- **Unexplained short stature**
- Left-sided outflow CHD (exclude: bicuspid AoV)
- Unexplained delayed or stalled puberty/menarche, or secondary amenorrhea
- Infertility
- Characteristic physical features (epicanthal folds, down-slated palpebral fissures, low-set ears, narrow palate, webbed neck, short broad neck

At least 2 of the following:

- Renal anomaly (horseshoe, hypoplasia/aplasia)
- Madelung deformity
- Neuropsychologic or psychiatric problems
- Multiple typical or melanocytic nevi
- CHD (include: BAC)
- Impaired hearing before 40 years old + short stature

Gravholt et al, Clinical Practice guidelines for the care of girls and women with Turner Syndrome; Eur J Endocrinol 2024



Postnatal Growth Pattern:

- Rapid downward trend in height centiles 0-2 yrs
- Height deficit established by 3 years
- Suboptimal linear growth through childhood
- Estrogen-mediated growth spurt is absent or minimal
- Limbs more affected than trunk: ↑U/L and sitting height

TS: Growth

- GH Rx offered at ≥ 2 yrs if evidence of growth failure, short stature, or likelihood of short stature
  - GH continued until bone age ≥ 14 yrs , GV < 2cm/year or patient satisfied
  - Start 1.3-1.5 mg/m^2/d (45-50 µg/kg/d) → 2 mg/m^2/d (68 µg/kg/d)
  - Maintain IGF-1 in nl range for age & puberty
- Success most likely if catch-up growth to normal range within 2 years of Rx and if Rx starts at least 4 years before puberty
- Adjunctive Rx with oxandrolone and/or very low-dose E2 supplementation not recommended

Noonan Syndrome & RASopathies

- AD inheritance; 2/3 have *de novo* mutation
- Due to **RAS/MAPK pathway hyperactivation**
- Clinically heterogeneous
- Mild hypertelorism, downslanting palpebral fissures, low-set/posteriorly rotated ears; pectus excavatum; kyphoscoliosis
- **Right** sided CHD (pulmonic stenosis, hypertropic cardiomyopathy)
- Mild/moderate intellectual disability
- Unilateral or bilateral cryptorchidism

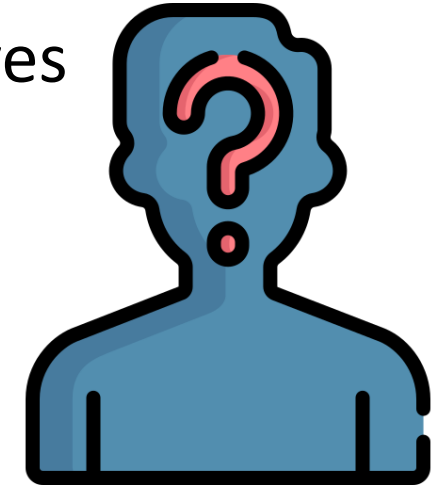
- Growth Pattern:
  - Normal birth weight and height
  - Postnatal growth failure
  - Delayed puberty with prolonged or absent adolescent growth phase
  - Mean AH -2 SDS
- Lean body/low BMI
- Dx: classical facial features or typical cardiac malformations
- 40% have ***PTPN11*** pathogenic variants
- May have GHD or GHR
- Rx: rhGH; variable efficacy

Prader Willi Syndrome

- Paternal imprinting of 15q11.2-q13 (70%)
  - 25% have maternal uniparental disomy (UDP(15q)m)
- Neonatal hypotonia, FTT in early infancy, followed by obesity
- Intellectual disability, behavioral disorders, small hands and feet
- Short stature
- Endocrinopathies: hypogonadotropic hypogonadism, GHD, central adrenal insufficiency
- Increased risk of premature death: sleep apnea, sudden death
- GH Rx increases linear growth, lean body mass, decreased fat mass
- GH Rx may also increase sudden death d/t worsening sleep apnea
  - Consider serial sleep studies before and after rhGH initiation

Idiopathic Short Stature

- Presumed inheritance of multiple sequence variants with cumulative mild, negative impact on growth
- Short stature, slowed linear GV, ± delayed skeletal maturation, ± attenuated pubertal growth spurt *without* familial short stature, chronic illnesses or apparent endocrinopathies
- Normal GH secretory dynamics
- Mixed response to rhGH and no clear data that GH Rx improves psychological, social, or educational function or that benefit exceeds risk in context of high cost and medicalization



Intrauterine Growth Restriction (IUGR)

- Birth weight or height < 3rd percentile
- 10-15% SGA infants will have short stature (90% exhibit catch-up), comprising ~20% all short children
- Etiology: abnormal GH production and secretory pattern; insensitivity to GH and IGF-1 activity
- SGA infants with rapid early childhood weight gain have increased risk of premature adrenarche, insulin resistance, functional ovarian hyperandrogenism, attenuated pubertal growth spurt
- Increased lifetime risk of CV disease, hypertension, and T2D

Causes of IUGR	
Intrinsic Fetal Abnormalities	Chromosomal disorders Syndromes (SRS, Noonan, PWS) Congenital infections Congenital anomalies
Placental Abnormalities	Abnormal implantation of the placenta Placental vascular insufficiency or infarction Vascular malformations
Maternal Disorders	**Malnutrition (#1 global cause)** Vascular disorders (HTN, toxemia, uncontrolled DM) Uterine malformations or constrained growth Drug ingestions (tobacco, **EtOH**, narcotics)

Diagnostic Approach to Short Stature

- Time course (prenatal, postnatal, or both)
- Inheritance pattern by family history (mono-, poly-, or oligogenic)
- Medical history and physical exam (intrinsic or extrinsic cause). Evaluate dental age.
- Anthropometrics (body proportions; compare weight and height gains)
- Skeletal maturation (bone age)
- Consider screening labs: CMP, CBC, ESR, TFTs, tTg IgA, IgA IGF-1, IGF-BP3 ± karyotype
  - IGF-1 must be interpreted relative to normative values by age and puberty

Consideration for GHD

- IGF-1 has incomplete sensitivity and specificity for GHD
  - Low IGF-1 can occur in **malnutrition**, GHI, *IGF-1* mutations, ALS deficiency
  - High IGF-1 can occur in *IGF-1R* and *PAPPA2* mutations
  - IGF-1 levels are stable, not pulsatile like GH concentrations
- GH stimulation testing
  - Serial GH measurements after administration of 2 different GH secretagogues
    - Clonidine, arginine, glucagon, insulin-induced hypoglycemia
  - GHD is *generally* defined as a peak GH < 10 mcg/L
  - Fraught with issues about false positives, threshold value, etc, etc
- Obtain head imaging (MRI) of pituitary if GHD is confirmed to exclude anatomical abnormalities or tumor

rhGH Therapy

- Increases GV and AH
  - Greatest impact with younger age at start and greater bone age delay
- Adverse Effects (<3%; usually acute): idiopathic intracranial hypertension, SCFE, progression of pre-existing scoliosis, fluid retention/edema
- Continue until GV < 2-2.5 cm/yr
- In those with previous malignancy: increase risk of meningioma. No increase risk of secondary malignancies.

FDA-Approved Pediatric Indications for GH Therapy
GHD
CKD
Turner Syndrome
SHOX haploinsufficiency
Noonan Syndrome
Prader-Willi Syndrome
SGA without catch-up growth
ISS

Note: FDA approval ≠ insurance coverage

Overgrowth/Tall Stature

Tall Stature

- Defined as length or height greater than the + 2 SDS (>97th percentile)
- Evaluation must consider age of onset, mid-parental height and pubertal status
- Is the growth velocity abnormally rapid?
  - Up-crossing of 2 major height percentiles between age 2 and onset of puberty
  - GV above the 90th percentile for age
    - > 9 cm/year between age 2-4 years
    - > 8.5 cm/year between 4-6 years
    - >6 cm/year or > 6.5 cm/year between 6 years to puberty in boys and girls, respectively

Overgrowth Syndromes

Fetal Overgrowth	Postnatal Overgrowth → Childhood Tall Stature	Postnatal Overgrowth → Adult Tall Stature
Maternal DM	Familial tall stature	
Sotos Syndrome		Androgen or E2 deficiency/resistance in males
Weaver Syndrome		Testicular feminization
Beckwith-Wiedemann		**Excess GH secretion**
Other IGF-II excess syndromes	Exogenous obesity	
Congenital hyperinsulinism	Excess GH secretion (McCune Alright, MEN1, NF1)	
	Precocious puberty	
	Marfan Syndrome	
	Klinefelter syndrome	
	Homocystinuria	
	XYY	
	Fragile X	
	Hyperthyroidism	

Fetal Overgrowth Syndromes (LGA)

- Maternal diabetes is #1 cause!
- **Sotos Syndrome** (“cerebral gigantism”)
  - 80% have a loss-of-function *NSD1* mutation
  - >90th percentile for height and weight at birth
  - Prominent forehead, dolichocephaly, macrocephaly, high arched palate, hypertelorism, prominent ears; large hands and feet with thickened subcutaneous tissue; intellectual disability
  - Rapid childhood growth with early epiphyseal fusion, yielding a normal AH
  - GH secretion and IGF levels are *normal*

Fetal Overgrowth Syndromes Cont'd

- **Beckwith-Wiedemann Syndrome**
  - Most common overgrowth syndrome, due to somatic growth and organomegaly
  - Excessive IGF-2, encoded by *IGF2*
  - Macrosomia with omphalocele or umbilical hernia
  - Macroglossia, renal medullary hyperplasia, neonatal hypoglycemia d/t islet cell hyperplasia
  - Embryonal tumor risk: Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma
  - Rapid childhood growth with early epiphyseal fusion, yielding a normal AH

Postnatal Statural Overgrowth

- **Obesity**
  - Increases estrogen by aromatization
  - Increased free IGF-1, leptin, prolactin, adrenal androgens
  - ➢ Rapid skeletal growth and early onset of puberty
  - Labs: Normal/high GH and IGF-1, hyperinsulinemia
  - Remember: obesity with *short stature/growth failure* is unusual and should prompt consideration for hypercortisolism, hypothyroidism, PWS, GHD
- **Precocious puberty**
  - Rapid childhood growth with decreased AH from predicted
- **Dosage effects of the SHOX gene**
  - Women with 47,XXX: mean AH is 5-10 cm taller than population mean
  - Men with 47,XXY: mean AH is 3.5 cm taller than population mean

Klinefelter Syndrome

- 47,XXY karyotype (3 active copies of SHOX)
- Clinical features:
  - Male with disproportionate tall stature with relatively long legs (arm span > height; ↓U/L ratio)
  - Small/firm testes with azoospermia (hypergonadotropic hypogonadism)
  - Gynecomastia
  - Learning disability

Excess GH Secretion

- **Pituitary gigantism**
- **GH secreting tumors**:
  - McCune Albright Syndrome (constitutive GNAS activation → somatotropic tumors & GH excess)
  - MEN1
  - Neurofibromatosis
  - Tuberous sclerosis
  - Carney Complex
- Dx: ↑IGF-1 and IGF-BP3, serum GH nl/↑, GH not suppressed during OGTT. If GH excess confirmed, must image the hypothalamus/pituitary gland
- Metabolic impact with severe/long-standing GH excess: insulin resistance/T2D, hyperTG, cardiovascular disease (HTN, LVH, cardiomyopathy), sleep apnea
- Rx: transsphenoidal resection (1st line), bromocriptine, octreotide, GH antagonist (Pegvisomant), radiotherapy (for refractory cases, high complication rate)

Marfan Syndrome vs Homocystinuria

Marfan Syndrome	Homocystinuria
Autosomal dominant	Autosomal recessive
Fibrillin-1 mutation, resulting in abnormal aggregation of fibrillin-1 which impairs microfibril formation	**Cystathionine synthase deficiency**
Shared Clinical Features: • Tall stature • Marfanoid appearance • Arachnodactyly • Ectopia lentis	
<u>Unique (non-overlapping features):</u> • Superior lens dislocation • Scoliosis • Joint laxity • **Aortic aneurysm**	<u>Unique (non-overlapping features):</u> • Inferior lens dislocation • **Intellectual impairment** (50% of those affected) • Fine, sparse hair • **Thromboembolic phenomena**


Q & A

Q1:

A 4-year-old girl is referred for evaluation of short stature. She was born at 39 weeks gestation with a birth weight of 2200 grams and length of 42 cm. She receives physical therapy for gross motor delays and was recently started on cyproheptadine for appetite stimulation. On examination, her height is -3.2 SDS and her weight is -3.9 SDS. Her annualized growth velocity over the past 2 years is 4.3 cm/year. She has a prominent forehead and micrognathia.

Which of the following is the most likely cause of her clinical presentation?

A. *FGF3* gain-of-function

B. *GHR* loss-of-function

C. *IGF-2* hypomethlyation

D. *SHOX* haploinsufficiency

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Q2:

An 11-year-old girl is seen in clinic for short stature. She has a distant history of cancer, diagnosed at 3 years of age, and in remission since age 5. Review of her growth data reveals a height percentile at the 50th percentile at 6 years of age, with subsequent decline in percentiles until 6 months ago. She has recently had a slight increase in height percentile, from the 1st to the 3rd percentile. Today, her height is 51" (3rd percentile) and weight is 70 lbs (25th percentile). Her mid-parental height is 65". Her arm span is 54". The distance from her pubis symphysis to the floor is 27.5 inches. She has Tanner 2 breasts and pubic hair.

Which of the following previous cancer treatments best explains her short stature?

A. Cranial radiation

B. Cyclophosphamide therapy

C. Spinal radiation

D. Tyrosine kinase inhibitor therapy

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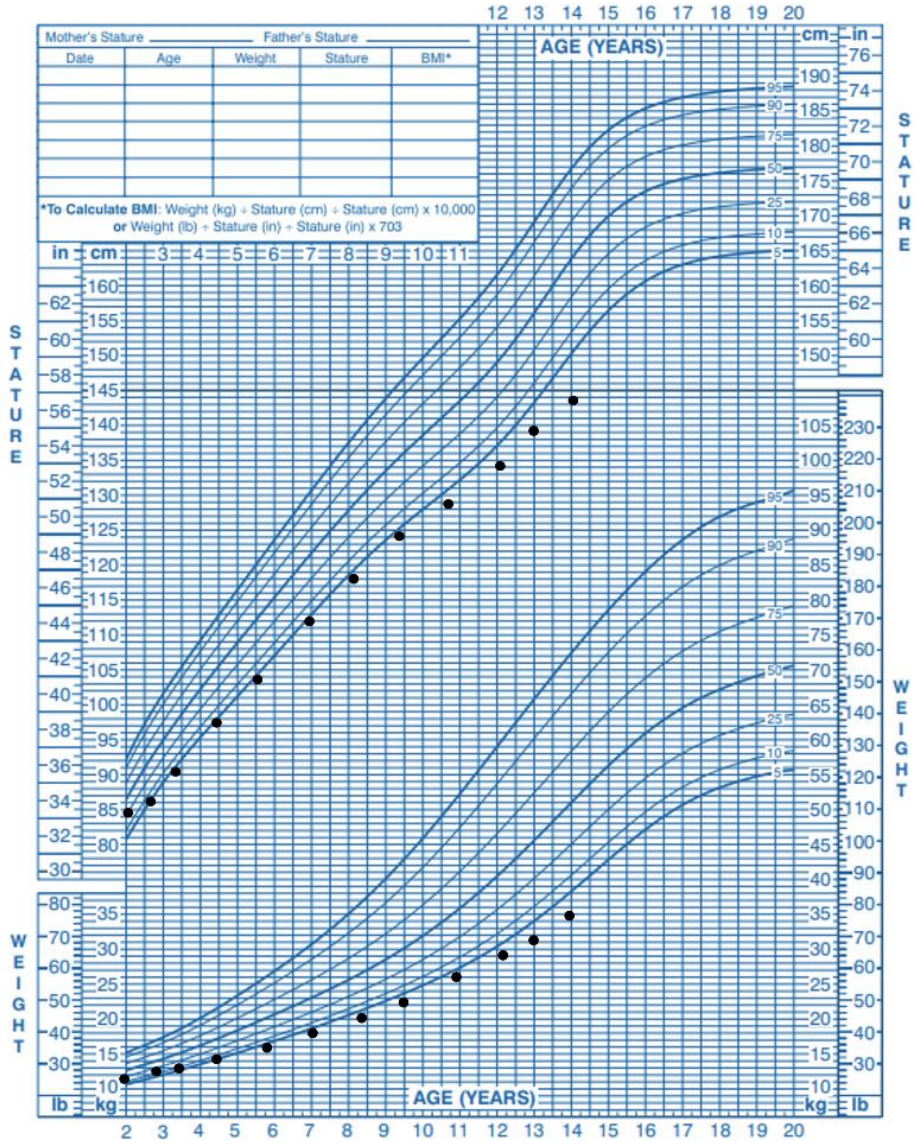
<u>Disproportionate Growth Failure</u>:
Arm Span (54") greater than Height (51")
Lower segment: 27.5"
Upper segment: 51 – 27.5 = 23.5
U/L = 23.5/27.5 = 0.85 (should be 1)

Q3:

A 14-year-old boy is seen for evaluation of poor growth. His growth curves are reviewed (Figure). His father is 70 inches tall and his mother is 61 inches tall. He denies any apocrine body odor, acne, or voice deepening. He takes cetirizine 10 mg daily and intranasal fluticasone 50 mcg once daily for environmental allergies. On examination, he is anxious but otherwise well-appearing. He has sparse axillary hair, Tanner 2 pubic hair and his testes are 3 mL bilaterally.

Which of the following would be most likely found during his growth evaluation?

	IGF-1 (ng/mL; reference range 168-576 ng/mL)	Peak GH level (ng/mL) after stimulation with arginine and clonidine	Skeletal (bone) age
A	25	3.2	11 years
B	195	9.9	12 year 6 months
C	357	11.4	14 years
D	85	10.5	11 years 6 months



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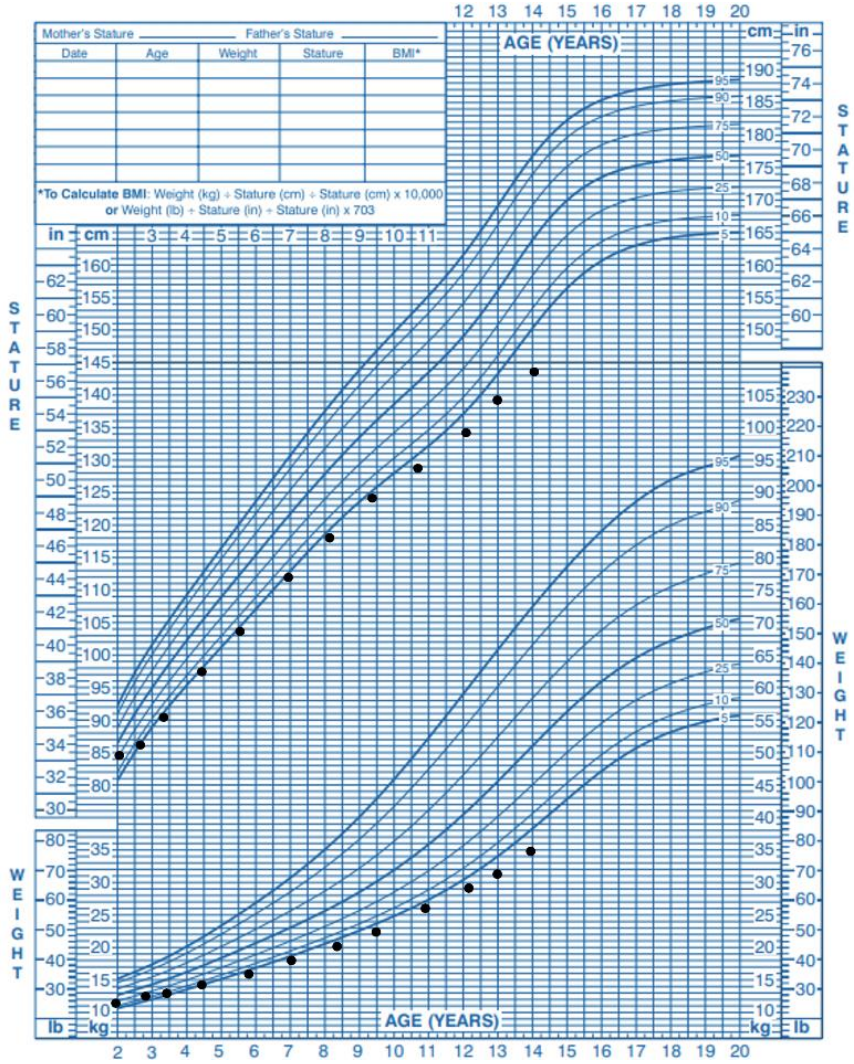

Q4:

A 9-year-old girl presents with accelerated linear growth. Her annualized growth velocity has been 15 cm/year over the past 18 months. On examination, her height is 158 cm (> 99th percentile) and her weight is 38 kg (90th percentile). Her mid-parental height is 163 cm (50th percentile). She is pre-pubertal with Tanner 1 breasts. IGF-1 level is 560 ng/mL and GH level is 10 ng/mL. Pituitary MRI reveals a 2.5 cm macroadenoma.

Which of the following is the recommend initial therapy for this child?

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B. Octreotide

C. Pegvisomant

D. Transsphenoidal pituitary surgery

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Q5:

An 8-year-old pre-pubertal boy with intellectual disability and myopia is referred for evaluation of tall stature. Review of his growth curves reveals steady increases in height percentiles since early childhood. On examination, his height is +3.7 SDS and his weight is +1.8 SDS. His mid-parental height calculation is +2 SDS. He has a thin body habitus with long, thin fingers. The hair on his scalp is thin and lightly colored. He has reduced joint mobility at his elbows and knees.

Which of the following is he most at risk of developing?

A. Thromboembolism

B. Gynecomastia

C. Aortic aneurysm

D. Wilms tumor

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