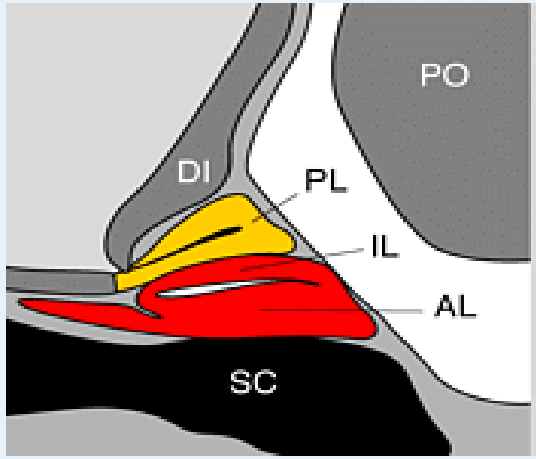
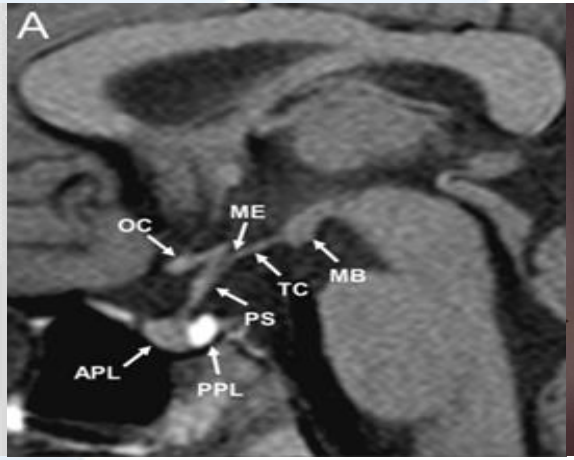
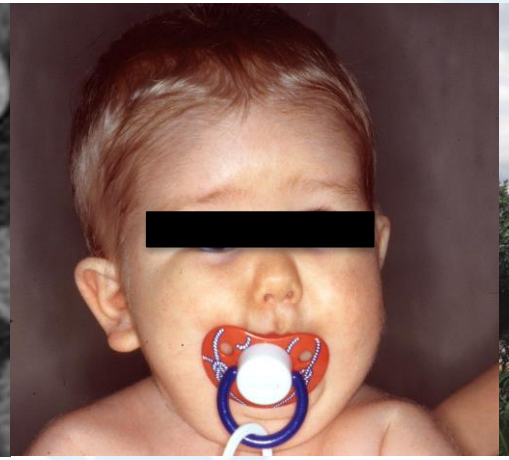
CURRENT PERSPECTIVES ON THERAPEUTIC OPTIONS FOR CHILDREN WITH GROWTH DISORDER

GH DEFICIENCY – HYPOPITUITARISM







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DISCLOSURES

Research Grants

- Merck Serono, Pfizer

Lecture Fees

- Ferring, Novo Nordisk, Merck Serono, Pfizer, Sandoz,

Advisory Boards

- Ascendis, Biomarin, Novo Nordisk, Pfizer, Merck Serono, Sandoz,

LEARNING OBJECTIVES

- Understand the efficacy of rhGH therapy in growth hormone deficiency
- Recognise the value and limitations of factors affecting the outcomes
- Gain knowledge about monitoring and safety

rhGH, recombinant human growth hormone

GH DEFICIENCY – HYPOPITUITARISM

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GH DEFICIENCY – HYPOPITUITARISM

- Early-to-late onset
- Incidence 1/4000-1/8000-10,000 births
- Most cases are sporadic
- Normal weight and length
- Subsequent variable post-natal growth failure

GH, growth hormone

Bosch L, et al. Front Pediatr. 2021;8:600962

GH DEFICIENCY – HYPOPITUITARISM

Congenital

- Transitory
- Permanent
- Evolving

Genetics

- GH1, GHRHR, RNPC3 mutations
- X-linked (SOX3)
- Transcription factor defect, gene mutation, deletion or Duplication (HESX1, POU1F1, OTX2, LHX4)

Syndromic

- MEHMO (Mental retardation, Epileptic seizures, Hypogonadism, Microcephaly, Obesity)
- Mutations in MAGEL2 (Schaaf-Yang syndrome) and L1CAM are Associated with Congenital Hypopituitarism and Arthrogryposis
- BRAF –Cardofaciocutaneous, SOD
- Others

Idiopathic

- Transitory in the majority
- Overlapping congenital/Genetic/syndromic

Acquired

- CNS tumours
- Radiotherapy (cranial irradiation for CNS tumours, other malignancies, BMT)
- TBI (accidental, after neurosurgery, subarachnoid haemorrhage)
- Infections (meningitis, encephalitis, tuberculosis, hypophysitis)
- Autoimmune (hypophysitis, APS, anti Pit1 antibodies)
- Infiltration (LCH, hemochromatosis, chronic blood transfusions, sarcoidosis)
- Chemotherapy
- Autoimmune

APS, autoimmune polyendocrine syndromes; BMT, bone marrow transplant; B-RAF, B-rapidly accelerated fibrosarcoma; CNS, central nervous system; GH, growth hormone; GH1, growth hormone 1; GHRHR, growth hormone-releasing hormone receptor; HESX1, HESX homeobox 1; L1CAM, L1 cell adhesion molecule; LCH, Langerhans' cell histiocytosis; LHX4, LIM homeobox 4; MAGEL2, MAGE family member L2; OTX2, orthodenticle homeobox 2; Pit1, pituitary-specific positive transcription factor 1; POU1F1, POU class 1 homeobox 1; RNPC3, RNA binding region (RNP1, RRM) containing 3; SOD, septo-optic dysplasia; SOX3, SRY-box transcription factor 3; TBI, traumatic brain injury.

1. Maghnie M, et al. J Clin Endocrinol Metab. 1991;73:79-83; 2. Arrigo T, et al. Eur J Endocrinol. 1998;139:84-88; 3. Di Iorgi N, et al. Clin Endocrinol (Oxf). 2012;76 161-176; 4. Di Iorgi N, et al Best Pract Res Clin Endocrinol Metab. 2016;30:705-736; 5. Hage C. et al. Nat Rev Endocrinol. 2021;10.1038/s41574-021-00539-5.

GH DEFICIENCY – HYPOPITUITARISM

1. Congenital

- Variable Timing of onset (Early neonatal to childhood presentation)
- Late/adult presentation
- Isolated GHD (evolving to CPHD/MPHD)
- Severe with Combined Pituitary Hormone Deficiencies (CPHD/MPHD) ± Syndromic Features

2. Genetic

- Genes implicated in early development
- Genes implicated in GH secretion/cell differentiation
- Digenic Inheritance
- Micro Rearrangements
- More complex

CPHD, combined pituitary hormone deficiency; GH, growth hormone; GHD, growth hormone deficiency; MPHD, multiple pituitary hormone deficiency

1. Maghnie M, et al. J Clin Endocrinol Metab. 1991;73:79-83; 2. Arrigo T, et al. Eur J Endocrinol. 1998;139:84-88; 3. Di Iorgi N, et al. Clin Endocrinol (Oxf). 2012;76 161-176; 4. Di Iorgi N, et al Best Pract Res Clin Endocrinol Metab. 2016;30:705-736

GH DEFICIENCY – HYPOPITUITARISM

3. Idiopathic – Environmental Factors – Polygenic hypothesis

- Overlap between congenital and genetic hypopituitarism
- Transitory in the majority of cases unless due to Pituitary Stalk Interruption Syndrome
- These forms could be associated with midline defects, eyes, ears, forebrain:
  - Agenesis of the corpus callosum
  - Septo-optic dysplasia
  - Microphthalmia-anophthalmia-coloboma (MAC)
  - Holoprosencephaly
  - Encephalocele
  - Hydrocephalus,
  - Cleft lip or palate, single central incisor etc.

GH, growth hormone; MAC, microphthalmia-anophthalmia-coloboma

1. Maghnie M, et al. J Clin Endocrinol Metab. 1991;73:79-83; 2. Arrigo T, et al. Eur J Endocrinol. 1998;139:84-88; 3. Di Iorgi N, et al. Clin Endocrinol (Oxf). 2012;76 161-176; 4. Di Iorgi N, et al Best Pract Res Clin Endocrinol Metab. 2016;30:705-736

GH DEFICIENCY – HYPOPITUITARISM

DOES PITUITARY PHENOTYPE MATTER? MRI/GENOTYPE RELEVANCE

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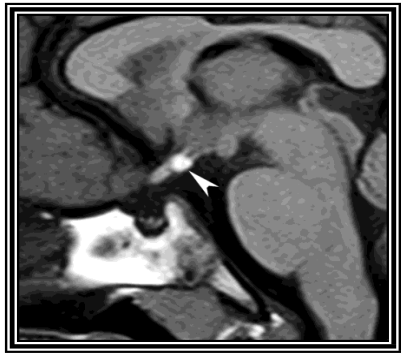
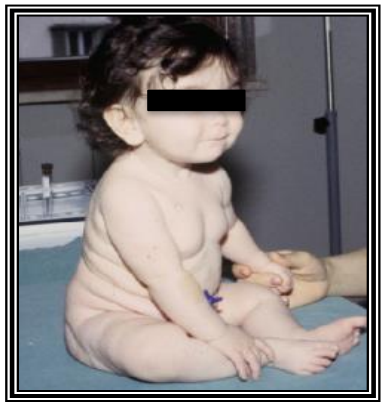
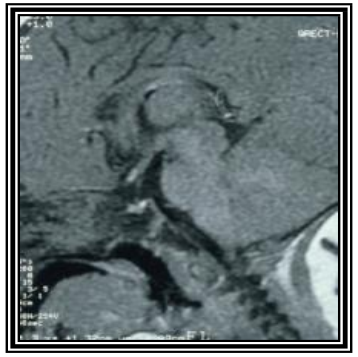
Idiopathic CPHD

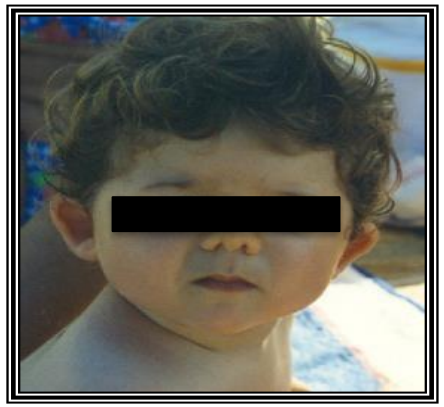


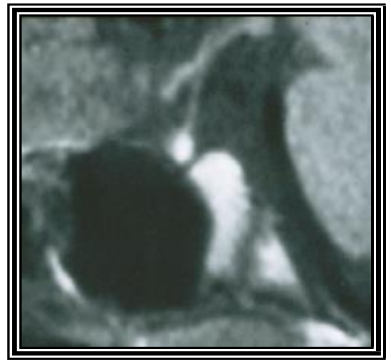
POU1F1(Pit-1)



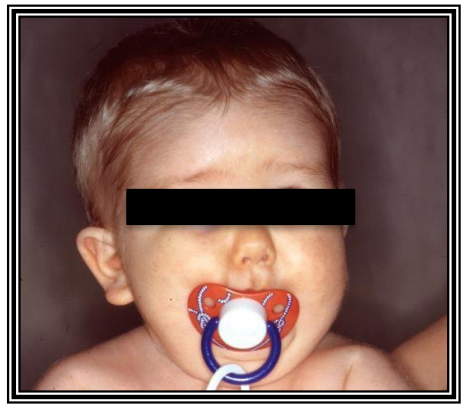


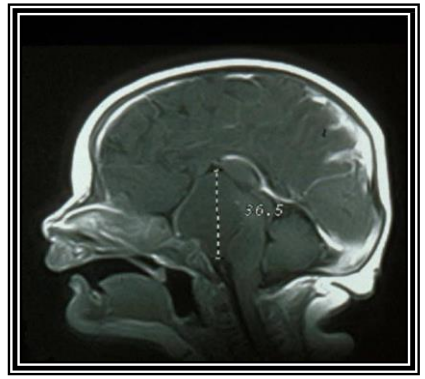
HESX-1-MPHD





HGLI3-MPHD





Authorisation obtained from all families

CPHD, combined pituitary hormone deficiency; GH, growth hormone; GLI3, GLI family zinc finger 3; HESX1, HESX homeobox 1; MPHD, multiple pituitary hormone deficiency; MRI, magnetic resonance imaging; Pit1, pituitary-specific positive transcription factor 1; POU1F1, POU class 1 homeobox 1

GH DEFICIENCY – HYPOPITUITARISM

PE connect®
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APPROVED DOSES OF RECOMBINANT HUMAN GH*

	Europe	United States
GHD (1985)	**0.025-0.035 mg/kg/d or 0.7-1.0 mg/m²/d BSA**	**0.024-0.034 mg/kg/d**
CRI (1993)	0.050 mg/kg/d or 1.4 mg/m²/d BSA	Up to 0.35mg/kg/w
TS (1996)	0.045-0.067 mg/kg/d or 1.3-2.0 mg/m²/d BSA	Up to 0.067 mg/kg/d
PWS (2000)	0.025-0.035 mg/kg/d (Switzerland)	0.034 mg/kg/d
SGA (2001)	0.035 mg/kg/d or 1.0 mg/m²/d BSA	Up to 0.067 mg/kg/d
ISS (2003)	Not approved[a]	Up to 0.067 mg/kg/d
SHOX Haploinsufficiency (2006)	0.045-0.050 mg/kg	0.045-0.050 mg/kg/d
Nonan Syndrome (2007)	0.033 or 0.066 mg/kg/d (Switzerland and Japan)	Up to 0.066 mg/kg/d

*Stated doses are based on selected formulations of recombinant human GH. Please check individual package inserts for specific prescribing information.

There are other indications not listed. There appeared to be a dose relationship (risk was highest in patients receiving doses >50 mcg/d (Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study.

BSA, body surface area; CRI, chronic renal insufficiency; GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; PWS, Prader–Willi syndrome; SGA, small-for-gestational-age; SHOX, short stature homeobox; TS, Turner syndrome

Carel JC, et al., J Clin Endocrinol Metab. 2012;97(2):416-25; Ranke MB, Wit JM. Nat Rev Endocrinol. 2018;14(5):285-300.

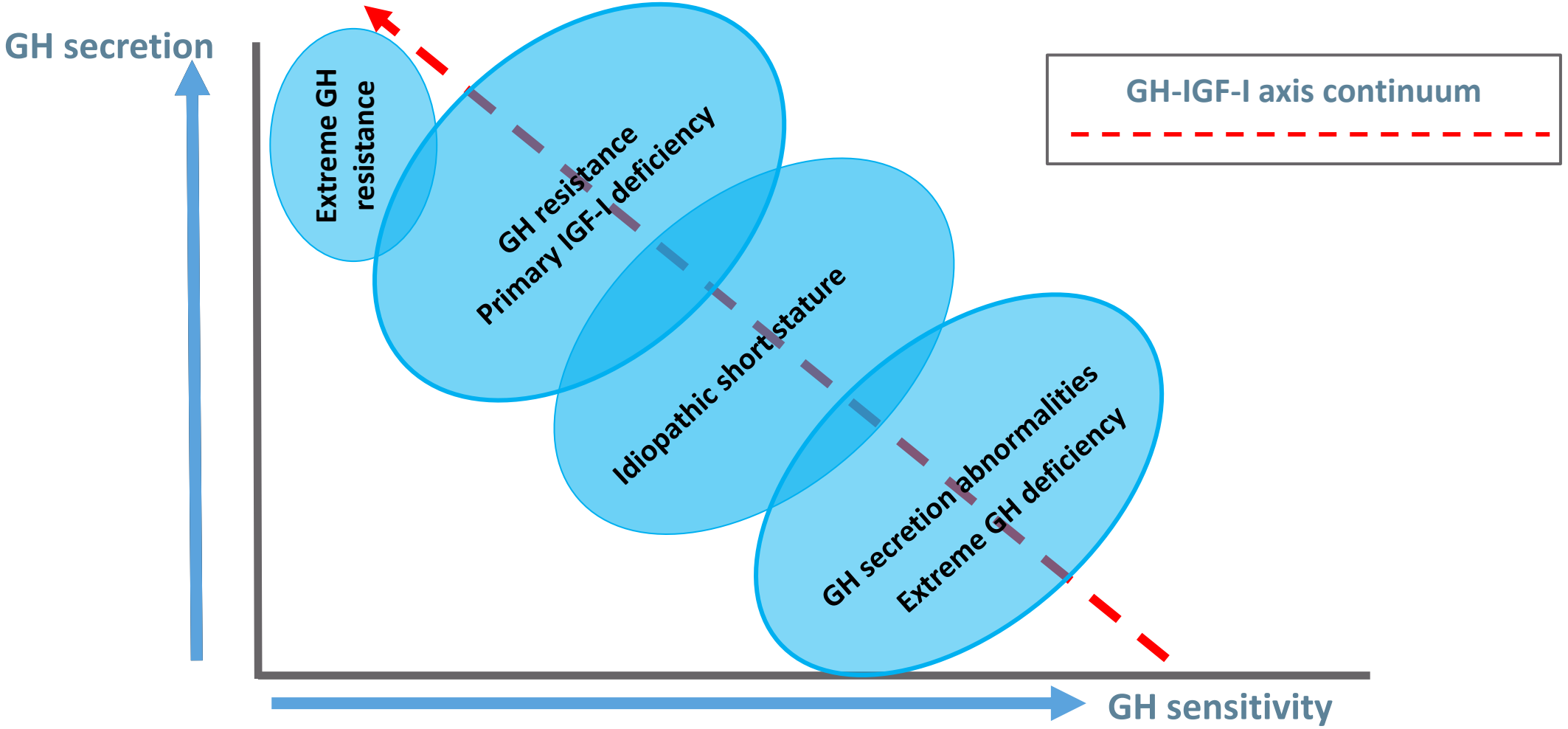
GH THERAPY – CLINICAL END POINTS

- Growth
- Maintenance of normal blood glucose concentrations (avoidance of hypoglycaemia)
- BMD (Increasing bone mineralisation)
- Body composition (Decreasing fat mass; increasing lean mass)
- Increasing bone strength & muscle mass
- Neuro-cognition and motor skills (Replacement therapy in GHD adults suggest that both GH and IGF-1 may enhance long-term working memory)
- There is an unmet need to capture the pleiotropic actions of GH in treated children

BMD, bone mineral density; GH, growth hormone; GHD, growth hormone deficiency; IGF-I, insulin-like growth factor 1

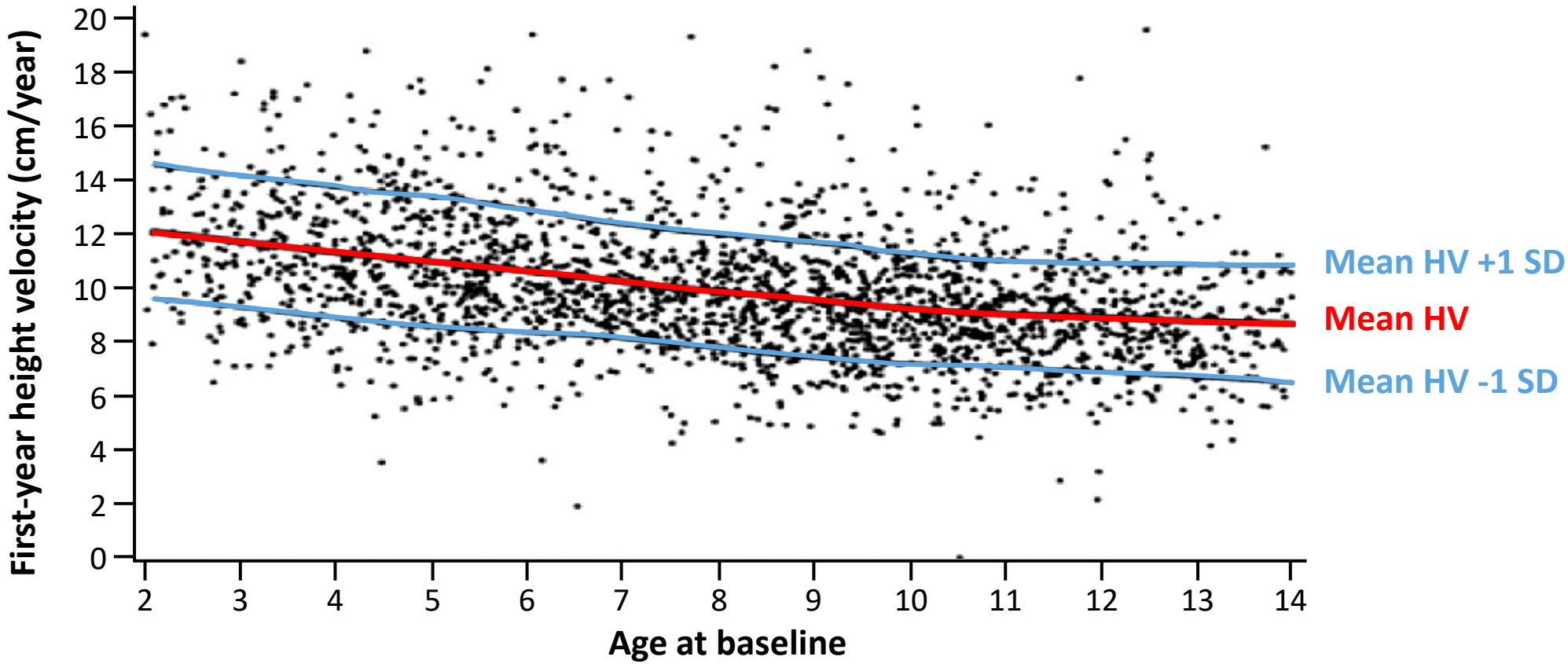
1. Richmond E, et al. Best Pract Res Clin Endocrinol Metab. 2016;30:749-755; 2. Deijen JB, et al. Psychoneuroendocrinology. 1996;21:313-322; 3. Deijen JB, et al. Psychoneuroendocrinology. 1998;23;45-55; 4. Burman P, et al. J Clin Endocrinol Metab. 1995;80:3585-3590; 5. Lijffijt M, et al. Neurosci Lett. 2003;353:123-126; 6. Scheepens A, et al. Horm Res. 2005;64:66-72; 7. van Dam PS. Horm Res. 2005;64:109-114; 8. Webb EA, et al. Brain. 2012;135:216-227; 9. Johannsson G et al Endocr Connect. 2018;7:R126-R134

THERAPEUTIC RESPONSES IN THE CONTEXT OF THE CONTINUUM OF GH-IGF-I AXIS DEFECTS



GH, growth hormone; IGF-I, insulin-like growth factor 1.
Savage MO, et al. Clin Endocrinol (Oxf). 2010;72:721-728

FIRST YEAR GROWTH RESPONSE: GREAT VARIABILITY



Prepubertal boys with idiopathic GHD

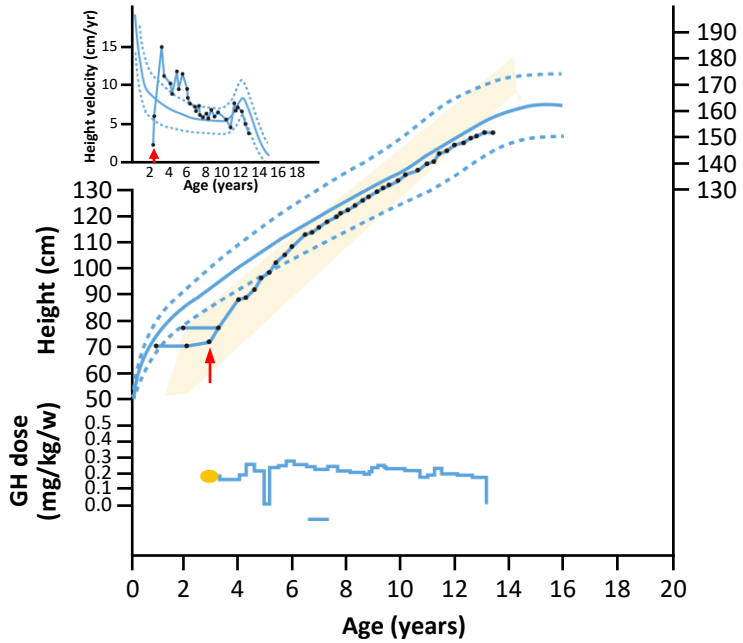
GHD, growth hormone deficiency; HV, height velocity; SD, standard deviation

Bakker B, et al. J Clin Endocrinol Metab. 2008;93:352-357

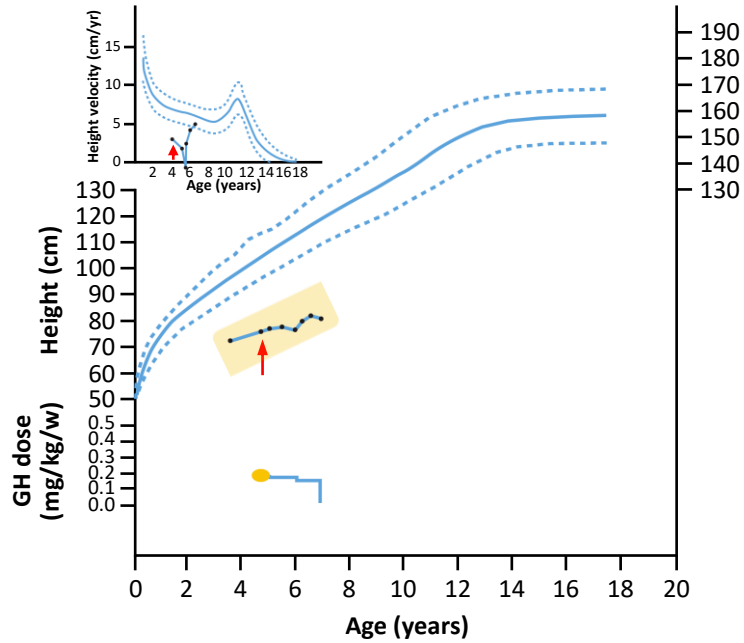
REAL NEED TO PERSONALISE AND OPTIMISE GH TREATMENT

- The response to growth hormone (GH) therapy is highly variable between individual patients[1]
- Current methods to evaluate first-year response are arbitrary[3]
- A polygenic risk captured 71.1% of the total variance in adult height based on UK Biobank data[4]
- A polygenic component of GH responsiveness (B4GALT4 and TBCE genes)[5]
- Single genomic test which can be linked to a prediction algorithm to improve clinical management[6]

SOME CHILDREN RESPOND VERY WELL TO GH AND REACH THEIR MID-PARENTAL HEIGHT[2]



OTHER CHILDREN RESPOND LESS WELL TO SIMILAR GH TREATMENT REGIMENS[3]



B4GALT4, beta-1,4-galactosyltransferase 4; GH, growth hormone; TBCE, tubulin folding cofactor E

1. Kaspers S, et al. Appl Health Econ Health Policy. 2013;11:237-249; 2. Cutfield W, et al. Acta Paediatr Suppl. 1999;88:72-75; 3. Ranke MB, et al. Horm Res Paediatr. 2013;79:51-67; 4. Lu T, et al. J Clin Endocrinol Metab. 2021;106:1918-1928; 5. Dauber A, et al. J Clin Endocrinol Metab. 2020;105:3203-3214; 6. Stevens A, et al. Pharmacogenomics J. 2021. DOI: 10.1038/s41397-021-00237-5

DIAGNOSIS DICTATES THE FIRST YEAR RESPONSE TO HGH THERAPY

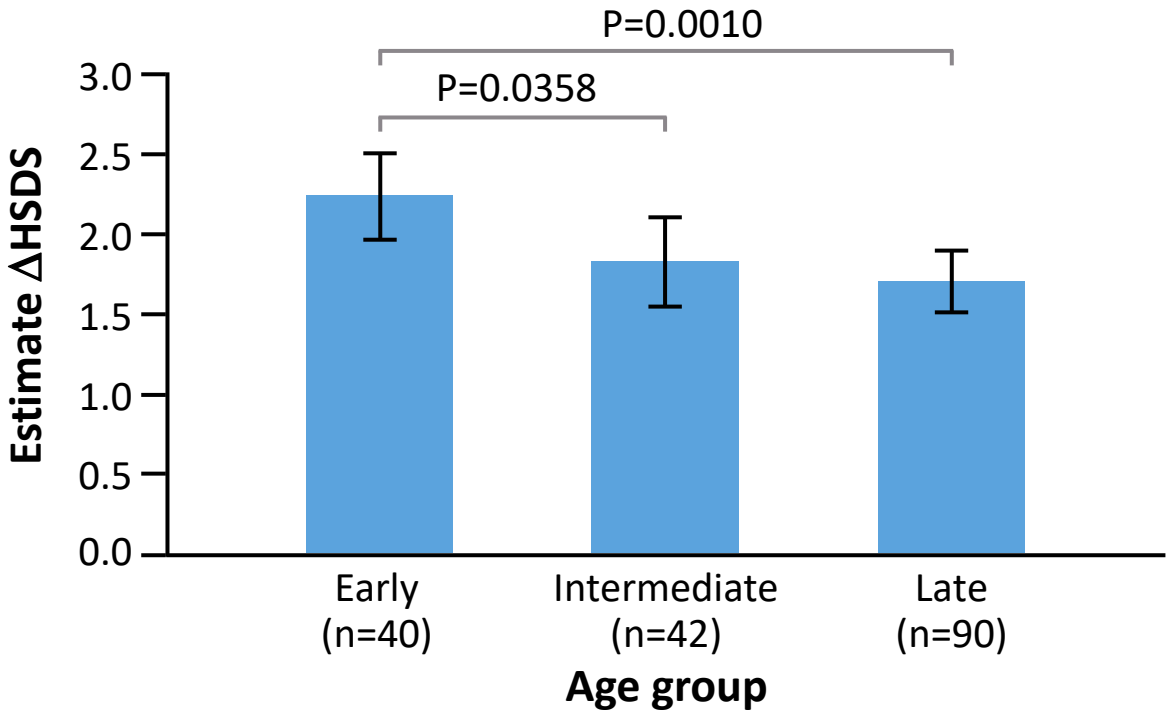
GROWTH RESPONSE OF PREPUBERTAL PATIENTS AFTER THE FIRST YEAR OF GH TREATMENT

	Severe GHD mean (SD)	GHD mean (SD)	TS mean (SD)	SGA mean (SD)
HV (cm/yr)	10.39 (3.08)	8.58 (2.07)	7.87 (1.81)	8.81 (1.82)
ΔHt SDS	1.11 (0.69)	0.74 (0.43)	0.68 (0.38)	0.81 (0.42)

GH, growth hormone; GHD, growth hormone deficiency; hGH, human growth hormone; HV, height velocity; Ht SDS, height standard deviation score; SGA, small for gestational age; TS, Turner syndrome

Ranke MB, et al. J Clin Endocrinol Metab. 2010;95:1229-1237

EARLY GROWTH HORMONE TREATMENT START IN CHILDHOOD GROWTH HORMONE DEFICIENCY IMPROVES NEAR ADULT HEIGHT: ANALYSIS FROM NORDINET® INTERNATIONAL OUTCOME STUDY

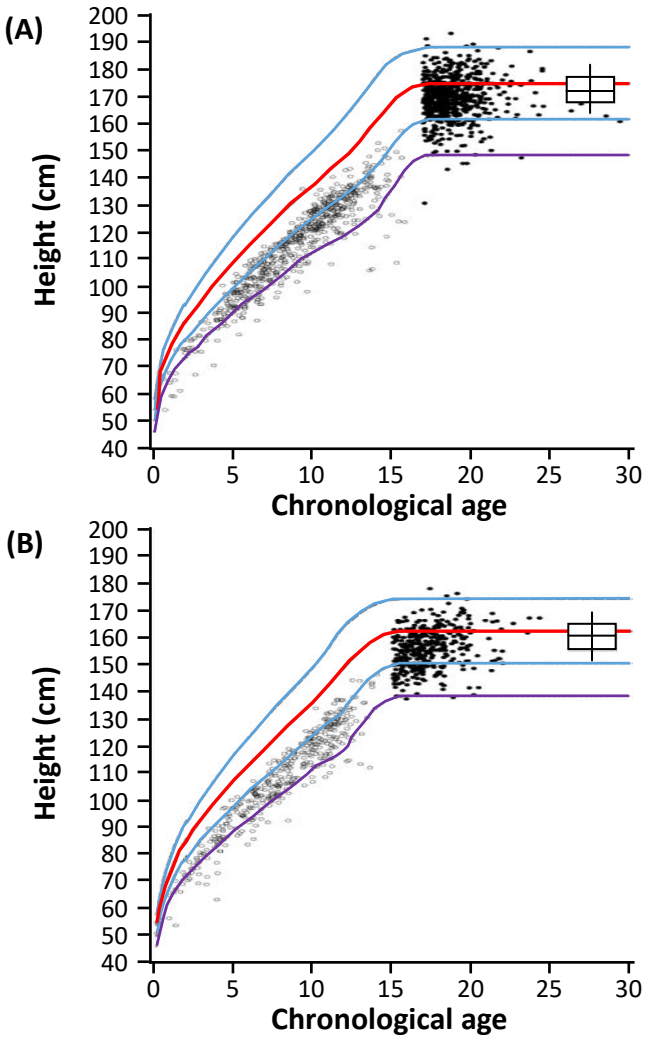


- Estimated change in HSDS from baseline to NAH
  - Early (girls aged <8 years; boys aged <9 years),
  - Intermediate (girls aged 8-10 years; boys aged 9-11 years)
  - Late (girls aged >10 years; boys aged >11 years) age group at GH treatment start
- Data are LS means (95% CI) corrected for baseline HSDS, average GH dose, target HSDS, GH severity and mid-parental height

CI, confidence interval; GH, growth hormone; HSDS, height standard deviation score; LS, least squares; NAH, near adult height

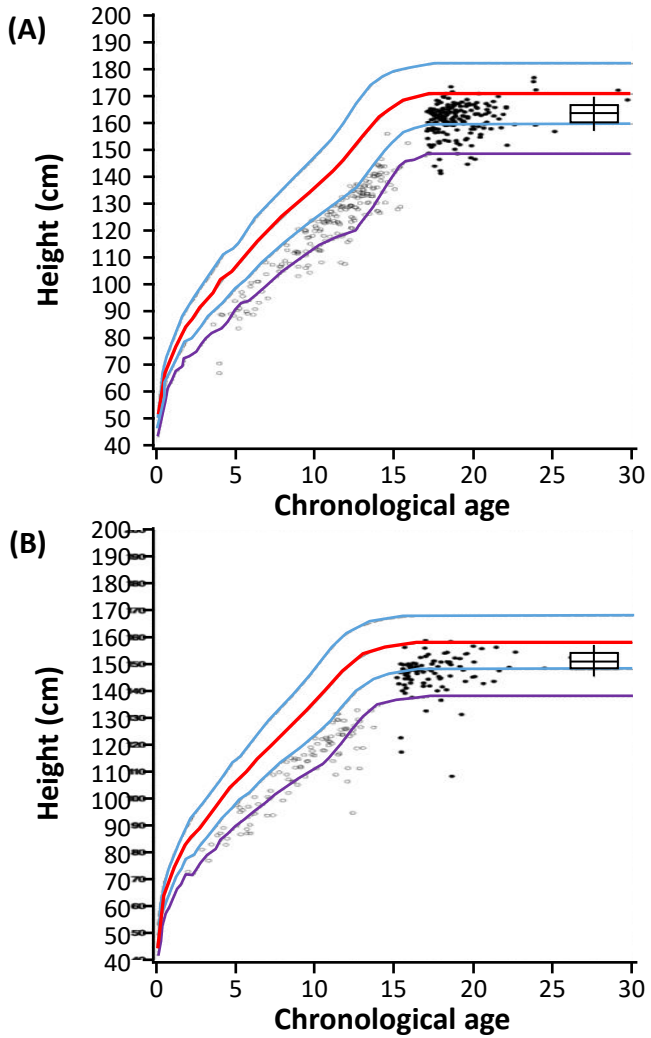
Polak M, et al. Eur J Endocrinol. 2017;177:421-429

NEED TO OPTIMIZE GH TREATMENT: EFFECT OF GH ON NEAR-FINAL HEIGHT



Starting height (○) and near-adult height (•) after GH treatment in male (A; n=505) and female (B; n=331) Caucasian children with idiopathic GHD.

Median initial GH dose: 0.20 mg/kg/week (equivalent to 0.03 mg/kg/day) Age at GH initiation 2.7-13 years

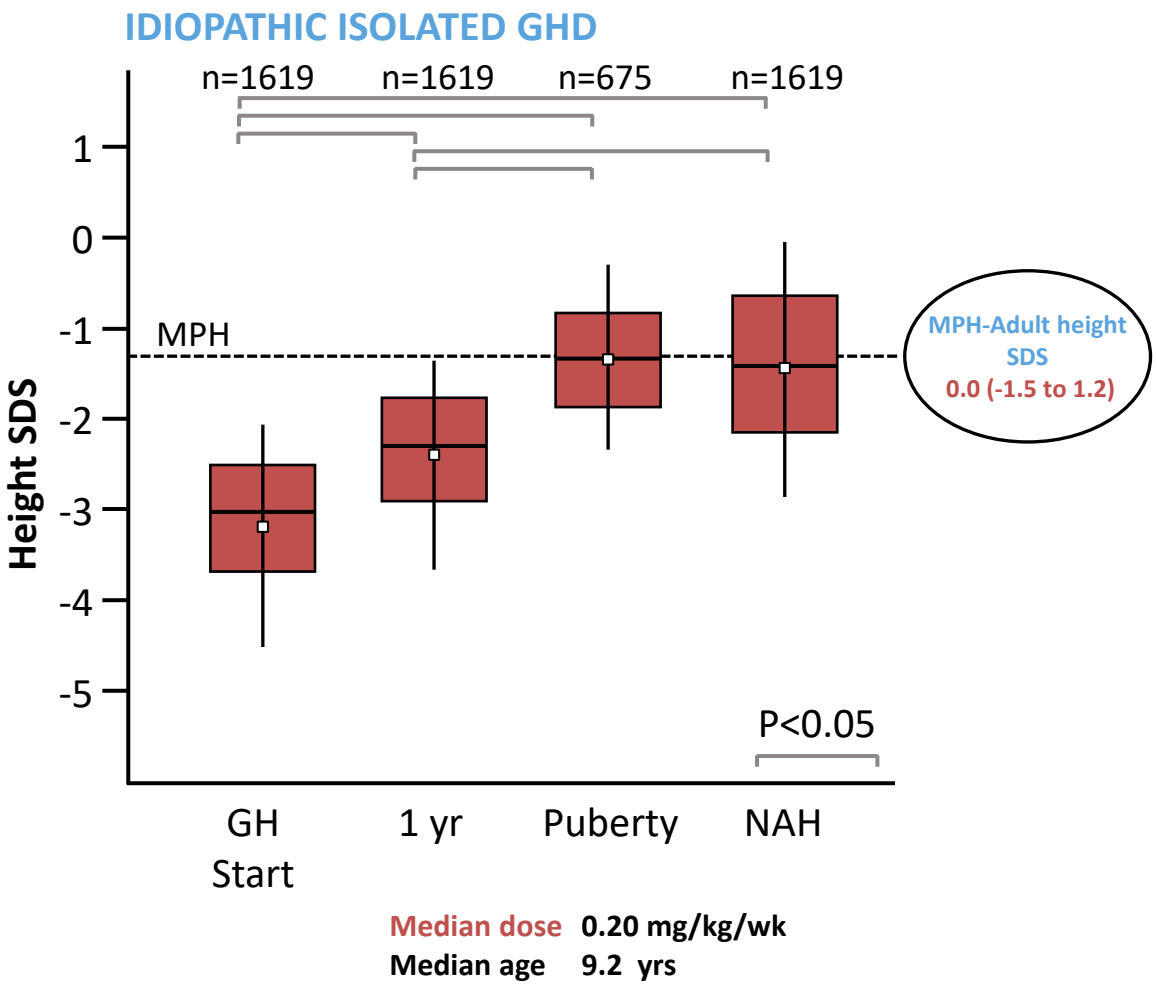


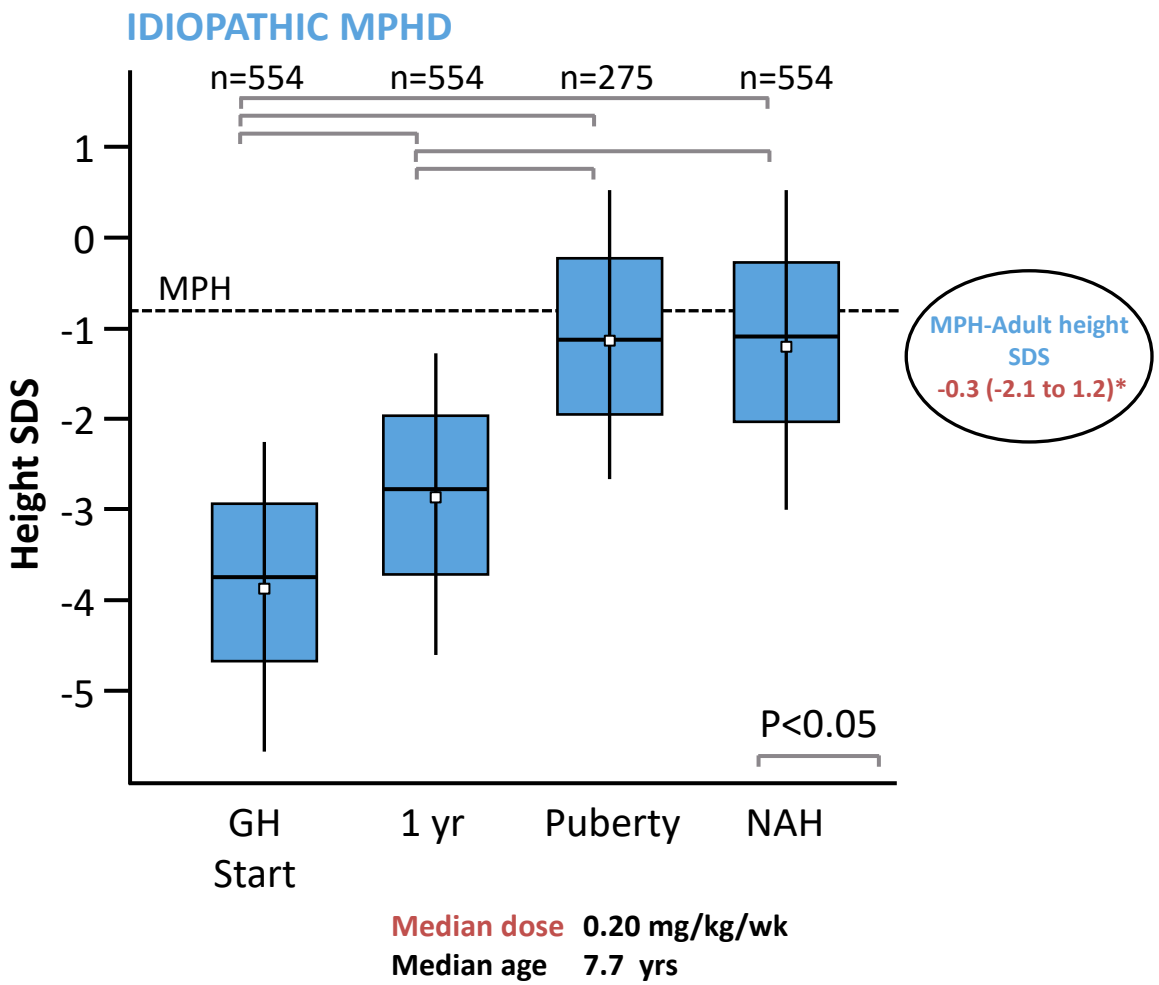
Starting height (○) and near-adult height (•) after GH treatment in male (A; n=198) and female (B; n=98) Japanese children with idiopathic GHD.

GH sensitivity, GH dose, age at treatment, Adherence, Genetics, Diagnosis, other factors

The curves represent means (*red lines*), ±2 sd (*blue lines*), and −4 sd (*purple lines*).
Box plots represent medians and 25th and 75th percentiles, with whiskers at the 10th and 90th percentiles. GH, growth hormone; GHD, growth hormone deficiency; SD, standard deviation
Reiter EO, et al. J Clin Endocrinol Metab. 2006;91:2047-2054

HEIGHT SDS IN ISOLATED IDIOPATHIC GHD AND IN IDIOPATHIC MPHD: KIGS DATABASE

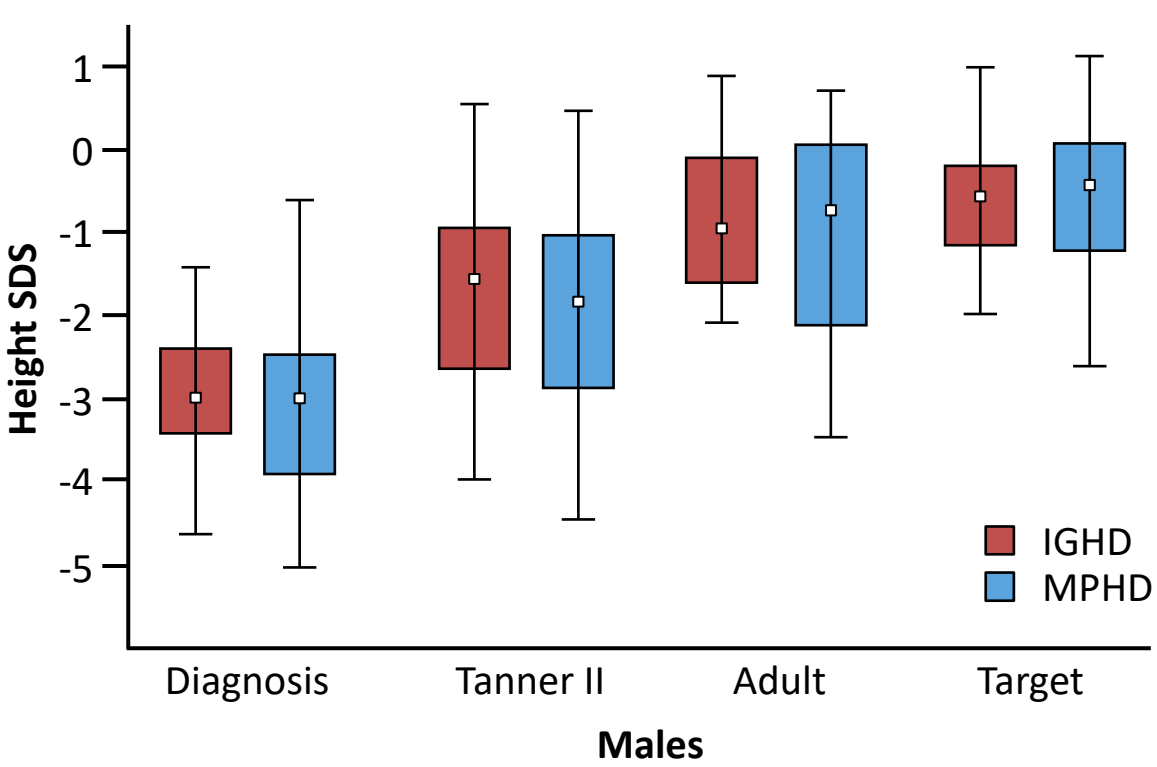


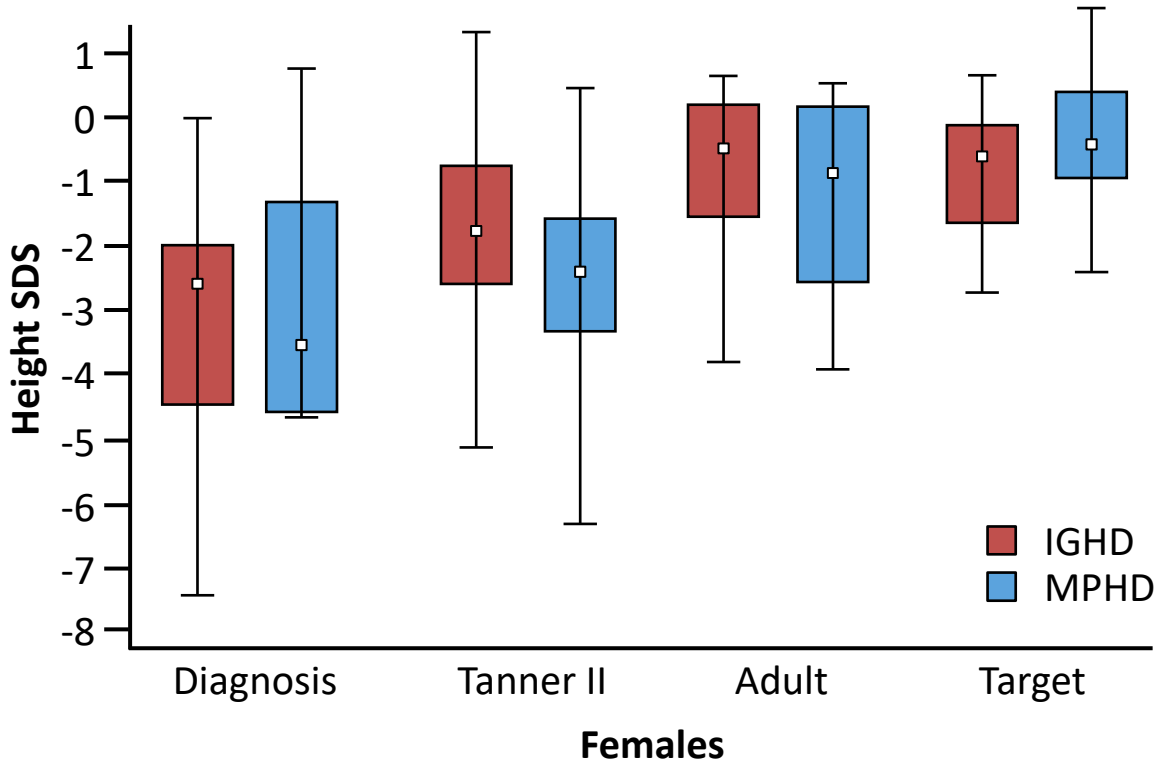


GH, growth hormone; GHD, growth hormone deficiency; KIGS, Pfizer International Growth Study Database; MPH, mid-parental height; MPHD, multiple pituitary hormone deficiency; NAH, nearly adult height; SDS, standard deviation score

Darendeliler F, et al. Horm Res Paediatr. 2011;76:42-46

ADULT HEIGHT IN PATIENTS WITH IGHD OR MPHD AND PITUITARY STALK INTERRUPTION SYNDROME





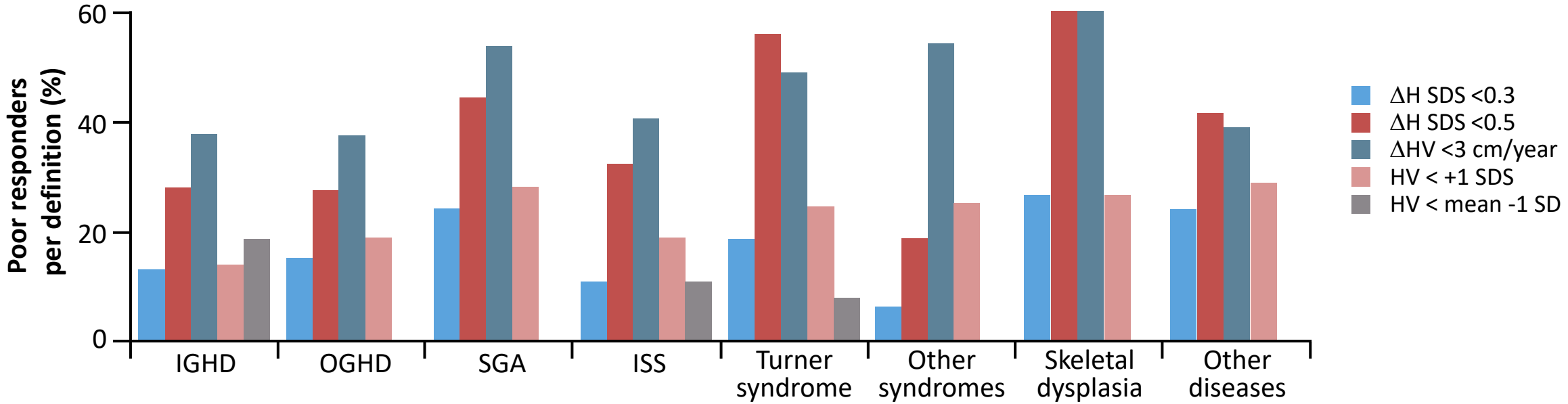
IGHD, isolated growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; SDS, standard deviation score

Maghnie M, et al. J Clin Endocrinol Metab. 2006;91:2900-2905

IDENTIFICATION AND MANAGEMENT OF POOR RESPONSE TO GROWTH-PROMOTING THERAPY IN CHILDREN WITH SHORT STATURE

PE connect® POWERED BY COR2ED

Proportion of poor responders after 1 year of standard GH therapy in 456 short prepubertal children according to different definitions in each diagnostic group



Evidence is increasing for an unacceptably high rate of poor or unsatisfactory response to growth-promoting therapy in many approved conditions

GH, growth hormone; HV, height velocity; IGHD, isolated growth hormone deficiency; ISS, idiopathic short stature; OGHD, organic growth hormone deficiency; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age

Bang P, et al. Horm Res Paediatr. 2011;75:335-45

MAIN FACTORS AFFECTING GH RESPONSE TO rhGH

PE connect® POWERED BY COR2ED

Differences can be attributed to:

- Age
- Birth weight SDS
- Maximum GH (Diagnosis)
- Height-MPH SDS (Genetics)
- Weight SDS
- Height velocity-previous year
- GH dose (IGF-I titration)
- Weekly GH dose
- Gender
- Bone age
- IGF-I value
- Growth response during the 1st year of GH therapy
- Duration of treatment
- Adherence
- Appropriate replacement of other (endocrine) therapies or unrecognised associated defects

And still poorly defined molecular and biochemical factors that may include:

- the structure and concentration of GH receptors
- the robustness of the post-receptor signaling cascade
- IGF-I transcriptional and translational efficiency
- epiphyseal responsiveness

GH, growth hormone; IGF-I, insulin-like growth factor 1; MPH, mid-parental height; rhGH, recombinant human growth hormone; SDS, standard deviation score

1. Ranke MB, et al. J Clin Endocrinol Metab. 1999;84:1174-1183; 2. Kaspers S, et al. Appl Health Econ Health Policy. 2013;11:237-249; 3. Cutfield W, et al. Acta Paediatr Suppl. 1999;88:72-75; 4. Ranke MB, et al. Horm Res Paediatr. 2013;79:51-67; 5. Lu T, et al. J Clin Endocrinol Metab. 2021;106:1918-1928; 6. Dauber A, et al. J Clin Endocrinol Metab. 2020;105:3203-3214; 7. Stevens A, et al. Pharmacogenomics J. 2021. DOI: 10.1038/s41397-021-00237-5; 8. Bagnasco F, et al. Endocr Pract. 2017;23:929-941; 9. Haverkamp F, et al. Clin Ther. 2008;30:307-316; 10. Fisher BG, et al. Horm Res Paediatr. 2013;79:189-196

ADHERENCE TO rhGH THERAPY – THE EVIDENCE BASE

- Few, but increasing number of studies
- Studies – vary in design, quality and definition of ‘adherence’
- Methods for assessing adherence have generally been poor
- Frequently relying on reporting by patients or carers
- Contrasting results depending on the method used to record adherence (we need objective measurements of adherence)
- Relationship between non-adherence and reduced linear growth
- A range of possible determinants have been identified

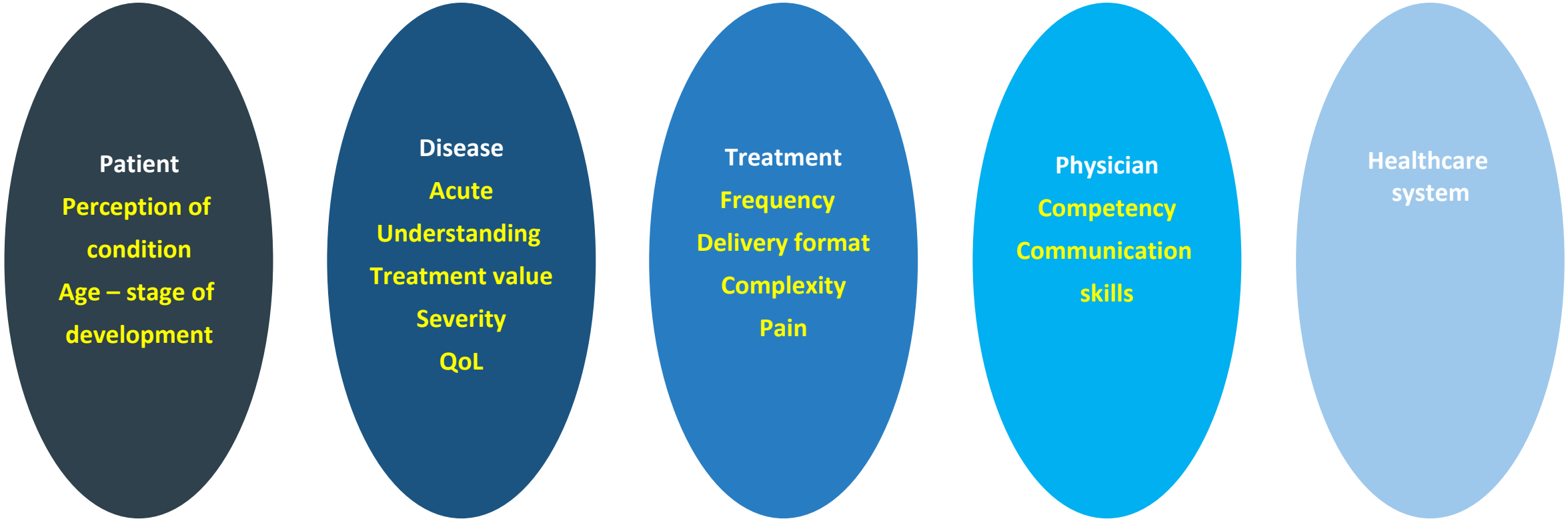
rhGH, recombinant human growth hormone

1. Fisher BG, et al. Horm Res Paediatr. 2013;79:189-196; 2. Cutfield WS, et al. PLoS One. 2011;6:e16223; 3. Gau M, et al. J Pediatr Endocrinol Metab. 2017;30:989-993; 4. Kapoor RR, et al. Arch Dis Child. 2008;93:147-148; 5. Graham S, et al. Horm Res Paediatr. 2018;90:221-227; 6. Farfel A, et al. Growth Horm IGF Res. 2019;44:1-5; 7. Rosenfeld RG, et al. Endocr Pract. 2008;14:143-154; 8. Lass N, et al. Horm Res Paediatr. 2015;84:240-247; 9. Aydın BK, et al. Endocr Pract. 2014;20:46-51; 10. Acerini CL, et al. Front Endocrinol (Lausanne). 2018;9:688

FACTORS WHICH MAY ADVERSELY AFFECT ADHERENCE

THE EVIDENCE BASE

- A range of possible determinants have been identified



QoL, quality of life

1. Bagnasco F, et al. Endocr Pract. 2017;23:929-941. 2. Haverkamp F, et al. Clin Ther. 2008;30:307-316; 3. Fisher BG, et al. Horm Res Paediatr. 2013;79:189-196

GH DEFICIENCY – HYPOPITUITARISM

PE connect®
POWERED BY COR2ED

WHY MONITOR GH THERAPY? – SAFETY

- GH therapy is given to patients systemically for long periods:
  - Often throughout childhood and into adulthood
  - The growth response is disease/condition-specific
  - Has the potential to be linked with other diseases

- The areas for ongoing surveillance:
  - Use of high-dose GH
  - Glucose homeostasis
  - Cancer risk

GH, growth hormone

Growth Hormone Research Society. J Clin Endocrinol Metab. 2001;86:1868-1870

SAFETY OUTCOMES DURING PAEDIATRIC GH THERAPY: FINAL RESULTS FROM THE PROSPECTIVE GeNeSIS OBSERVATIONAL PROGRAM

- **Study included 22,311 GH-treated children from 827 sites in 30 countries; mean ± SD follow-up of 4.2 ± 3.2 years**
  - GH deficiency (63%)
  - idiopathic short stature (13%)
  - Turner syndrome (8%)
- T2DM was elevated [SIR: **3.77** (95% CI: 2.24, 5.96)], but 72% had risk factors (n = 18)
- **T2DM incidence was elevated compared with the general population, however, most cases had T2DM risk factors**

CI, confidence interval; GH, growth hormone; SD, standard deviation; SIR, standardised incidence ratio; T2DM, type 2 diabetes mellitus.
Child C, et al. J Clin Endocrinol Metab. 2019;104:379-389

SAGhE EVALUATED THE SAFETY AND APPROPRIATENESS OF GH TREATMENT IN EUROPE

SAGhE: LONG TERM SAFETY OF rhGH TREATMENT

Total number of patients = 25,229

Risk groups	
1a	• Isolated GHD • ISS
1b	• SGA without catch-up growth
2	• Multiple pituitary hormone deficiency • Defined paediatric syndromes associated with an increased mortality risk (i.e. Turner syndrome) • Benign pituitary tumours • Severe craniofacial or other malformations • Severe chronic paediatric diseases
3	• Patients who were previously treated for cancer, craniopharyngioma • Chronic renal insufficiency

(rh)GH, (recombinant human) growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; SAGhE, Safety and Appropriateness of Growth hormone treatments in Europe; SGA, small for gestational age

1. Carel J-C, et al. J Clin Endocrinol Metab. 2012;97:416-425; 2. Poidvin A, et al. Neurology. 2014;83;780-786; 3. Sävendahl L, et al. J Clin Endocrinol Metab. 2012;97:E213-217; 4. Albertsson-Wikland K, et al. J Clin Endocrinol Metab. 2016;101:2149-2159; 5. Lars Sävendahl et al. Lancet Diabetes Endocrinol 2020; 8: 683–92

MORTALITY AND MORBIDITY: CONFLICTING REPORTS

French Cohort[1,2]

- IGHD, ISS, SGA
  - **Higher mortality** (dose related)
  - **Higher SMR for circulatory diseases,** incl. cerebrovascular disease
  - **Higher Stroke SIR** (all types)

Belgian, Netherlands, Sweden[3]

- IGHD, ISS, SGA
  - **No CVD or cancer deaths**

Sweden[4]

- IGHD, ISS, SGA
  - **No increased mortality** (controlling for birth characteristics)

observed/expected deaths were not increased in childhood rhGH–treated IGHD, ISS, and SGA patients when applying an advanced sex-specific mortality model adjusting for birth characteristics

CVD, cardiovascular disease; IGHD, idiopathic growth hormone deficiency; ISS, idiopathic short stature; rhGH, recombinant human growth hormone; SGA, small for gestational age; SIR, standardised incidence ratio; SMR, standardised mortality rate1. Carel J-C, et al. J Clin Endocrinol Metab. 2012;97:416-425; 2. Poidvin A, et al. Neurology. 2014;83;780-786; 3. Sävendahl L, et al. J Clin Endocrinol Metab. 2012;97:E213-217; 4. Albertsson-Wikland K, et al. J Clin Endocrinol Metab. 2016;101:2149-2159

GH SAFETY WORKSHOP 2016
SAGhe 2020 (24,232 PATIENTS)

Majority view of the effect of GH treatment for approved indications on cancer risk in children and adults (including those with a childhood-onset of GH deficiency

Age at onset of GH treatment	New primary cancer	Recurrence of previous primary cancer in cancer survivors	Second or subsequent neoplasms
Child	No evidence for GH treatment effect Level: robust	No evidence for GH treatment effect Level: robust	Risk present but diminishes with time from onset of GH treatment Level: suggestive
Adult	No evidence for GH treatment effect Level: Suggestive	Insufficient data available	Insufficient data available

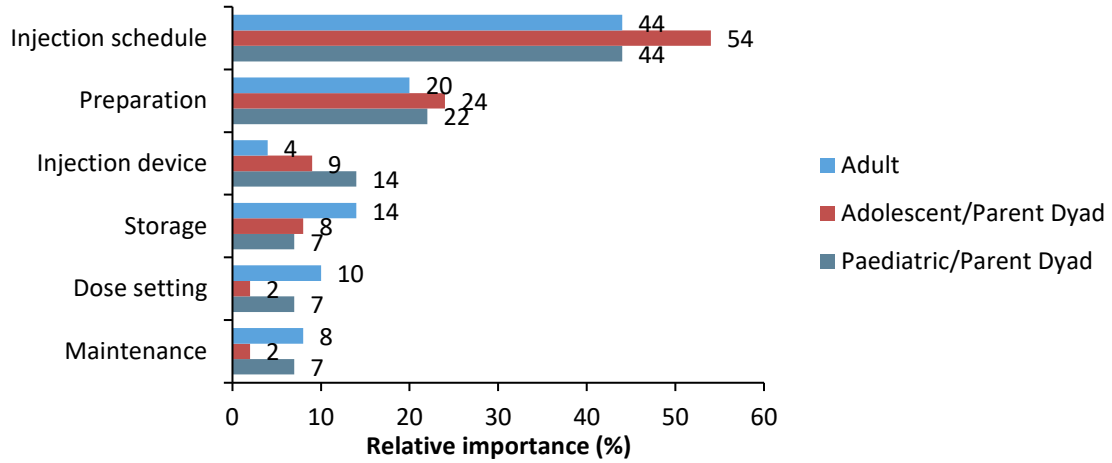
Robust: multiple supportive publications; Suggestive: <3 supportive publications; Insufficient: inadequate published evidence

GH, growth hormone; SAGhE, Safety and Appropriateness of Growth hormone treatments in Europe;
Allen DB, et al. Eur J Endocrinol. 2016;174:P1-9; Lars Sävendahl et al. Lancet Diabetes Endocrinol 2020; 8: 683–92

GH DEFICIENCY – HYPOPITUITARISM

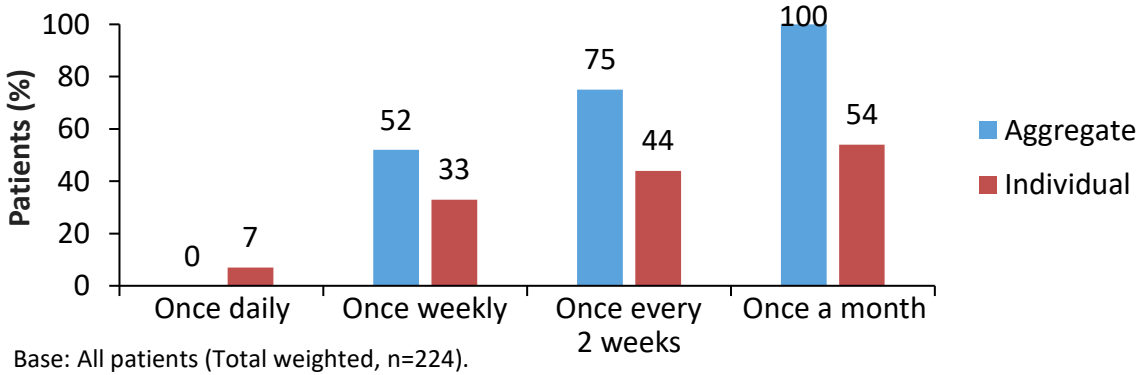
PATIENTS PREFER A LESS FREQUENT INJECTION REGIMEN FOR TREATING GHD

AVERAGE RELATIVE IMPORTANCE OF ATTRIBUTES BY PATIENT COHORT



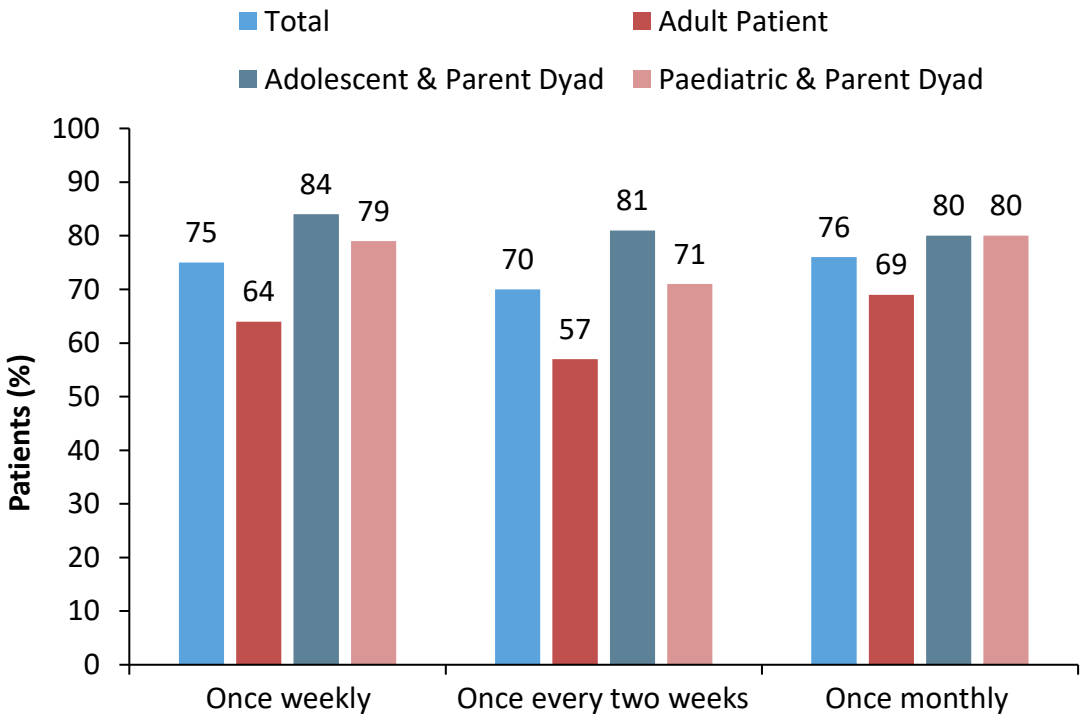
Base: All patients (Total weighted, Adult, n=75; Adolescent Dyad, n=79; Paediatric Dyad, n=70

AVERAGE RELATIVE UTILITY OF INJECTION SCHEDULE ATTRIBUTE



Base: All patients (Total weighted, n=224).

PERCENTAGE OF PARTICIPANTS THAT WOULD CHOOSE THE NEW PROFILE OVER CURRENT TREATMENT



Base: All patients (Total weighted, n=224; Adult, n=75; Adolescent n=79; Paediatric Dyad, n=70).

GHD, growth hormone deficiency

McNamara M, et al. Patient Prefer Adherence. 2020;14:781-793

OVERVIEW OF THE DEVELOPMENT HISTORY OF LAGH ANALOGUES

- Depot formulation
- PEGylated Formulations
- Pro-drug formulation
- Non-covalent albumin binding GH compound(s)
- GH Fusion Proteins

- No longer being developed
- Ongoing studies
- Phase 3 trial in CGHD suggest non inferiority
- Completed Phase 3 study in CGHD and data submitted to FDA and EMA

CGHD, combined growth hormone deficiency; EMA, European Medicines Agency; FDA, Food and Drug Administration; GH, growth hormone; LAGH, long-acting growth hormone

1. Yang Y, et al. Endocrine. 2019;65:25-34; 2. Miller BS, et al. J Clin Endocrinol Metab. 2020;105:e2121-2133; 3. Yuen KCJ, et al. Front Endocrinol (Lausanne). 2021;12:637209; 4. Bidlingmaier M, et al. J Clin Endocrinol Metab. 2021;106:e2367-2369

LONG-ACTING GROWTH HORMONE ANALOGUES

- Currently, two LAGH analogs are marketed in Asia, one recently approved in the United States, another previously approved but not marketed in Europe, and several others proceeding through various stages of clinical development
- Shot-term efficacy and safety data
- Several practical questions still remain, including
  - possible differences in dose initiation between naïve and switch-over patients
  - methodology of dose adjustment/s
  - timing of measuring serum IGF-I levels
  - metabolic effects
  - antibodies
  - durability of efficacy
  - safety
  - cost-effectiveness
- Long-term surveillance of safety and efficacy of LAGH analogs (Different LAGH) are needed
- There is no evidence to support differences in the effects of long-acting GH compared with those of daily GH **(7 studies)**
- More RCTs that focus on the safety of high-dose long-acting GH treatment, especially the detection of adverse events caused by elevated levels of serum IGF-1, are needed in the future

GH, growth hormone; IGF-I, insulin-like growth factor 1; LAGH, long-acting growth hormone; RCT, randomised clinical trial

1. Yang Y, et al. Endocrine. 2019;65:25-34; 2. Miller BS, et al. J Clin Endocrinol Metab. 2020;105:e2121-2133; 3. Yuen KCJ, et al. Front Endocrinol (Lausanne). 2021;12:637209; 4. Bidlingmaier M, et al. J Clin Endocrinol Metab. 2021;106:e2367-2369

KEY CONCLUSIONS

- Despite the many years of research, controversies remain regarding etiology, diagnosis, and management of GHD children
- rhGH treatment is efficacious and children achieve increase in growth velocity and adult height appropriate for target range (Adult height range -1.5 to -0.8 SDS)
- Age at onset of rhGH therapy has been demonstrated to be negatively correlated with change in HSDS and the adult height outcome of the patient
- Main factors affecting adult height: age at start of GH, peak GH, parental height, GH dose, adherence
- Good safety profile but long-term safety data are still needed
  (evidence-based intervention strategies for optimising treatment and safety profiles)
- Several forms of long-acting rhGH are currently under development with new challenges

GH, growth hormone; GHD, growth hormone deficiency; rhGH, recombinant human growth factor; (H)SDS, (height) standard deviation score

PRIMARY IGF-1 DEFICIENCY

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Chief of Endocrinology

Children's National Hospital

Washington, DC, USA

DISCLOSURES

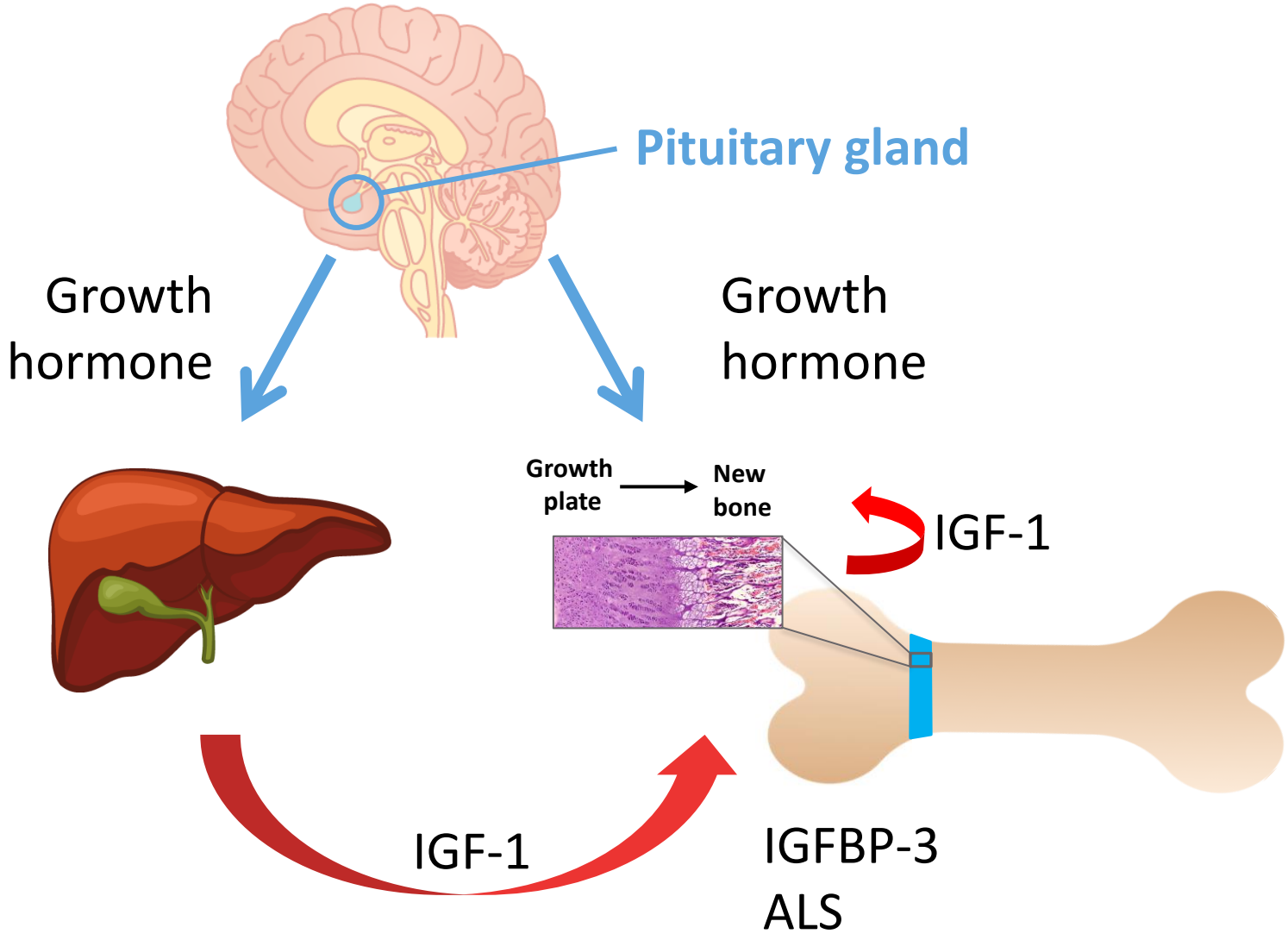
- Dr Dauber has served as a consultant for Biomarin, Novo Nordisk and Ascendis
- Dr Dauber is currently receiving research funding from Biomarin

AGENDA

- Brief overview of the growth hormone/IGF-1 signalling axis
- Genetics of growth hormone insensitivity/resistance
- Efficacy and safety of recombinant IGF-1 treatment in primary IGF-1 deficiency

IGF-1, insulin-like growth factor 1

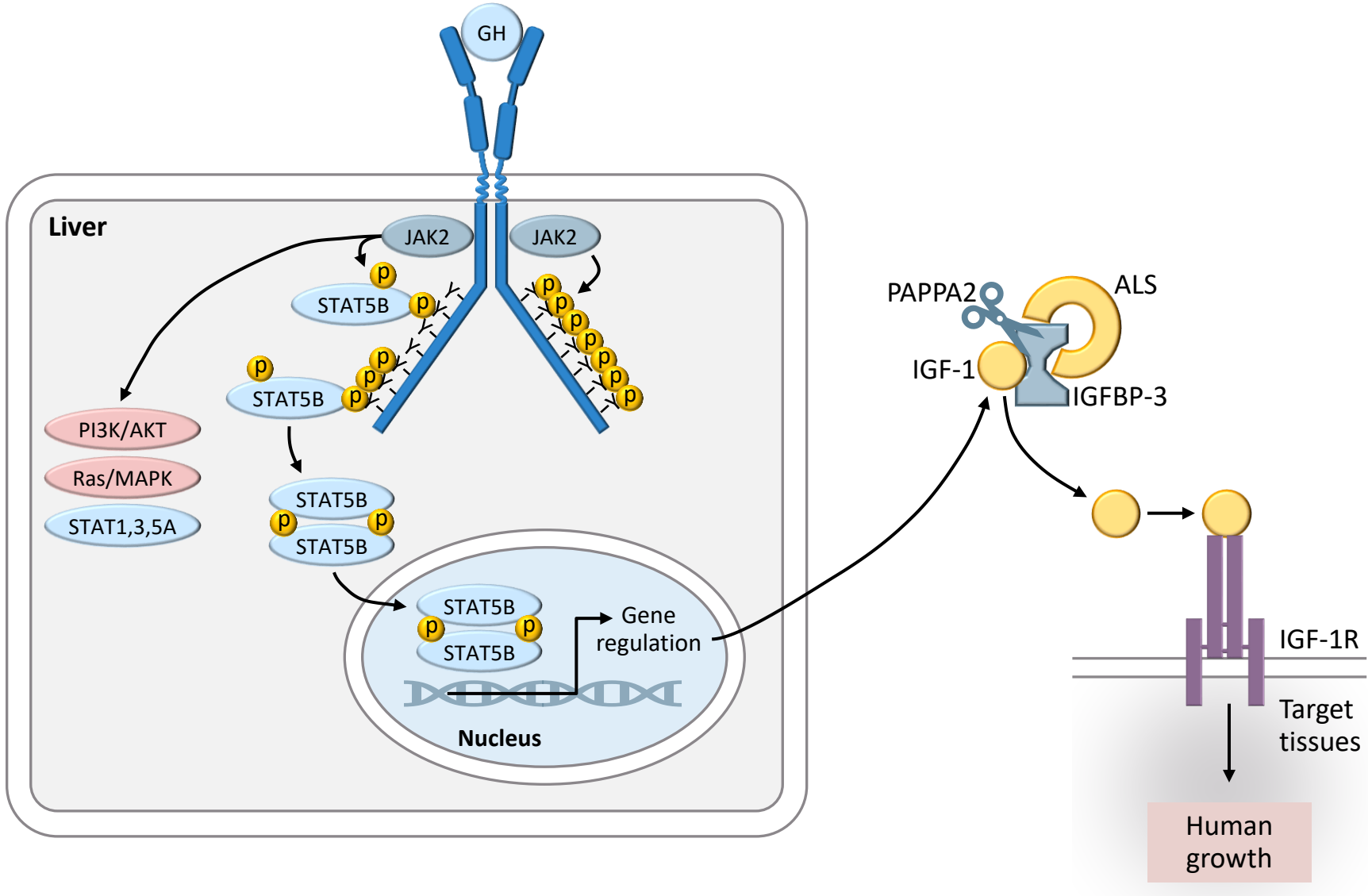
GROWTH HORMONE/IGF-1 PATHWAY



ALS, acid-labile subunit; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor-binding protein 3

Storr HL, et al. Endocr Rev. 2019;40:476-505

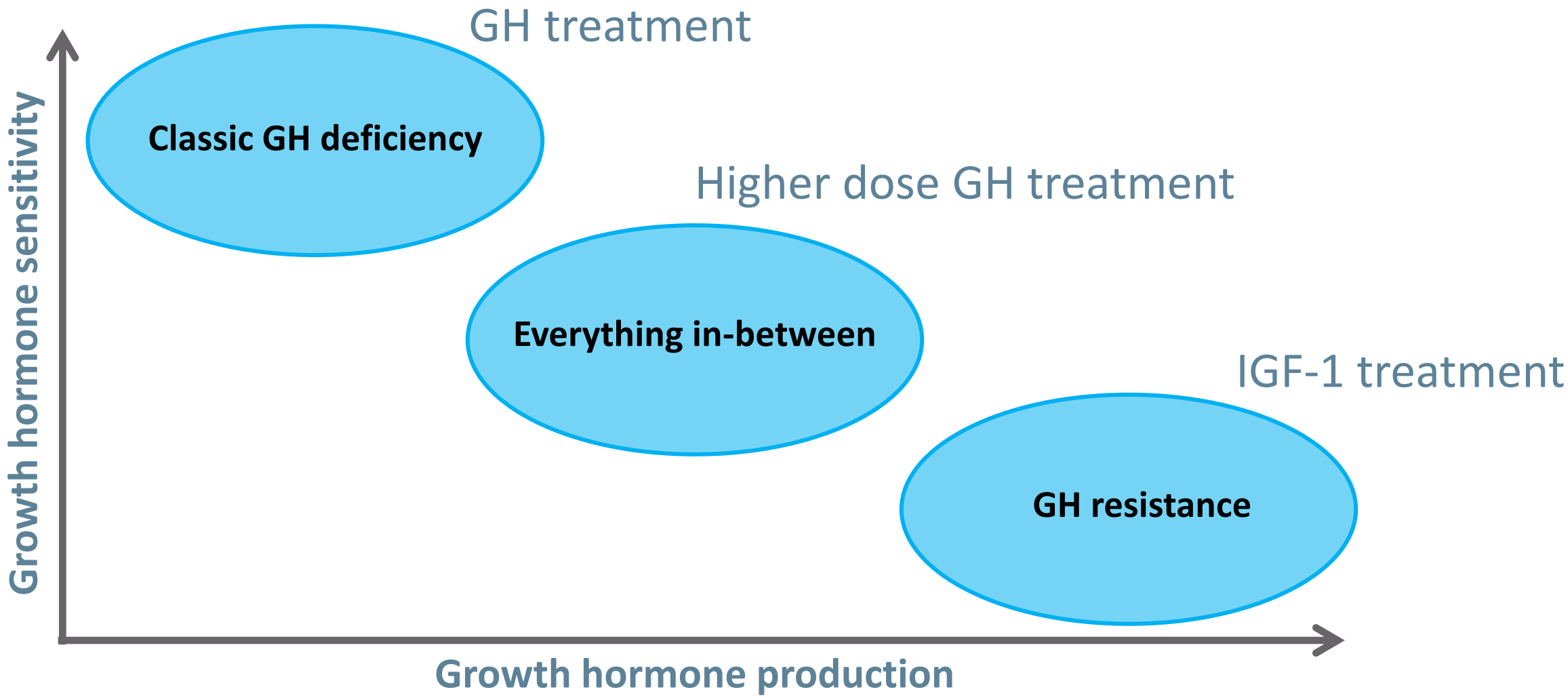
GROWTH HORMONE SIGNALLING PATHWAY



AKT, v-akt murine thymoma viral oncogene homolog; ALS, acid-labile subunit; GH, growth hormone; JAK2, Janus kinase 2; IGF-1(R), insulin-like growth factor 1 (receptor); IGFBP-3, insulin-like growth factor-binding protein 3; MAPK, mitogen-activated protein kinase; P, phosphorylated residue; PAPPA2, pregnancy-associated plasma protease A2; PI3K, phosphatidylinositol 3-kinase; Ras, rat sarcoma virus; STAT, signal transducer and activator of transcription; Y, tyrosine

Storr HL, et al. Endocr Rev. 2019;40:476-505

TRADITIONAL ENDOCRINOLOGIST VIEW OF GROWTH TREATMENT



GH, growth hormone; IGF-1, insulin-like growth factor 1

WHAT IS PRIMARY IGF-1 DEFICIENCY?

IGF-1 DEFICIENCY WHICH IS NOT SECONDARY TO:

- Growth hormone deficiency
- Malnutrition
- Chronic steroid use
- Hypothyroidism

SEVERE PRIMARY IGF-1 DEFICIENCY IS DEFINED BY THE FDA AS:

- Height ≤ -3 SDS
- Basal IGF-1 ≤ -3 SDS (in EU IGF-1 <2.5%)
- Normal or elevated growth hormone levels

IGF-1 DEFICIENCY WHICH IS DUE TO:

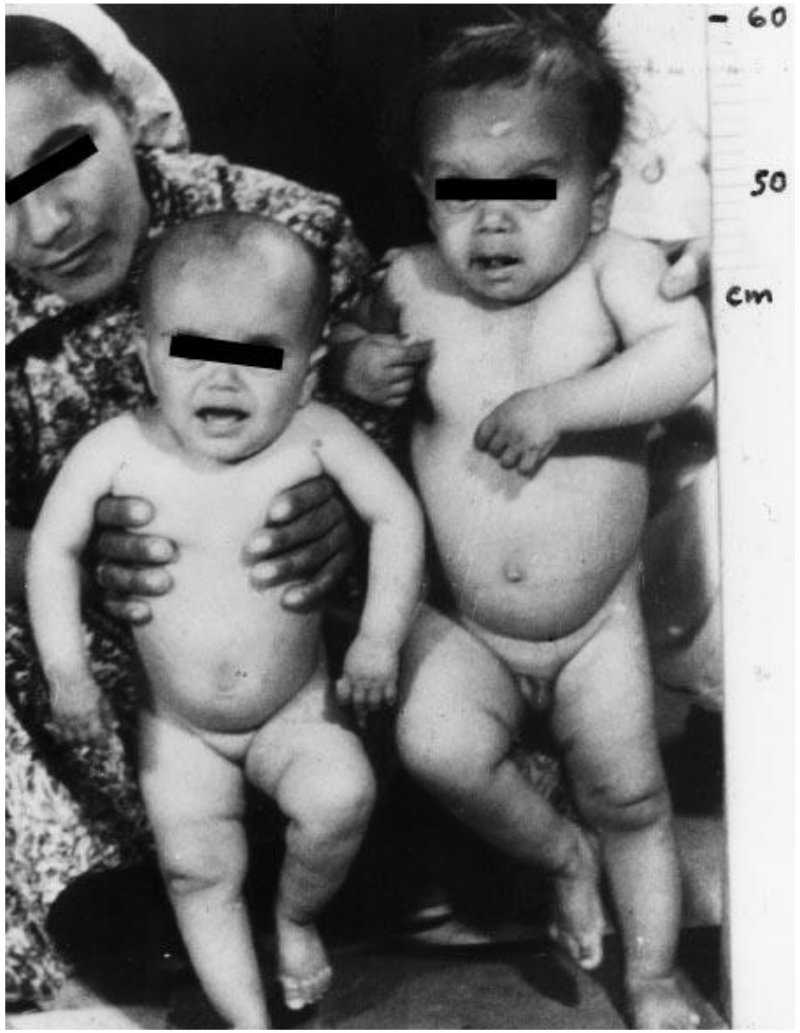
- Genetic defects downstream of growth hormone

IGF-1, insulin-like growth factor 1; SDS, standard deviation score

Increlex (mecasermin) [prescribing information]. Ipsen Biopharmaceuticals Inc., December 2019; Increlex (mecasermin) (SmPC).

LARON SYNDROME – CLASSIC GROWTH HORMONE INSENSITIVITY

- Clinical syndrome first described by Dr. Zvi Laron in 1966[1]
  - Phenotype of hypopituitarism
  - Elevated growth hormone levels
- Found to be due to mutations in the growth hormone receptor (GHR) in 1989[2]

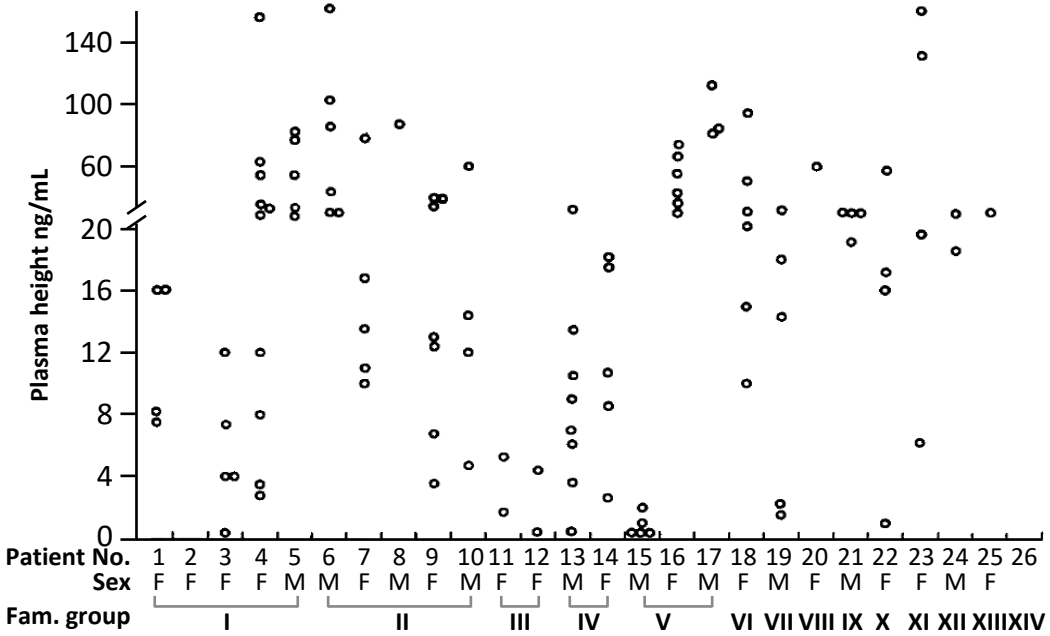


1. Laron Z. J Clin Endocrinol Metab. 2004;89:1031-44; 2. Amselem S, et al. N Engl J Med. 1989;321:989-95

CLINICAL PRESENTATION OF LARON SYNDROME

- Extreme post-natal short stature (-4 to -10 SDS)
- Craniofacial disproportion with midface hypoplasia
- Small external genitalia in males
- Sparse and thin hair
- Delayed motor development
- Small hands and feet
- Delayed dentition
- Delayed puberty
- Hypoglycaemia
- High pitched voice

HIGH GROWTH HORMONE LEVELS

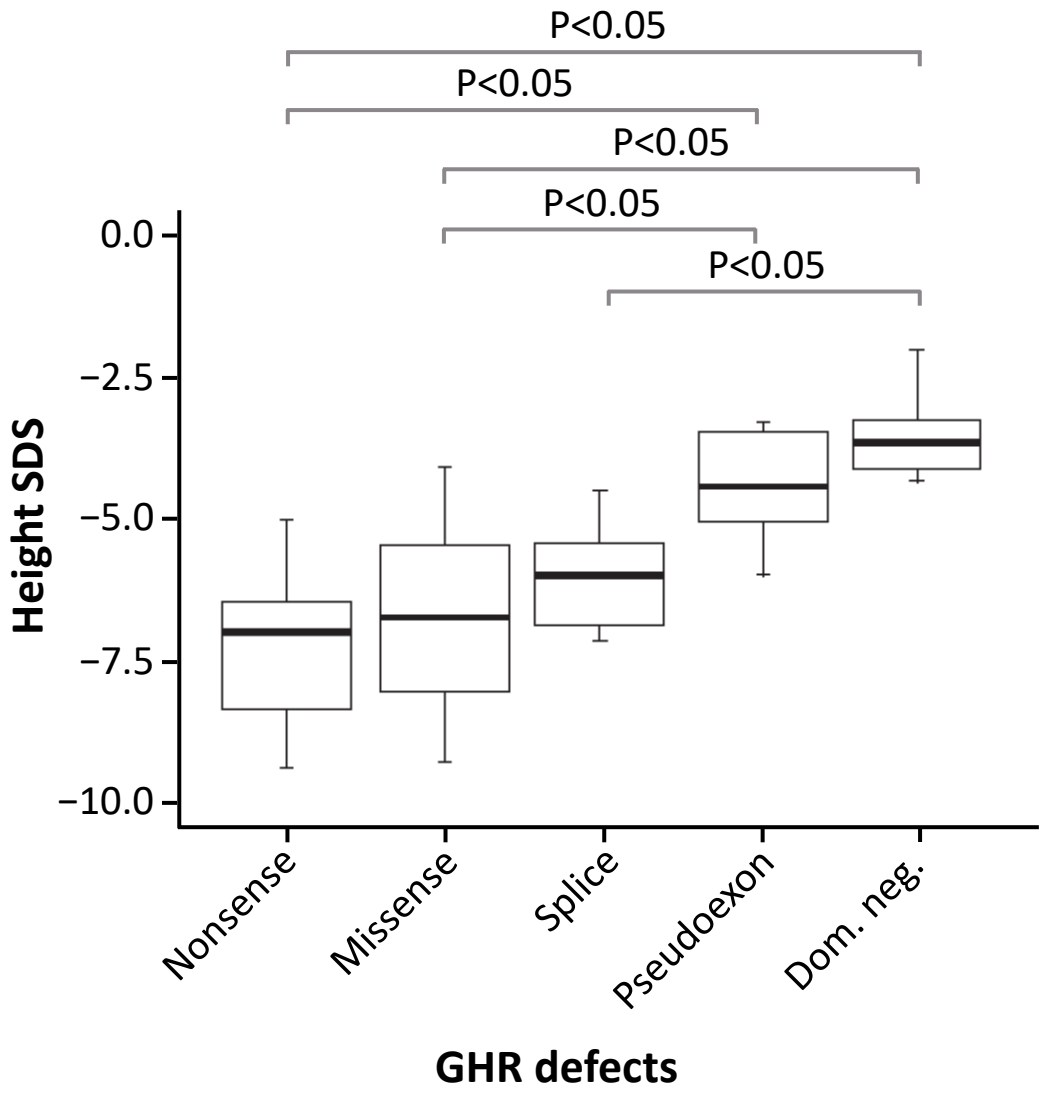


- Low IGF-1, IGFBP-3, ALS
- Minimal increase in IGF-1/IGFBP-3 upon growth hormone stimulation

ALS, acid-labile subunit; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor-binding protein 3; SDS, standard deviation score

Laron Z. J Clin Endocrinol Metab. 2004;89:1031-44

PHENOTYPIC SPECTRUM OF GHR MUTATIONS



- Biallelic mutations lead to most severe phenotype
- Mutation in intron 6 leads to insertion of a pseudoexon – adds 36 amino acids to protein
  - Wide clinical spectrum
- Dominant-negative mutations
  - Milder phenotype

GHR, growth hormone receptor; SDS, standard deviation score

David A, et al. Endocr Rev. 2011;32:472-97

MUTATIONS IN THE GH/IGF-1 AXIS CAN PRESENT WITH GROWTH HORMONE INSENSITIVITY

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SUMMARY OF PHENOTYPIC AND BIOCHEMICAL FEATURES IN THE RANGE OF GH–IGF-1 AXIS DEFECTS

Gene defect/phenotype	*GHR*	*STAT5b*	*PTPN11*	*IGF-1*	*IGFALS*	*IGF-1R*	Bioinactive GH	*GH1* with anti-GH antibodies
Severe growth failure	+/−	+	−	+	−	−	−	+
Mild growth failure	−/+	−	+	−	+	+	+	−
Mid-face hypoplasia	+/−	+/−	−	−	−	−	−	+
Other facial dysmorphism	−	−	+	+	−	+	−	−
Deafness	−	−	−	+/−	−	−	−	−
Microcephaly	−	−	−	+	−	+	−	−
Intellectual delay	−	−	−/+	+	−	+/−	−	−
Puberty delay	+/−	+/−	+/−	−	+	−	−	−
Immune deficiency	−	+	−	−	−	−	−	−
Hypoglycaemia	+	−/+	−	−	−	−	−	−
Hyperinsulinemia	−	−	−	+/−	+	−	−	−
IGF-1 deficiency	+	+	−/+	+/−	+	−	+	+
IGFBP-3 deficiency	+	+	−/+	−	+	−	+	+
ALS deficiency	+	+	−/+	−	+	−	+	+
GH excess	+	+	−	+/−	+	−	−	−
GHBP deficiency	+/−	−	−	−	−	−	−	−
Homozygous or compound heterozygous mutations	+	+	−	+	+	−	−/+	+
Heterozygous mutations	−	−	+	−/+	−	+	+/−	−

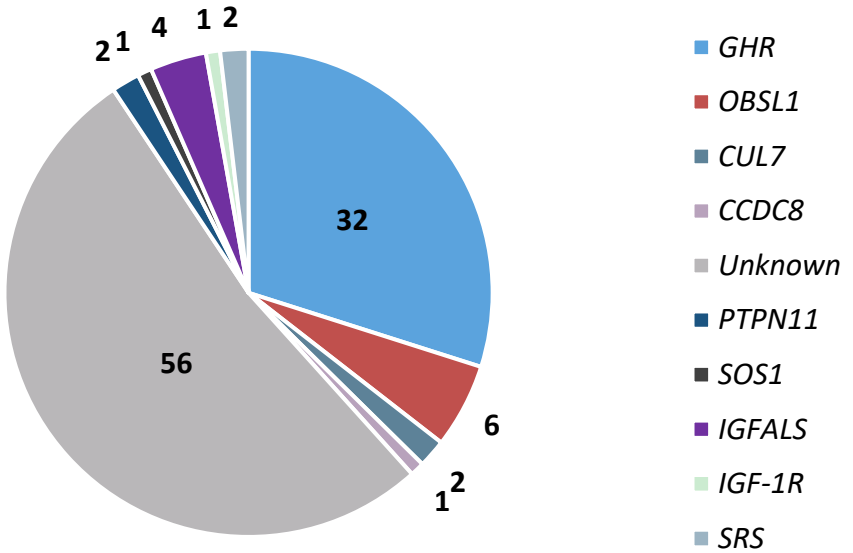
+, positive; −, negative; +/−, predominantly positive; −/+ predominantly negative

ALS, acid-labile subunit; GH(R), growth hormone (receptor); GHBP, growth hormone-binding protein; IGF-1(R), insulin-like growth factor 1 (receptor); IGFALS, insulin-like growth factor binding protein acid labile subunit; IGFBP-3, insulin-like growth factor-binding protein 3; PTPN11, protein tyrosine phosphatase non-receptor type 11; STAT5b, signal transducer and activator of transcription 5b

David A, et al. Endocr Rev. 2011;32:472-97

EXOME SEQUENCING IDENTIFIED ADDITIONAL GENES PRESENTING WITH GH OR IGF-1 INSENSITIVITY

- 107 patients
  - 96 GH insensitivity
  - 11 IGF-1 insensitivity
- Candidate gene sequencing followed by WES
- Identified genes with overlapping phenotype with classic GHI



Positive genetic diagnosis in 51/107 cases (48%)
Candidate gene sequencing alone 38/107 (36%)

Comparison of mean height SDS, IGF-1 SDS and peak GH levels (means ± SD) between individuals with genetic defects and those with no molecular diagnosis

	No genetic diagnosis (Group 1)	GHR and GHR 6ψ mutations (Group 2)	3M gene mutations (Group 3)	Any genetic diagnosis (Group 4)	P value (95% CI)		
					Group 1 vs Group 2	Group 1 vs Group 3	Group 1 vs Group 4
Height SDS	−3.7 ± 1.2 (n=50)	−5.7 ± 1.9 (n=31)	−5.7 ± 0.9 (n=9)	−5.2 ± 1.8 (n=51)	**<0.0001** (1.3-2.6)	**<0.0001** (1.2-2.8)	**<0.0001** (0.89-2.1)
IGF-1 SDS	−2.1 ± 1.5 (n=48)	−3.7 ± 1.9 (n=26)	−1.6 ± 1.0 (n=8)	−3.0 ± 2.0 (n=42)	**<0.0001** (0.87-2.45)	0.3682 (−1.6-0.6)	**0.0128** (0.2-1.63)
Peak GH	21.6 ± 17.1 (n=51)	93.7 ± 212.3 (n=31)	21.4 ± 13.4 (n=9)	68.1 ± 173.3 (n=48)	**0.0177** (12.9-131.3)	0.9676(−12.3-11.8)	0.0594 (−1.88-94.9)

3M gene mutations, mutations identified in *CUL7, CCDC8* and *OBSL1*

CCDC8, coiled-coil domain-containing 8; CI, confidence interval; CUL7, cullin 7; GH(R), growth hormone (receptor); IGF-1, insulin-like growth factor 1; IGF1R, insulin-like growth factor 1 receptor; IGFALS, insulin-like growth factor binding protein acid labile subunit; OBSL1, obscurin-like cytoskeletal adaptor 1; PTPN11, protein tyrosine phosphatase non-receptor type 11; SOS1, son of sevenless homolog 1; SD, standard deviation; SDS, standard deviation score; SRS, Silver–Russell syndrome; WES, whole exome sequencing

Shapiro L, et al. Eur J Endocrinol. 2017;177:485-501

TREATMENT WITH RECOMBINANT IGF-1 CAN IMPROVE HEIGHT IN PATIENTS WITH IGF-1 DEFICIENCY

PE connect® POWERED BY COR2ED

BASELINE AND MOST RECENT CHARACTERISTICS FOR ALL SUBJECTS

	GHRD	GHIS	GHAB	Total
N (males/females)	28 (18/10)	39 (24/15)	9 (4/5)	76 (46/30)
IGF-1 SDS baseline	−4.5 ± 1.8 (−7.5, −0.7) 27	−4.3 ± 1.8 (−9.5, −1.5) 35	−4.0 ± 1.6 (−6.6, −2.0) 7	−4.4 ± 1.8 (−9.5, −0.7) 69
Height velocity baseline (cm/yr)	2.9 ± 1.6 (0.5, 5.6) 21	2.8 ± 2.0 (0, 7.7) 33	2.1 ± 1.1 (0.2, 3.6) 8	2.7 ± 1.8 (0, 7.7) 62
Duration of treatment (yr)	5.0 ± 3.6 (0.1, 12.1)	3.7 ± 2.5 (0.04, 12.5)	5.5 ± 3.0 (0.5, 9.5)	4.4 ± 3.0 (0.04, 12.5)
Age baseline (yr)	8.2 ± 4.9 (1.7, 17.1)	7.2 ± 4.1 (1.7, 17.5)	9.5 ± 4.5 (2.6, 16.6)	7.8 ± 4.5 (1.7, 17.5)
Age last	13.1 ± 3.8 (6.9, 21.4)	10.9 ± 4.3 (3.2, 20.2)	15.0 ± 3.2 (10.7, 20.6)	12.2 ± 4.2 (3.2, 21.4)
Height SDS baseline	−6.1 ± 1.6 (−8.4, −3.2)	−6.3 ± 1.7 (−9.3, −2.8)	−8.2 ± 2.4 (−12.1, −5.0)	−6.5 ± 1.8 (−12.1, −2.8)
Height SDS last	−5.2 ± 1.6 (−9.0, −1.5)	−4.9 ± 1.8 (−8.8, −1.4)	−6.0 ± 1.8 (−8.6, −2.7)	−5.1 ± 1.8 (−9.0, −1.4)
Weight SDS baseline	−5.7 ± 3.3 (−12.5, −0.2)	−6.4 ± 2.7 (−11.4, −1.7)	−10.3 ± 7.8 (−27.2, −1.1)	−6.6 ± 4.0 (−27.2, −0.2)
Weight SDS last	−3.5 ± 2.8 (−10.3, 1.1)	−3.5 ± 2.8 (−9.9, 0.6)	−5.1 ± 4.3 (−12.6, 0.9)	−3.7 ± 3.0 (−12.6, 1.1)
BMI SDS baseline	0.0 ± 1.4 (−3.1, 2.2) 27	−0.3 ± 1.0 (−2.8, 1.8) 38	−0.4 ± 1.2 (−1.7, 1.6) 9	−0.2 ± 1.2 (−3.1, 2.2) 74
BMI SDS last	0.4 ± 1.2 (−2.1, 2.4)	0.3 ± 1.2 (−2.6, 1.9)	0.2 ± 1.4 (−2.2, 2.2)	0.3 ± 1.2 (−2.6, 2.4)
Bone age baseline (yr)	5.8 ± 4.5 (0.3, 14.3) 28	4.4 ± 2.3 (0.6, 8.3) 30	5.8 ± 4.2 (1.5, 13.7) 7	5.1 ± 3.8 (0.1, 14.3) 65
Bone age last	11.4 ± 4.2 (4.1, 18) 28	8.4 ± 3.5 (2.5, 15.6) 28	13.4 ± 1.5 (10.6, 15.4) 7	10.3 ± 4.1 (2.5, 18) 63

All data are expressed as mean ± SD, with range in parentheses, with or without frequency. The number of determinations is displayed when the number of subjects examined is less than 76 or the variable is not defined for subjects of certain age (e.g. BMI SDS)

BMI, body mass index; GHAB, growth hormone-neutralising antibodies; GHIS, growth hormone insensitivity syndrome; GHRD, growth hormone receptor deficiency; IGF-1, insulin-like growth factor 1; SD, standard deviation; SDS, standard deviation score

Chernausek SD, et al. J Clin Endocrinol Metab. 2007;92:902-10

FINAL HEIGHT DATA

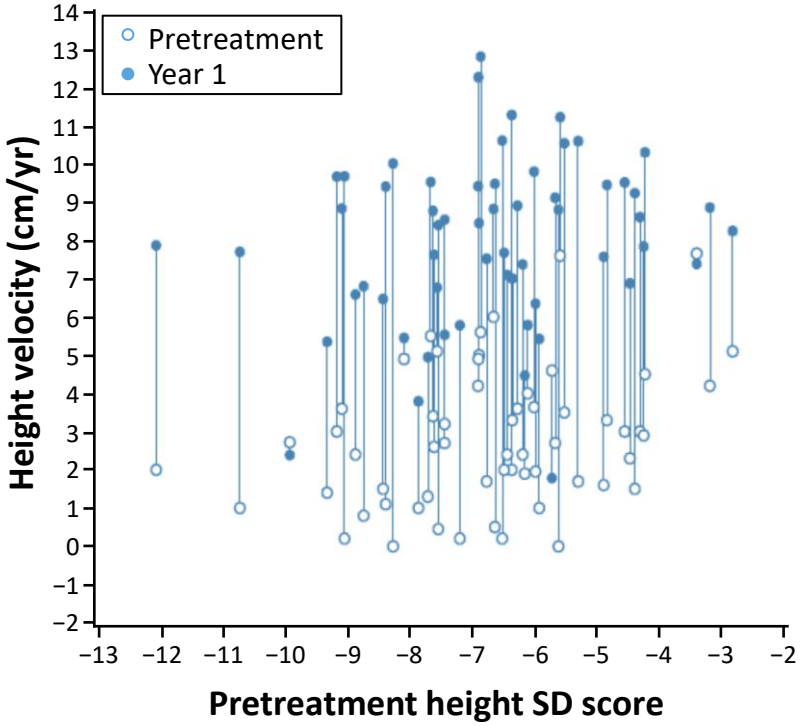
SUBJECTS AT OR NEAR FINAL HEIGHT

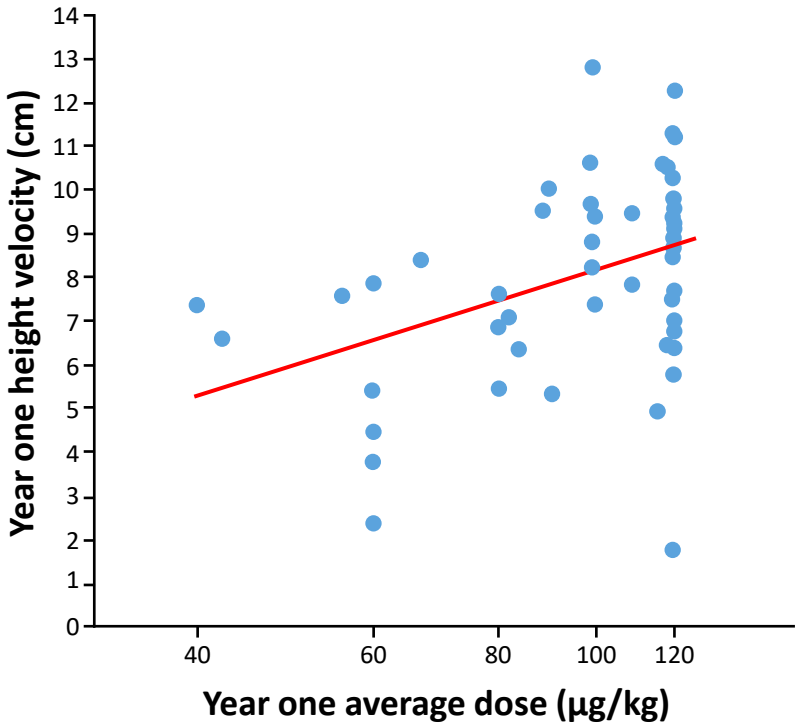
	Male 1	Male 2	Female 1	Female 2	Female 3	Female 4
Baseline age (yr)	9.7	13.0	5.0	15.2	8.2	8.2
Treatment duration (yr)	7.7	8.4	9.9	5.4	6.6	6.6
Initial height (cm)	111.2	99.4	92.7	86.1	85.1	92.7
Initial height SD score	−4.2	−7.5	−3.4	−12.1	−9.1	−7.2
Final height (cm)	164.4	142.0	150.2	112.0	121.2	120.8
Final height SD score	−1.5	−4.8	−1.8	−7.8	−6.3	−6.4
Change (cm)	53.1	42.6	57.5	25.9	36.1	28.1
PAH (cm)	141	123	133	89	110	118
GnRH agonist treatment	No	Yes	Yes	Yes	No	No
Diagnostic category	GHRD	GHRD	GHIS	GHAB	GHAB	GHAB

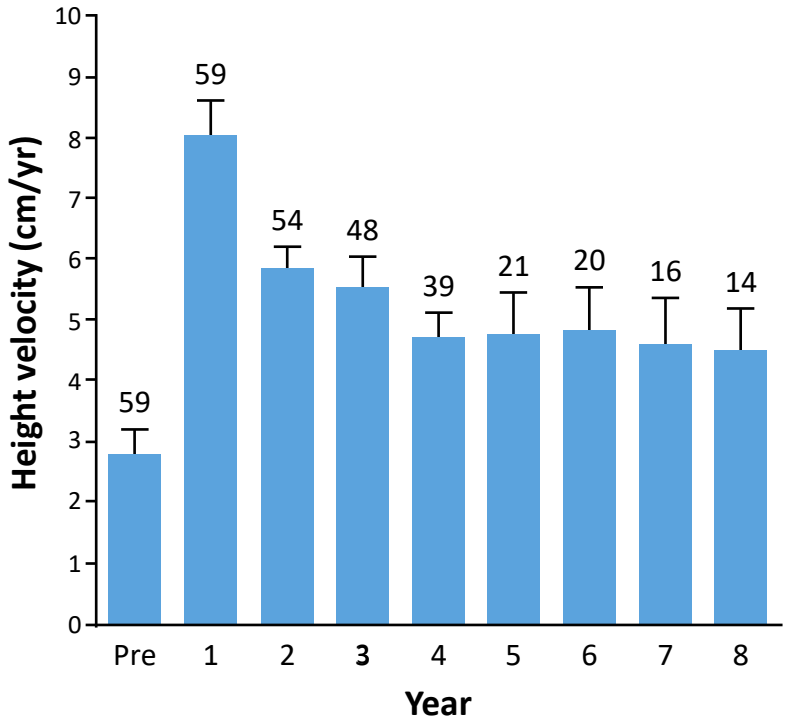
GHAB, growth hormone-neutralising antibodies; GHIS, growth hormone insensitivity syndrome; GHRD, growth hormone receptor deficiency; GnRH, gonadotropin-releasing hormone; PAH, predicted adult height; SD, standard deviation

Chernausek SD, et al. J Clin Endocrinol Metab. 2007;92:902-10

RECOMBINANT IGF-1 EFFECT IS DOSE DEPENDENT AND HIGHEST IN 1ST YEAR







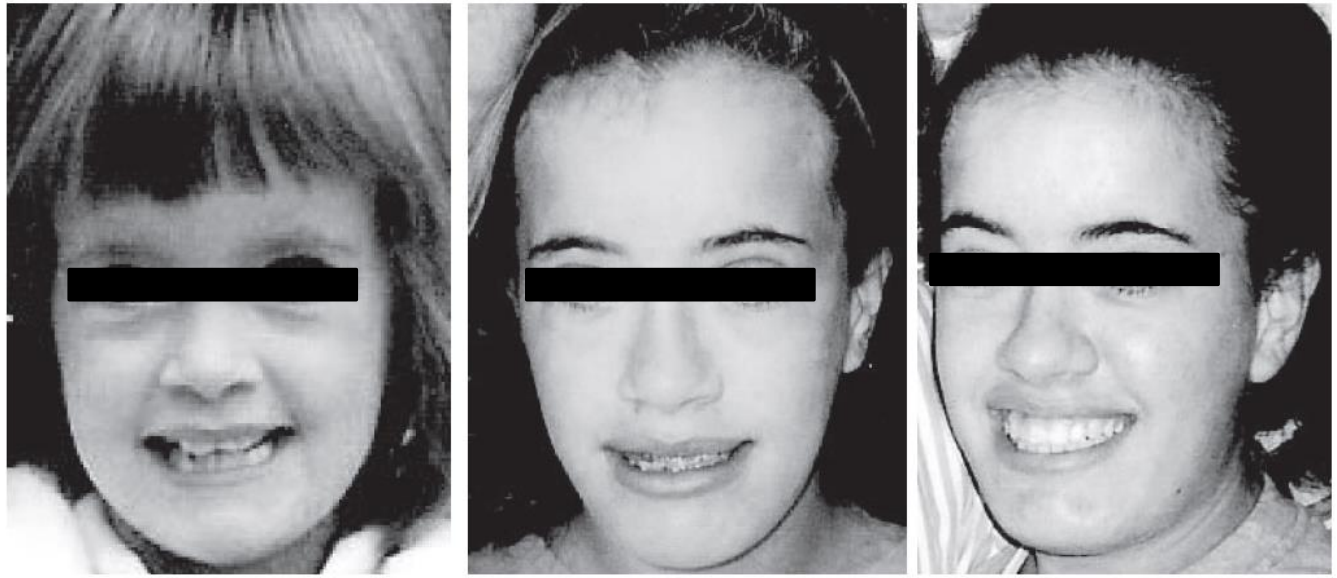
Number of subjects at each year is indicated

IGF-1, insulin-like growth factor 1; SD, standard deviation

Chernausek SD, et al. J Clin Endocrinol Metab. 2007;92:902-10

ADVERSE EVENT PROFILE

Adverse event	No. of subjects (%)
Related to IGF-1 metabolic effects	
Hypoglycaemia	37 (49)
Hypoglycaemic seizure	4 (5)
Related to lymphoid tissue growth	
Hypoacusis	17 (22)
Snoring	17 (22)
Tonsillar/adenoidal hypertrophy	17 (22)
Tympanostomy tube placement	12 (16)
Sleep apnoea	3 (4)
Tonsillectomy/adenoidectomy	8 (11)
Thymic hypertrophy	8 (35)
Other	
Injection site lipohypertrophy	24 (32)
Orthorpedic event (arthralgia, myalgia, and/or skeletal pain)	15 (20)
Intracranial hypertension	3 (4)
Nephrolithiasis	2 (3)



Age 4 yr, before IGF-1 | Age 10 yr, 6 yr Rx | Age 15 yr, 1 yr after Rx

IGF-1, insulin-like growth factor 1; Rx, prescription

Chernausek SD, et al. J Clin Endocrinol Metab. 2007;92:902-10

EU INCRELEX GROWTH FORUM DATABASE INSIGHTS

BASELINE CHARACTERISTICS OF ALL ENROLLED PATIENTS AND SUBGROUPS OF THE REGISTRY POPULATION: TREATMENT-NAÏVE/PREPUBERTAL PATIENTS AND PREVIOUSLY TREATED/PUBERTAL PATIENTS

Characteristic	All enrolled patients (N=195)			Treatment-naïve/prepubertal patients (N=110)			Previously treated/pubertal patients (N=82)		
	N	Mean ± SD [95% CI]	Median (25th, 75th percentile)	N	Mean ± SD [95% CI]	Median (25th, 75th percentile)	N	Mean ± SD [95% CI]	Median (25th, 75th percentile)
Female, n	195	67 (34.4%) [28.1; 41.3]	N/A	110	44 (40.0%) [31.3; 49.3]		82	23 (28.0%) [19.5; 38.6]	N/A
Age at first injection, years	195	10.1 ± 4.0 [9.5; 10.7]	10.6 (6.8, 13.2)	110	8.5 ± 3.5 [7.8; 9.2]	8.3 (5.8, 11.2)	82	12.0 ± 3.6 [11.2; 12.8]	12.4 (10.2, 14.5)
Height, cm	183	116.5 ± 20.0 [113.6; 119.4]	118.5 (100.6, 133.5)	105	110.2 ± 19.3 [106.5; 113.9]	110.1 (96.0, 125.5)	75	124.2 ± 17.8 [120.1; 128.2]	126.6 (112.0, 137.1)
Height SDS	183	−3.5 ± 1.3 [−3.7; −3.3]	−3.2 (−4.4, −2.6)	105	−3.4 ± 1.3 [−3.6; −3.1]	−3.0 (−3.9, −2.5)	75	−3.8 ± 1.3 [−4.1; −3.4]	−3.3 (−4.6, −2.7)
GH test: stimulated, ng/mL	133	27.8 ± 38.7 [21.1; 34.4]	16.8 (11.3, 29.0)	78	24.4 ± 25.0 [18.7; 30.0]	15.6 (11.0, 26.1)	52	32.9 ± 53.6 [18.0; 47.8]	18.1 (11.4, 39.0)
Height velocity, cm/year	109	4.8 ± 1.7 [4.5; 5.1]	4.7 (3.9, 5.6)	57	5.0 ± 1.9 [4.5; 5.5]	5.1 (4.0, 6.2)	51	4.6 ± 1.5 [4.2; 5.0]	4.4 (3.8, 5.4)
Primary diagnosis: SPIGFD, n	195	165 (84.6%) [78.9; 89.0]	N/A	110	99 (90.0%) [83.0; 94.3]	N/A	82	63 (76.8%) [66.6; 84.6]	N/A
Prior growth-promoting therapy, n	195	65 (33.3%)[a] [27.1; 40.2]	N/A		N/A	N/A		N/A	N/A

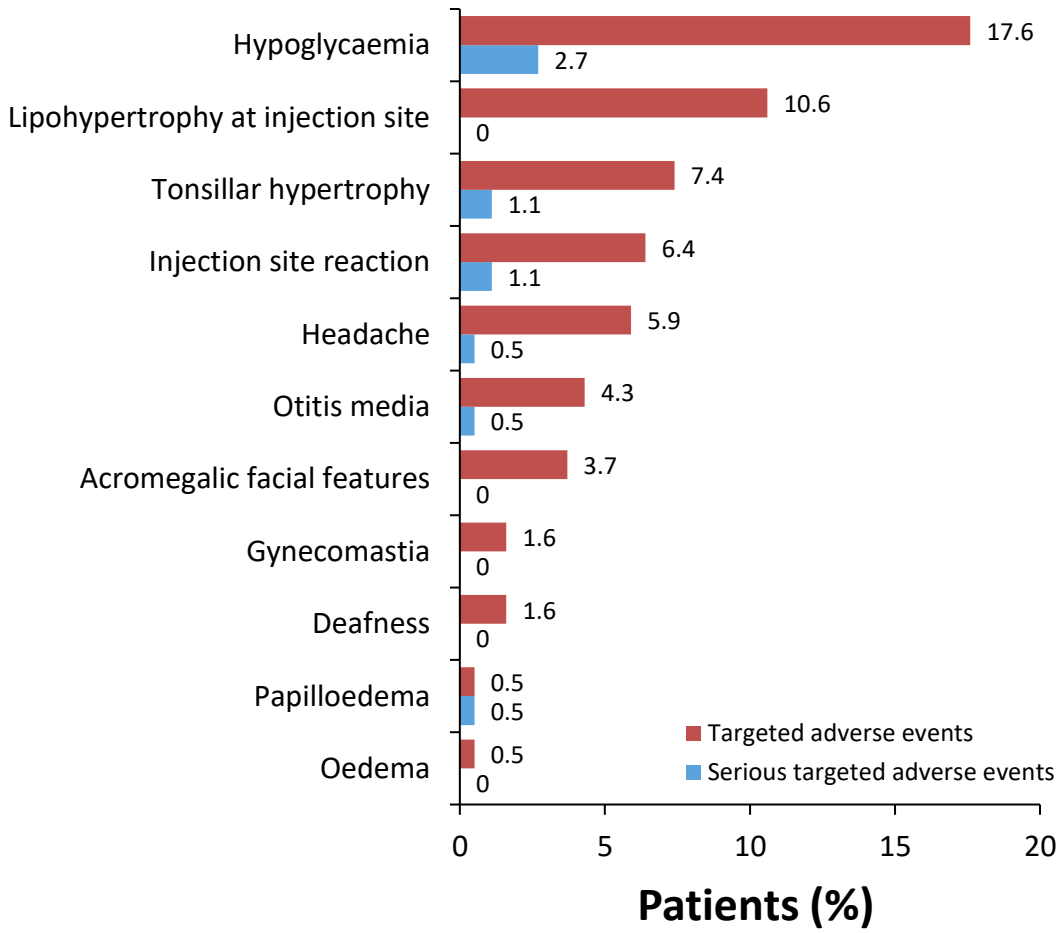
[a] rhGH in 52 (80.0%) and rhIGF-1 in 21 (32.3%)

CI, confidence interval; GH, growth hormone; rhGH, recombinant human GH; rhIGF-1, recombinant human insulin-like growth factor 1; SD, standard deviation; SDS, standard deviation score; SPIGFD, severe insulin-like growth factor 1 deficiency

Table adapted from Bang P, et al. Horm Res Paediatr. 2015;83:345-57

EU INCRELEX GROWTH FORUM DATABASE TAKE-HOME POINTS

- Mean 1st year height velocity 6.9 cm/yr
  - Prepubertal naïve patients 7.3 cm/yr[1]
- Predictors of increased height SDS were[1]:
  - Younger age at rhIGF-1 initiation
  - Female sex
  - Lower baseline height SDS
- Not all patients actually met the SPIGFD[1] diagnostic criteria
- No new safety signals[1]
- Height SDS improvement in 1st year was better in patients with Laron Syndrome[2]



rhIGF-1, recombinant human insulin-like growth factor 1; SDS, standard deviation score; SPIGFD, severe insulin-like growth factor 1 deficiency

1. Bang P, et al. Horm Res Paediatr. 2015;83:345-57; 2. Bang P, et al. Eur J Endocrinol. 2021;184:267-276

SAFETY WARNING

MALIGNANT NEOPLASIA:

- There have been postmarketing reports of malignant neoplasia in pediatric patients who received treatment with INCRELEX
- The tumours were observed more frequently in patients who received INCRELEX at higher than recommended doses or at doses that produced serum IGF-1 levels above the normal reference ranges for age and sex
- Monitor all patients receiving INCRELEX carefully for development of neoplasms. If malignant neoplasia develops, discontinue INCRELEX treatment

Increlex (mecasermin) [prescribing information]. Ipsen Biopharmaceuticals Inc.; December 2019

CONCLUSIONS

- Severe primary IGF-1 deficiency is most commonly associated with mutations in the growth hormone receptor
- There is a spectrum of genetic variants that can present with IGF-1 deficiency
- Recombinant IGF-1 therapy can be effective when treating patients with SPIGFD but the results are not as robust as seen with growth hormone in patients with severe growth hormone deficiency
- Monitoring for hypoglycaemia and symptoms associated with tonsillar hypertrophy is important when initiating therapy with recombinant IGF-1
- Therapy is most efficacious when prescribed in patients who meet the approved indication

IGF-1, insulin-like growth factor 1; SPIGFD, severe insulin-like growth factor 1 deficiency

THERAPIES FOR MANAGEMENT OF SHORT STATURE IN PUBERTY: USE OF AROMATASE INHIBITORS

Nelly Mauras, MD

Chief, Division of Endocrinology, Diabetes & Metabolism
Nemours Children's Health System, Jacksonville, Florida
& Professor Of Pediatrics, Mayo College of Medicine

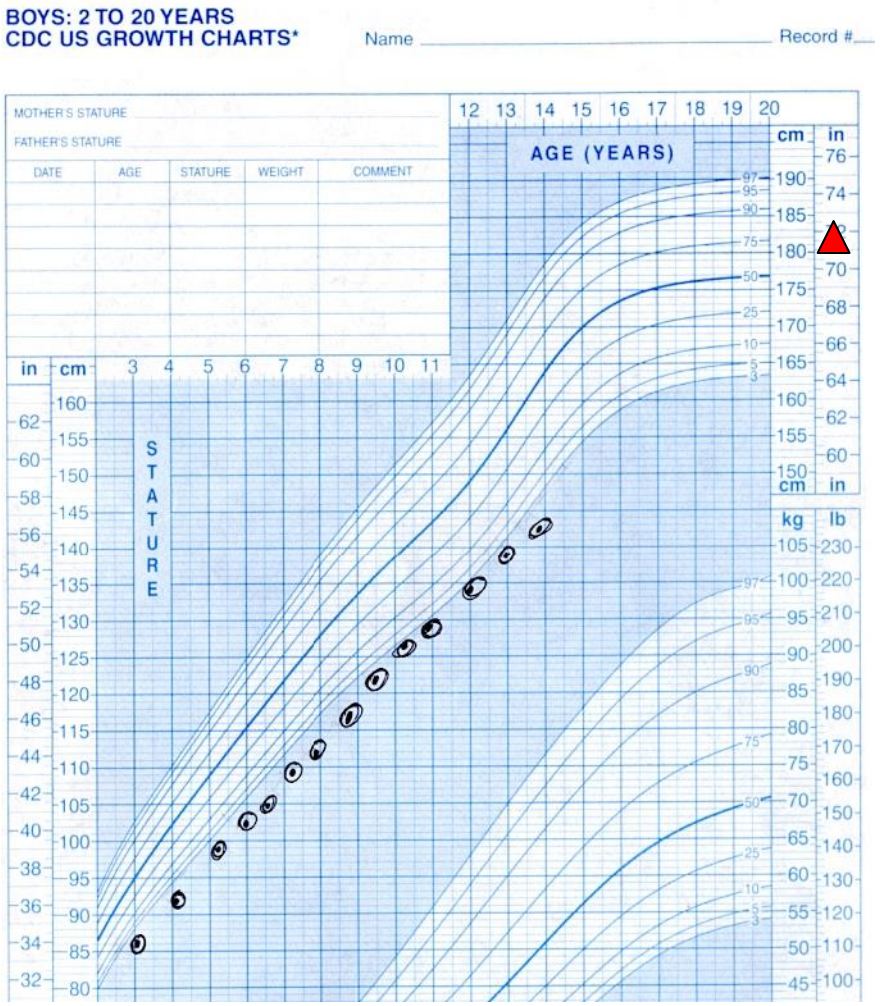
DISCLOSURE STATEMENT
NELLY MAURAS, MD

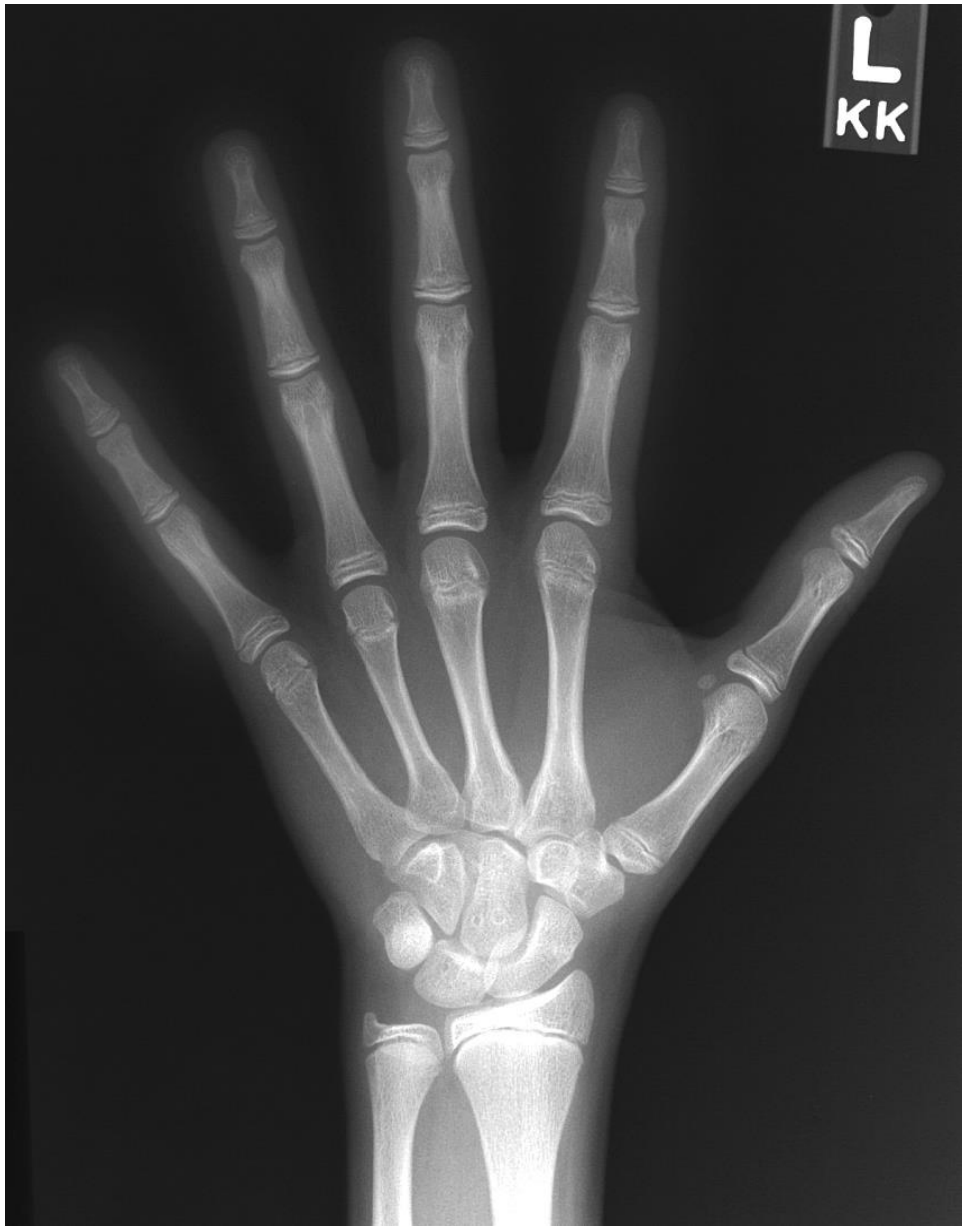
Research Support

Novo Nordisk

OPKO

Abbvie

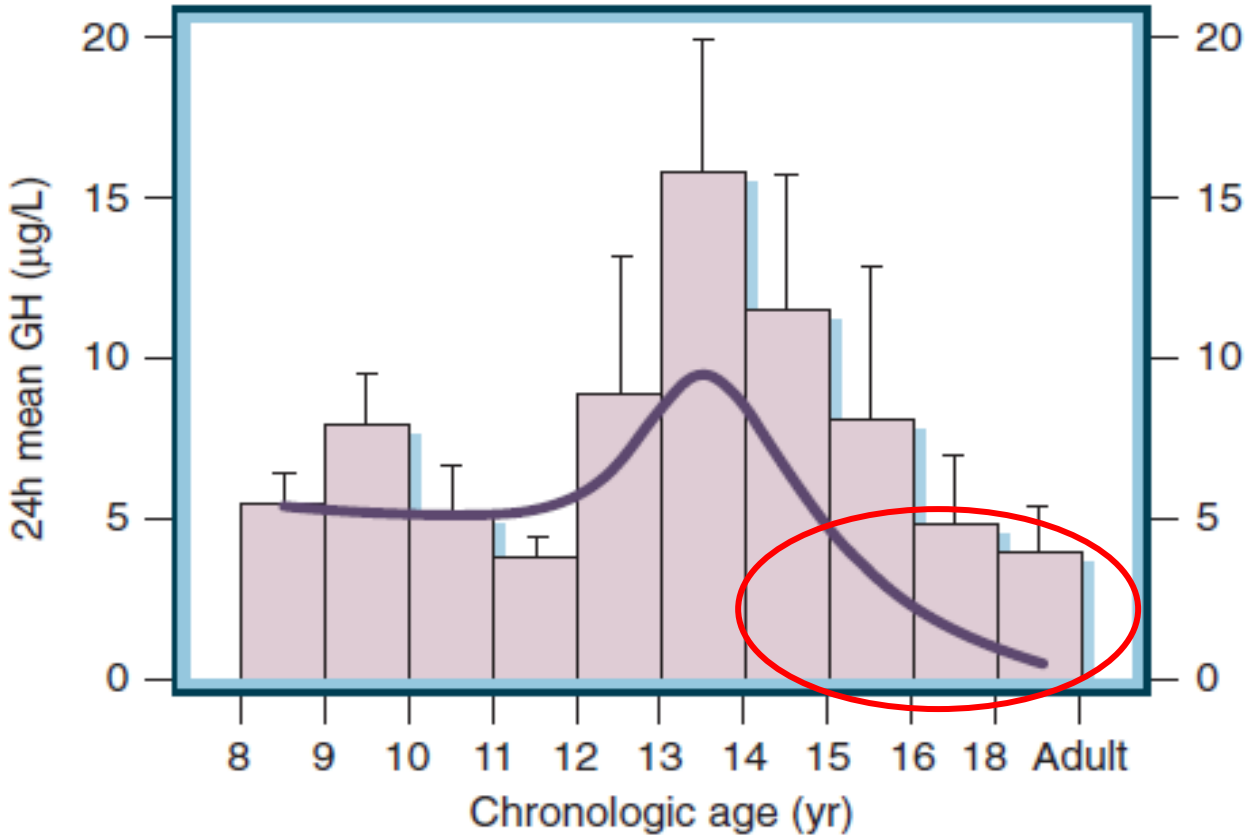




PE connect®
POWERED BY COR2ED

BACKGROUND

Starting treatment in children with significant short stature during puberty is limited by the tempo of epiphyseal fusion as impacted by sex steroids.

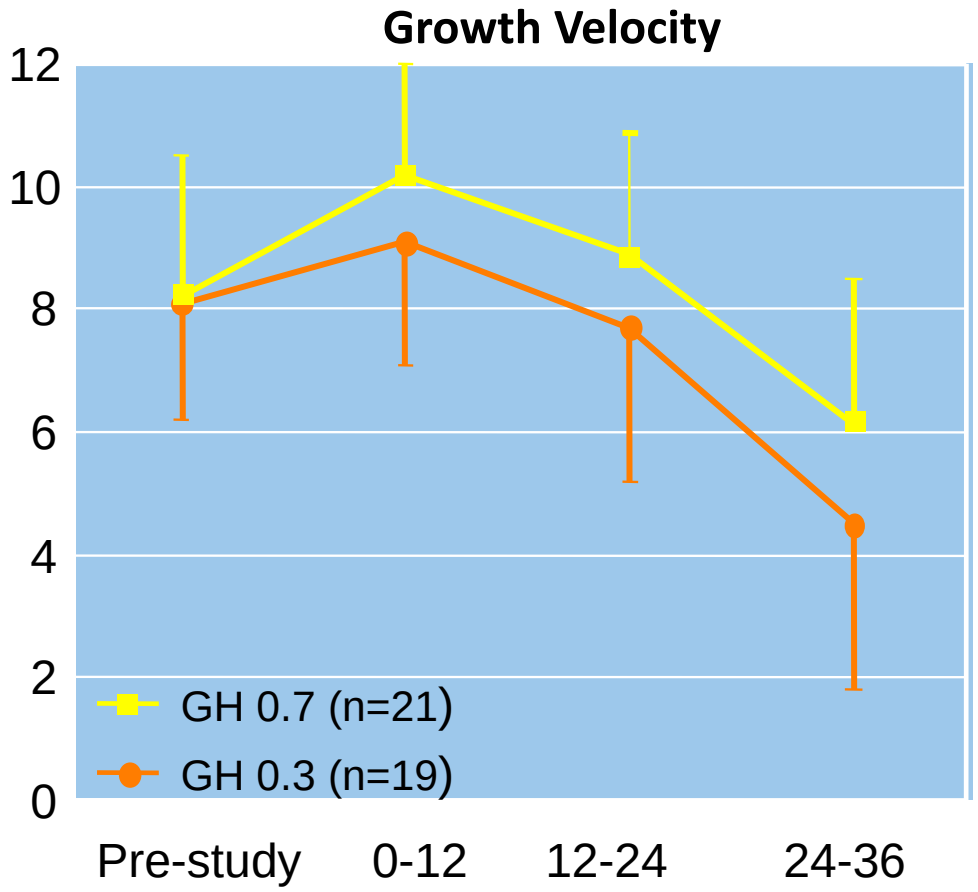


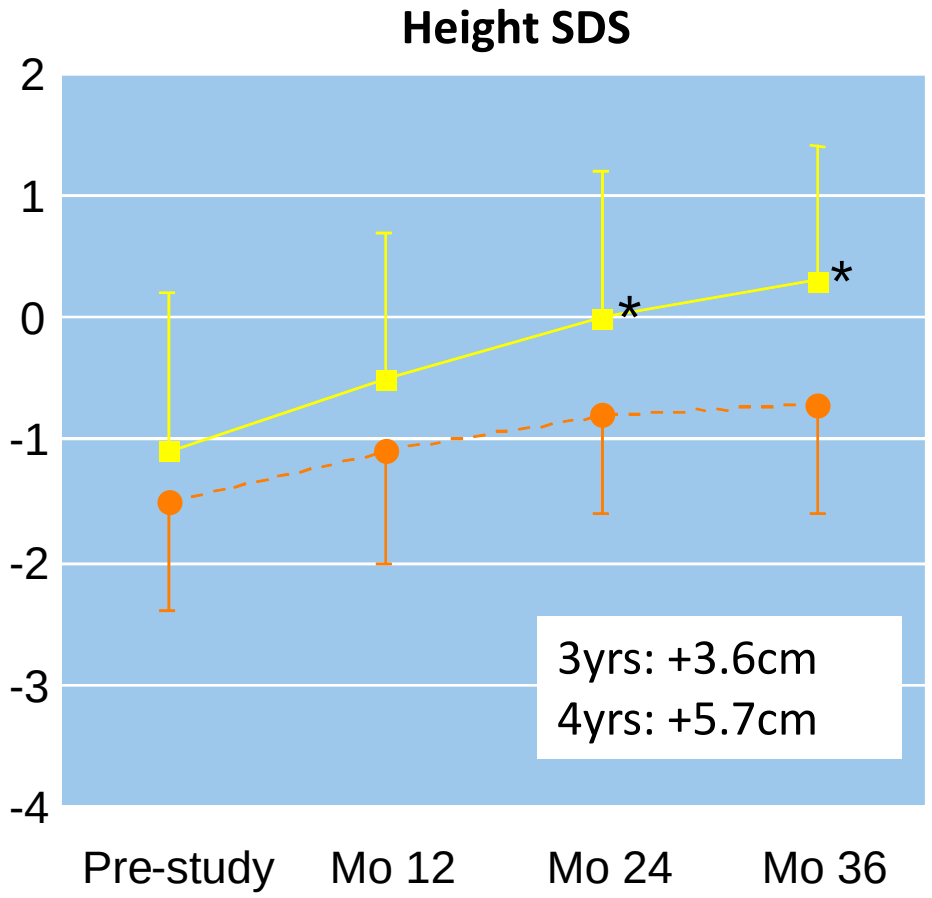
Martha P, JCEM 1989

High Dose Recombinant Human Growth Hormone (GH) Treatment of GH-Deficient Patients in Puberty Increases Near-Final Height: A Randomized, Multicenter Trial*

NELLY MAURAS, KENNETH M. ATTIE, EDWARD O. REITER, PAUL SAENGER, JOYCE BAPTISTA, AND THE GENENTECH, INC., COOPERATIVE STUDY GROUP†

JCE&M, 85; 2000





COMBINATION TREATMENT WITH GH AND GNRHA MAY RESULT IN 5-10CM OF HEIGHT GAIN

PE connect® POWERED BY COR2ED

Near Final Height in Pubertal Growth Hormone (GH)-Deficient Patients Treated with GH Alone or in Combination with Luteinizing Hormone-Releasing Hormone Analog: Results of a Prospective, Randomized Trial*

Mericq V, JCEM 2000

GHD

Adult Height in Short Children Born SGA Treated with Growth Hormone and Gonadotropin Releasing Hormone Analog: Results of a Randomized, Dose-Response GH Trial

Lem AJ, JCEM 2012

SGA

Effectiveness of the Combined Recombinant Human Growth Hormone and Gonadotropin-Releasing Hormone Analog Therapy in Pubertal Patients with Short Stature due to *SHOX* Deficiency

Scalco RC, JCEM 2010

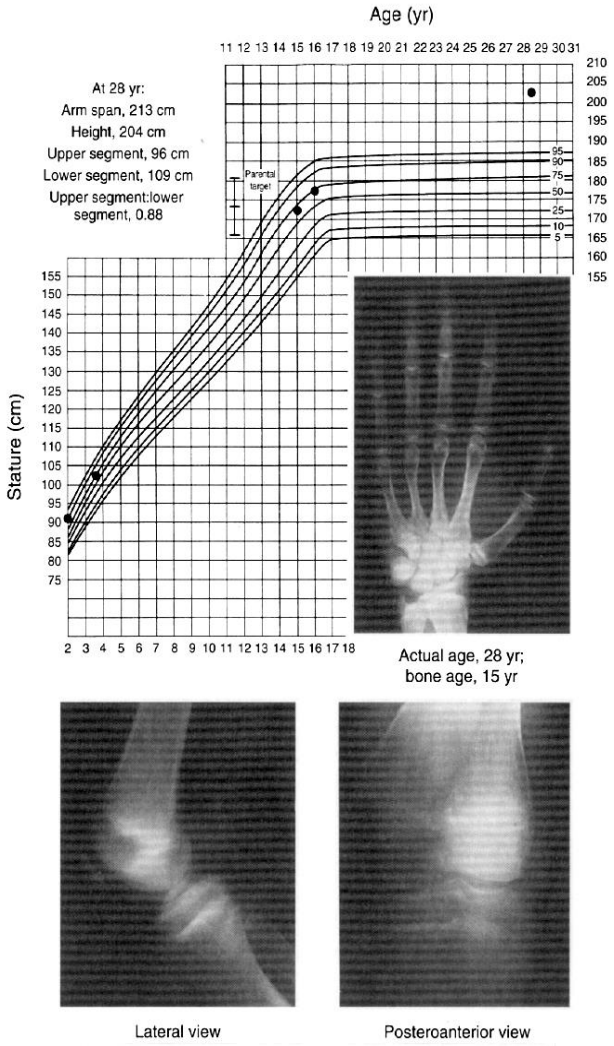
SHOX

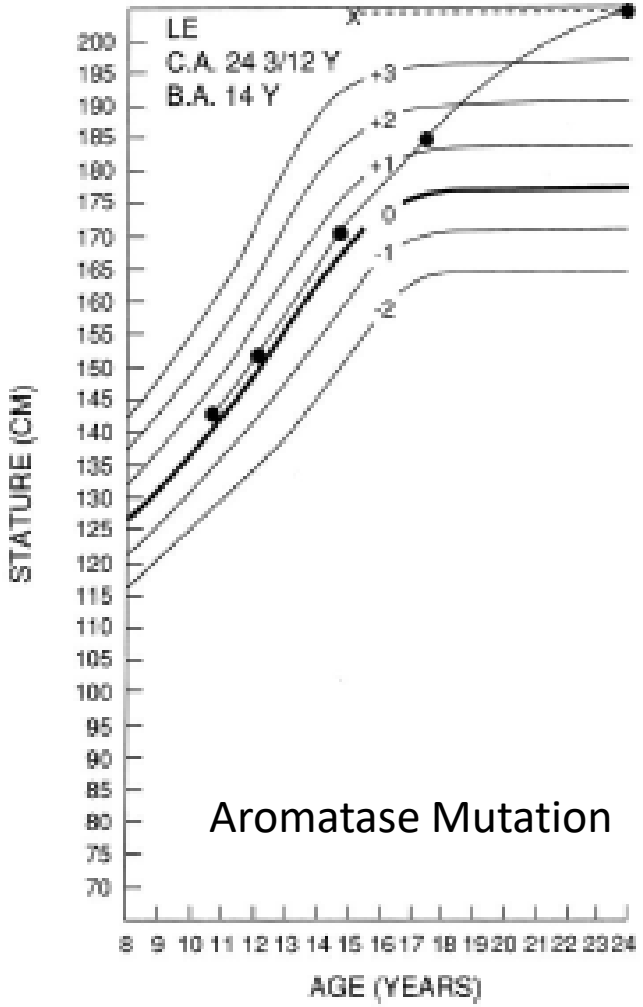
Effects of Combined Gonadotropin-Releasing Hormone Agonist and Growth Hormone Therapy on Adult Height in Precocious Puberty: A Further Contribution*

Pucarelli I, JPEM 2003

CPP

ESTROGEN RECEPTOR AND AROMATASE MUTATIONS IN MEN



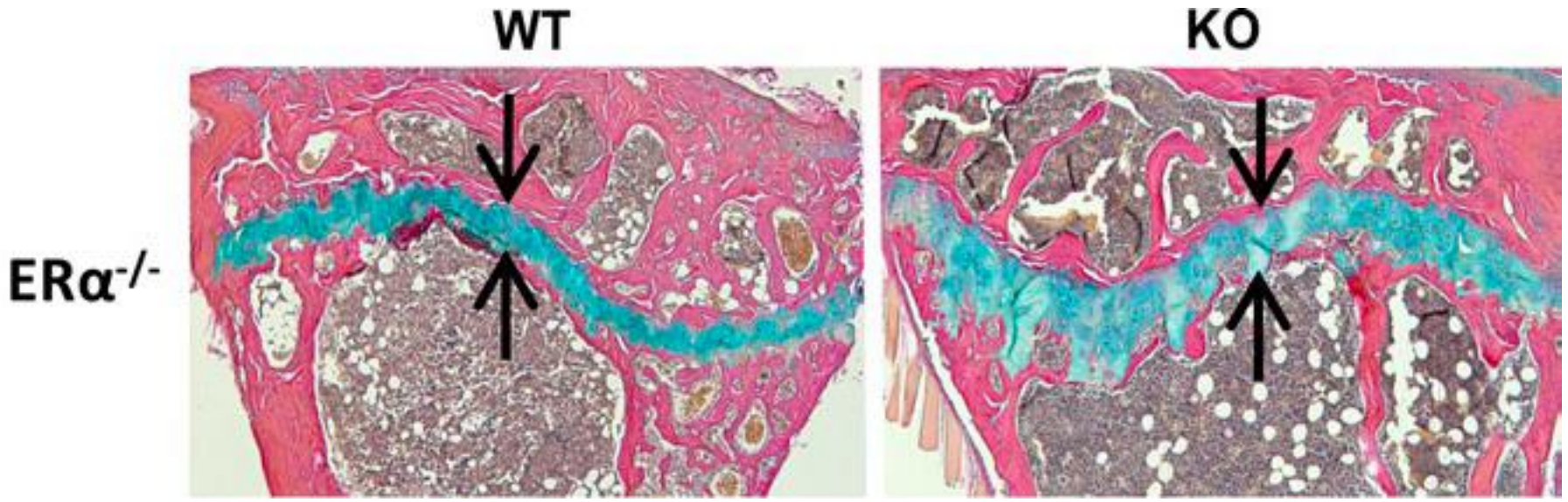


Smith, et al, NEJM, 331;1994
Morishima, et al, JCEM 80; 1995

The role of estrogen receptor α in the regulation of bone and growth plate cartilage

A. E. Börjesson · M. K. Lagerquist · S. H. Windahl · C. Ohlsson

Cell Mol Life Sci 2013

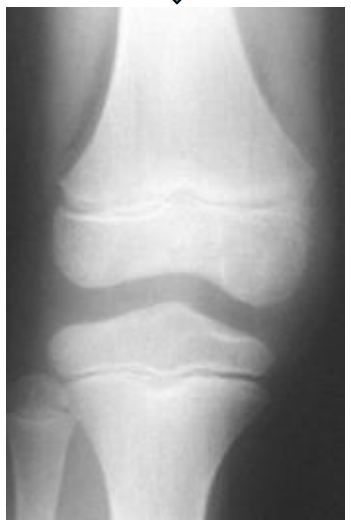


ERα is the main mediator of estrogenic effects on growth plate reduction in mice and growth plate closure in man

SEX STEROIDS DUAL EFFECTS ON GROWTH

Estrogen

GH (IGF-I)

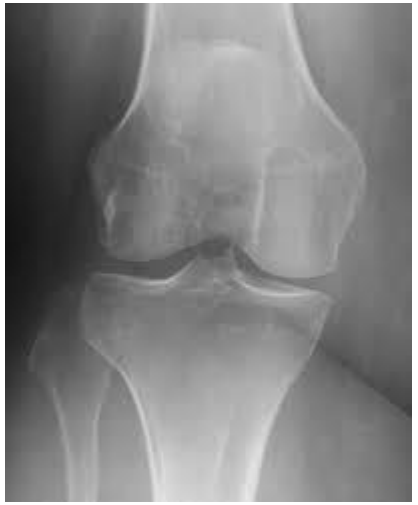


Linear Growth

progenitor cells in the resting zone chondrocytes

structural senescence

Nilssen O, et al. Endocrinol 2014

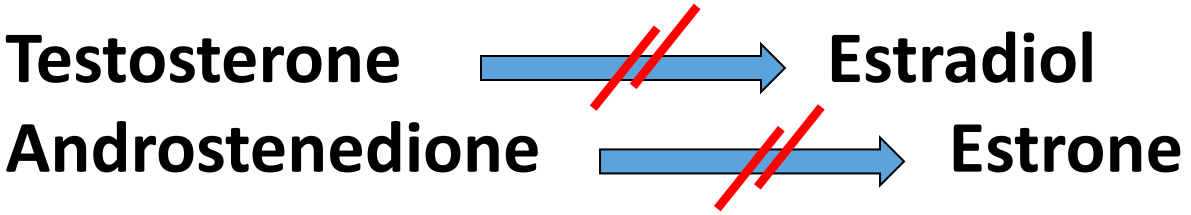


+ ERα

Linear Growth

AROMATASE P450 (ESTROGEN SYNTHETASE)

- **Product of the CYP19 gene which catalyzes the conversion of C19 androgenic steroids to estrogens**

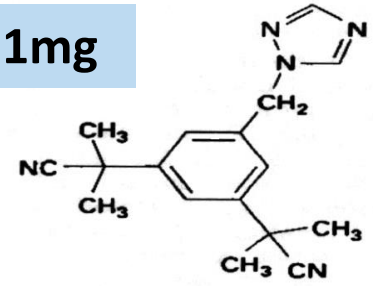


- **Expressed in a number of tissues including: ovary, adipose, liver, muscle, bone, syncytiotrophoblast, and breast tumors**

AROMATASE INHIBITORS

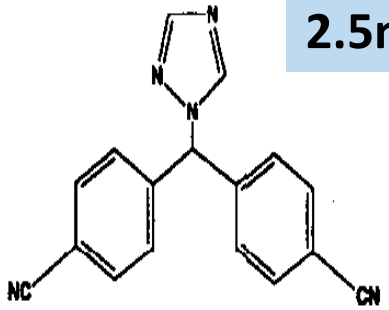
Anastrozole

1mg



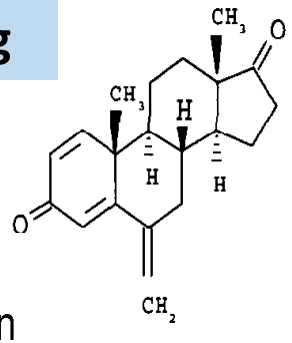
Letrozole

2.5mg



Exemestane

25mg



aromasin

PK, PD similar to women

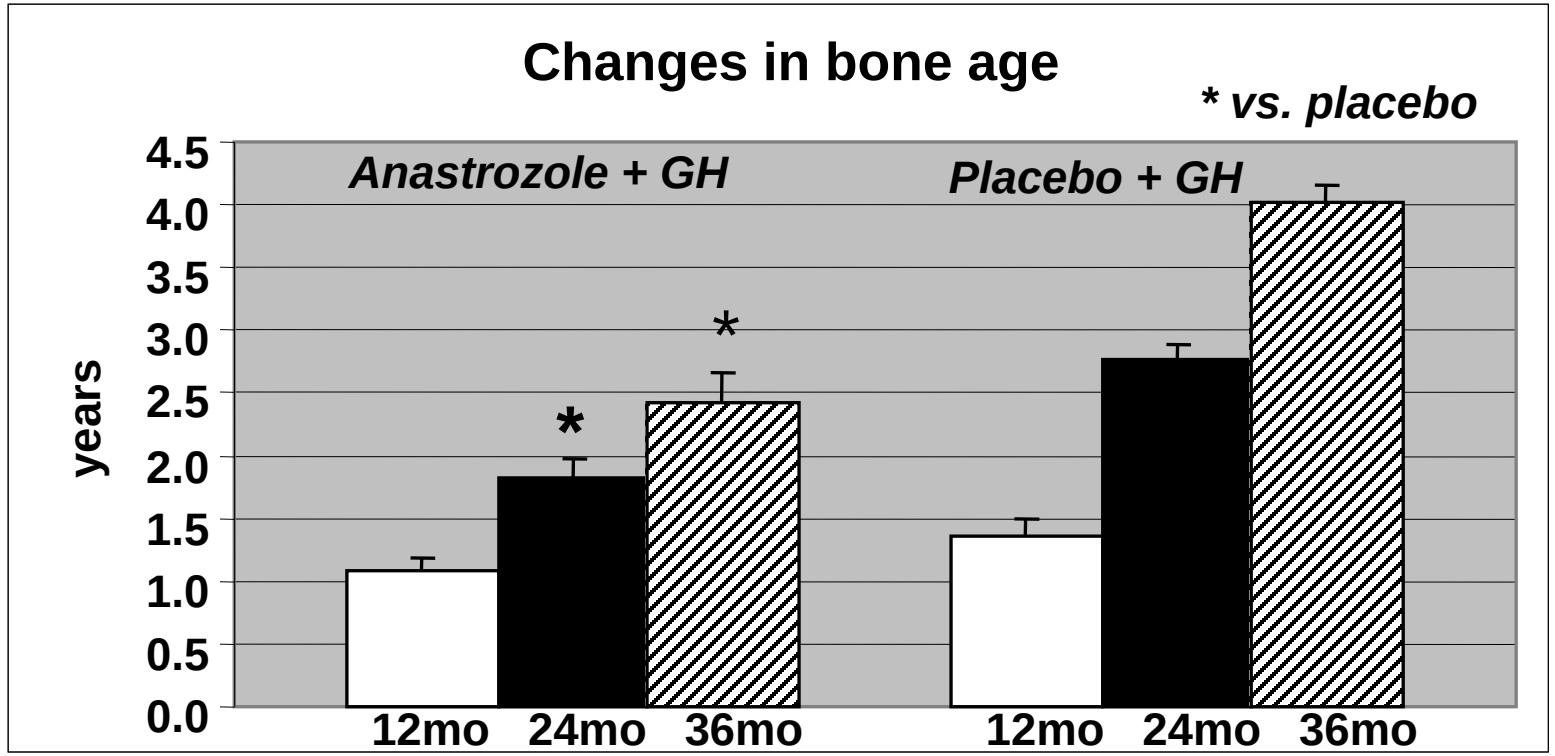
Mauras, et al JCEM 94; 2009
Mauras, et al JCEM 88; 2003

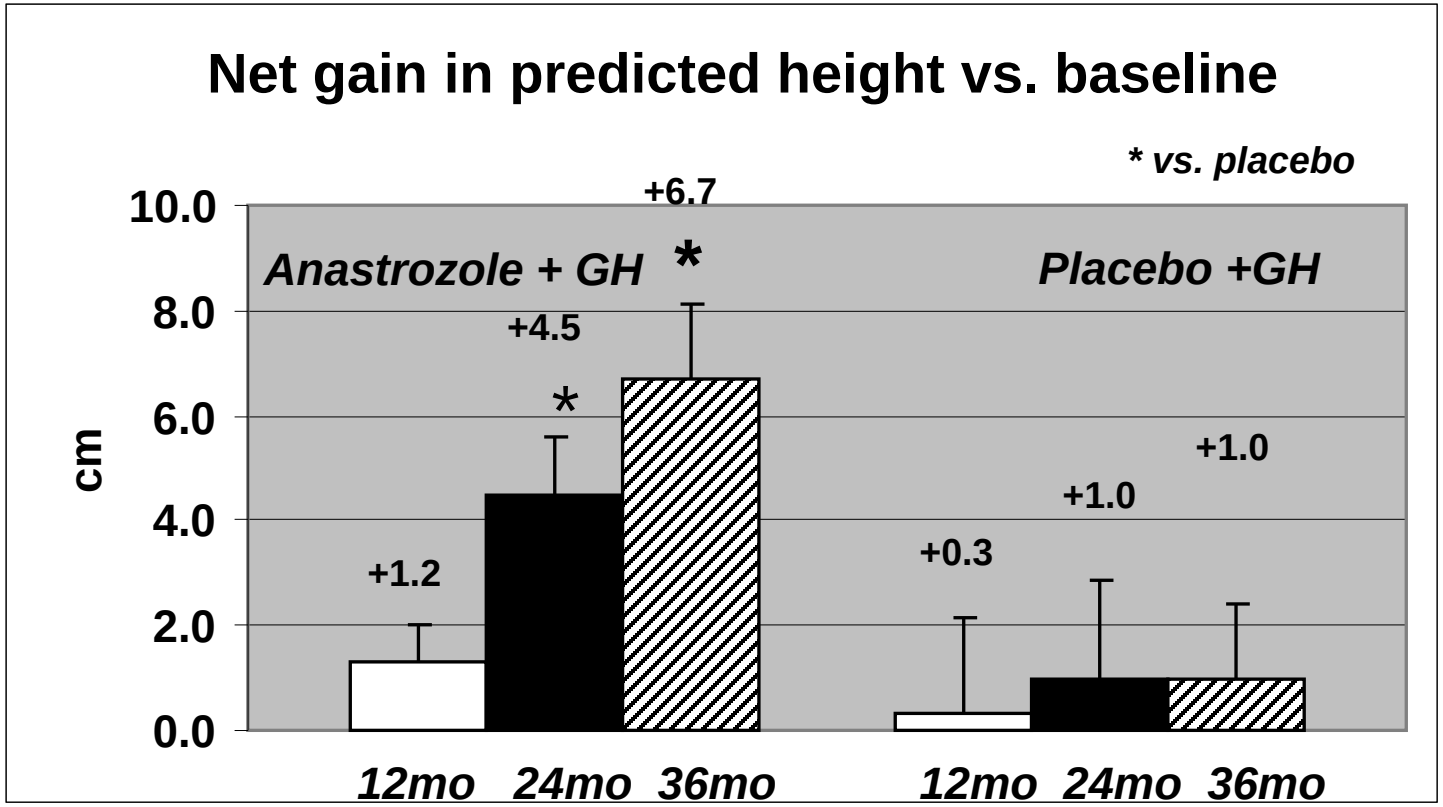
Anastrozole Increases Predicted Adult Height of Short Adolescent Males Treated with Growth Hormone: A Randomized, Placebo-Controlled, Multicenter Trial for One to Three Years

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM 2008

Nelly Mauras, Lilliam Gonzalez de Pijem, Helen Y. Hsiang, Paul Desrosiers, Robert Rapaport, I. David Schwartz, Karen Oerter Klein, Ravinder J. Singh, Anna Miyamoto, and Kim Bishop

- N=52 boys with GHD
- Age: 14.0 ± 0.2 yrs, all pubertal
- Rx 1.0mg/d of Anastrozole or PL x 3yrs or cessation of growth





Mauras, et al. JCEM 2008

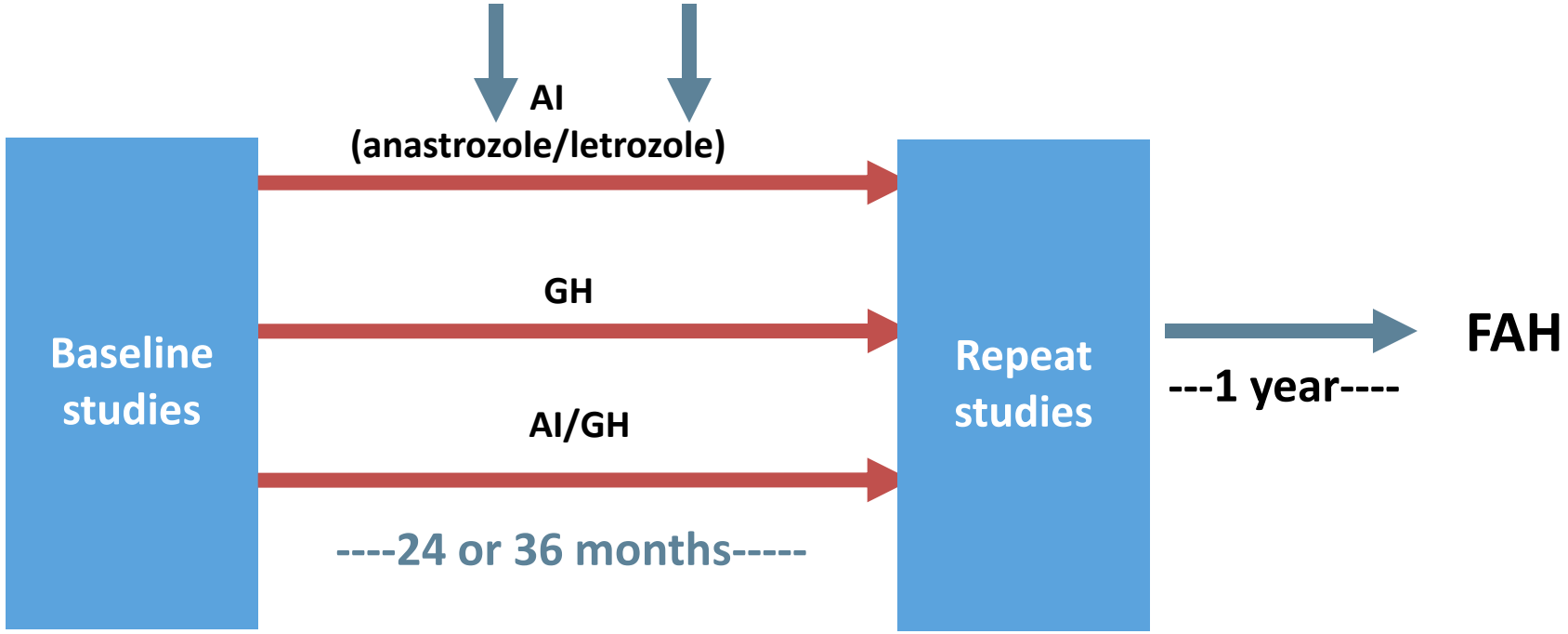
JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Randomized Trial of Aromatase Inhibitors, Growth Hormone, or Combination in Pubertal Boys with Idiopathic, Short Stature

Nelly Mauras, Judith L. Ross, Priscila Gagliardi, Y. Miles Yu, Jobayer Hossain, Joseph Permuy, Ligeia Damaso, Debbie Merinbaum, Ravinder J. Singh, Ximena Gaete, and Veronica Mericq

Dec 2016

PROTOCOL STUDY FLOW



***Anthropometry, BA, DEXA, Lateral spine, Hormones, Safety Labs, QoL**

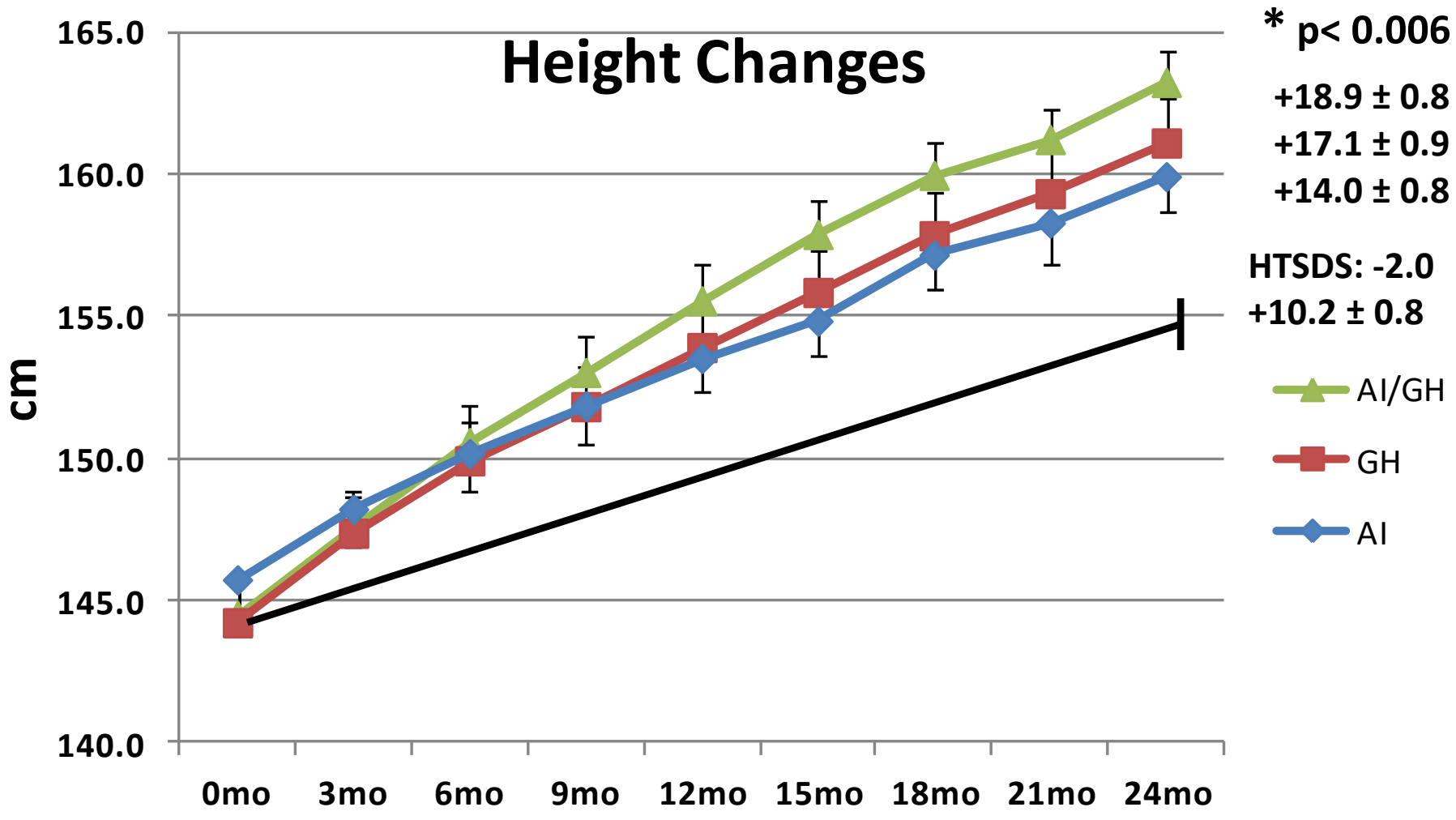
Mauras, et al. JCEM 2016

CLINICAL CHARACTERISTICS OF STUDY SUBJECTS

	Total	AI	GH	AI/GH
N	76	25	25	26
Age (yrs)	14.1 ± 0.1	14.2 ± 0.2	14.1 ± 0.2	14.0 ± 0.2
HT SDS	-2.3 ± 0.0	-2.2 ± 0.1	-2.4 ± 0.1	-2.3 ± 0.1
BA (yrs)	12.8 ± 0.2	12.7 ± 0.3	12.9 ± 0.3	12.7 ± 0.2
Testosterone (ng/dl) (nmol/L)	223 ± 22 (7.74 ± 0.76)	205 ± 37 (7.11 ± 1.28)	244 ± 39 (8.47 ± 1.35)	222 ± 37 (7.70 ± 1.28)

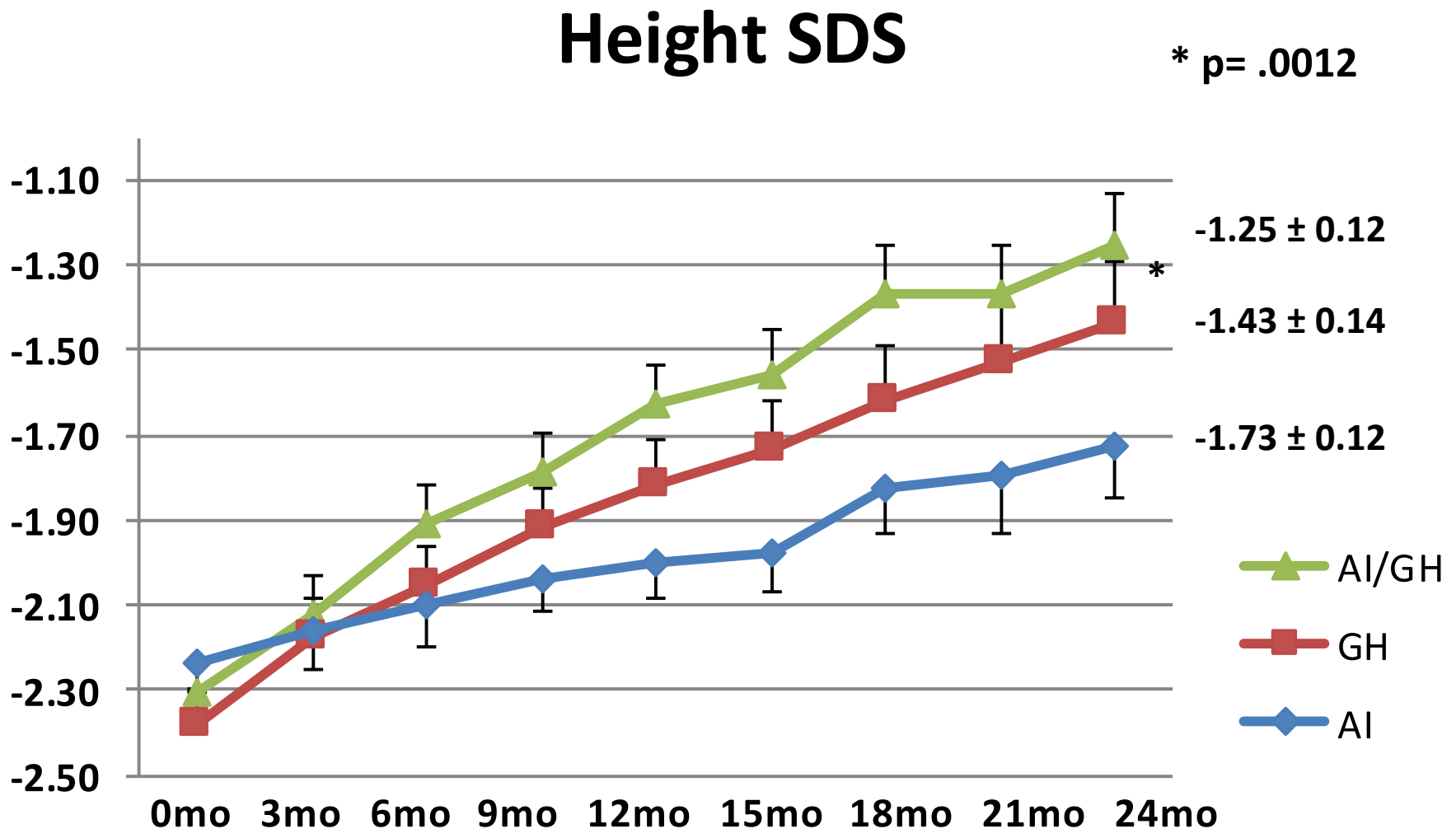
Mauras, et al. JCEM 2016

HEIGHT CHANGES



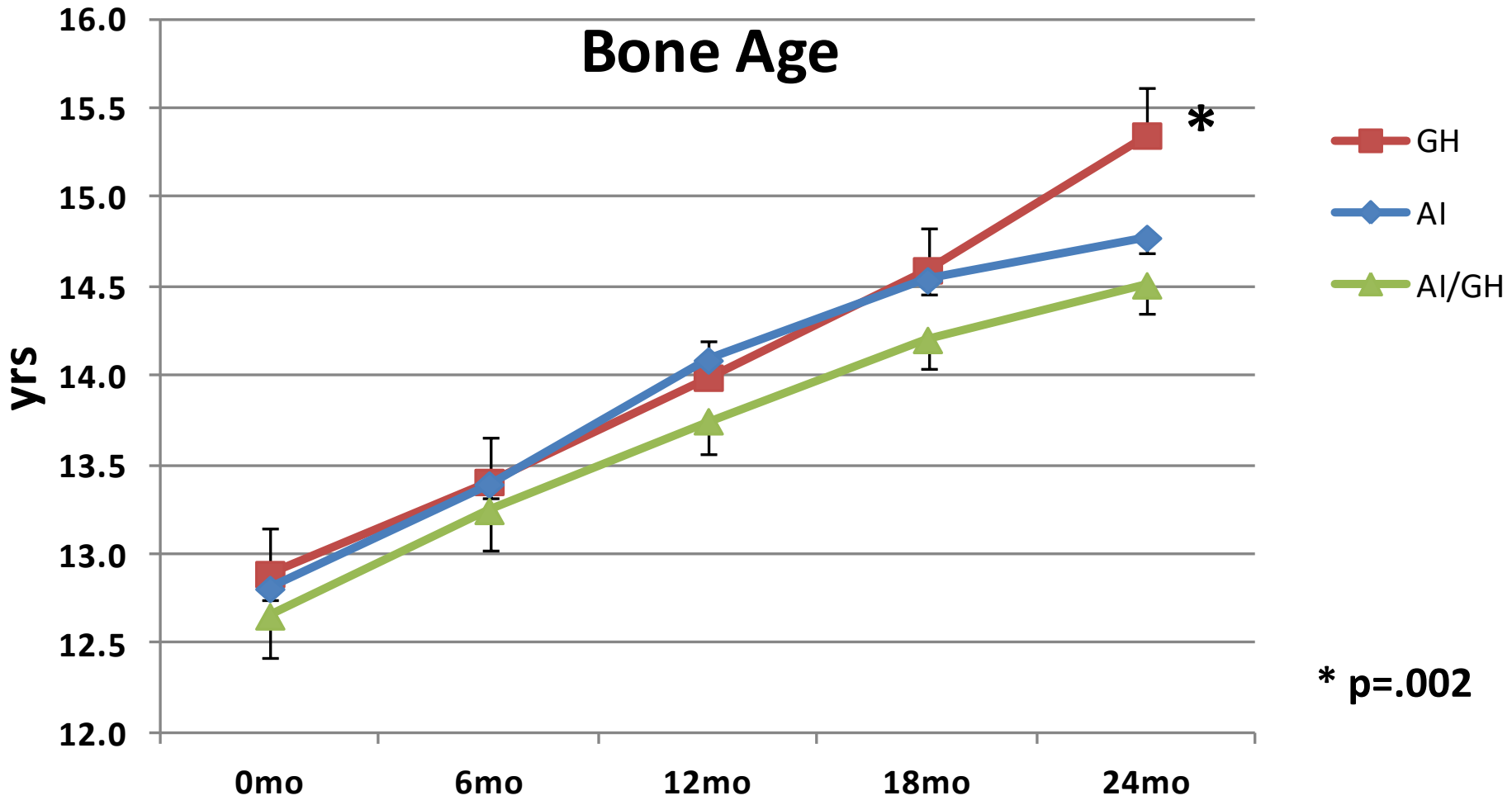
Mauras, et al. JCEM 2016

HEIGHT SDS



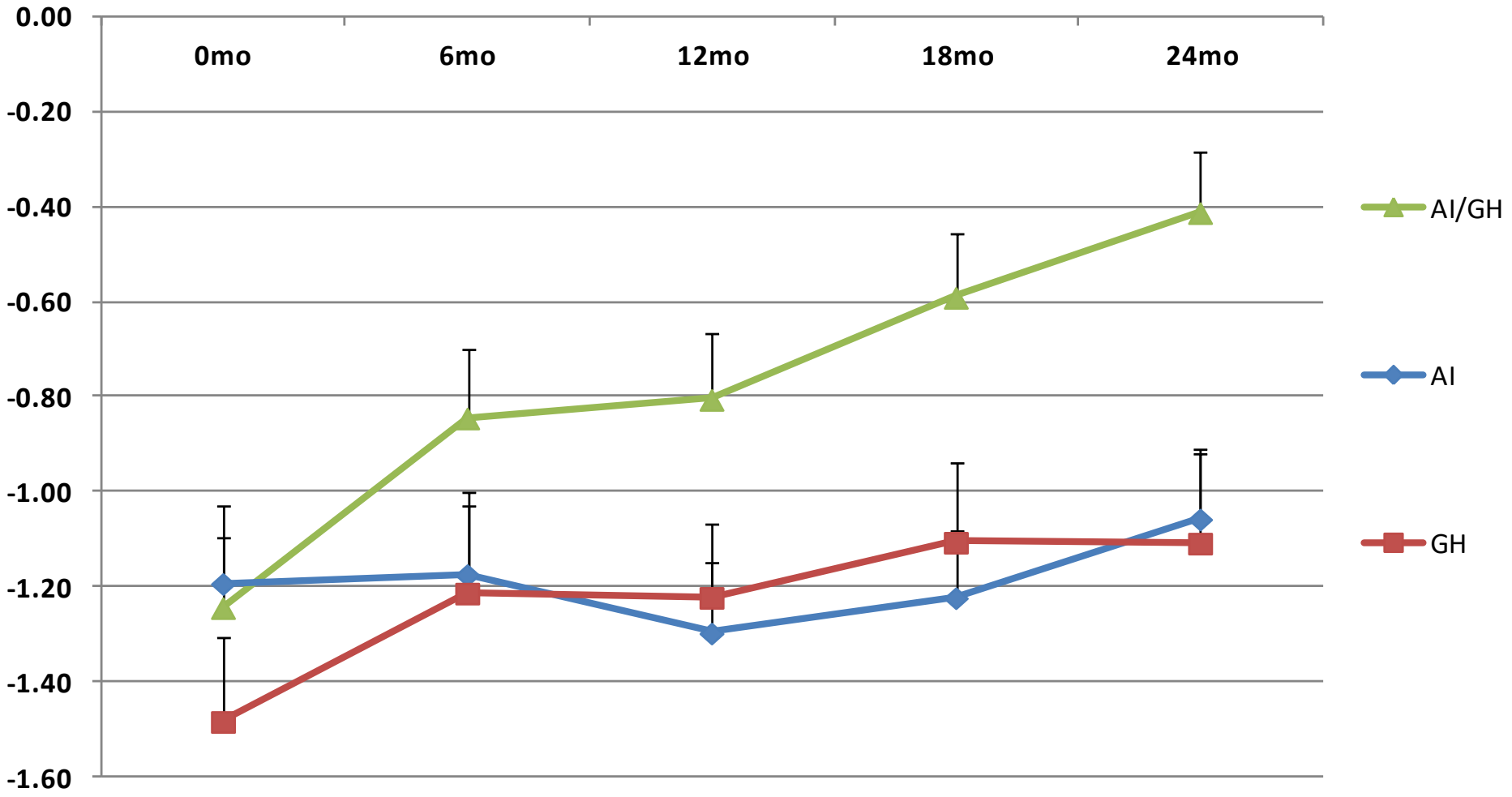
Mauras, et al. JCEM 2016

BONE AGE



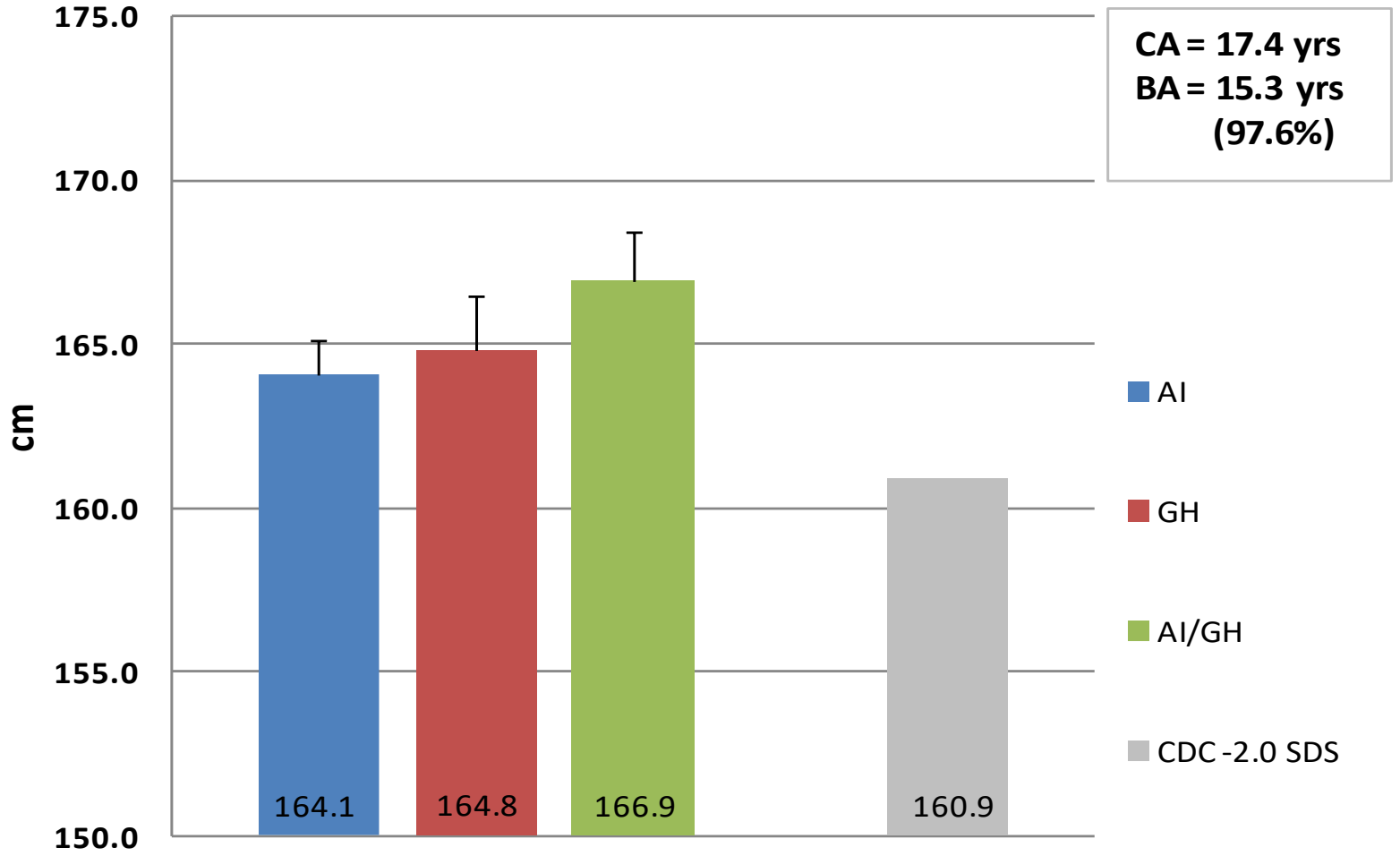
Mauras, et al. JCEM 2016

HTSDS FOR BONE AGE



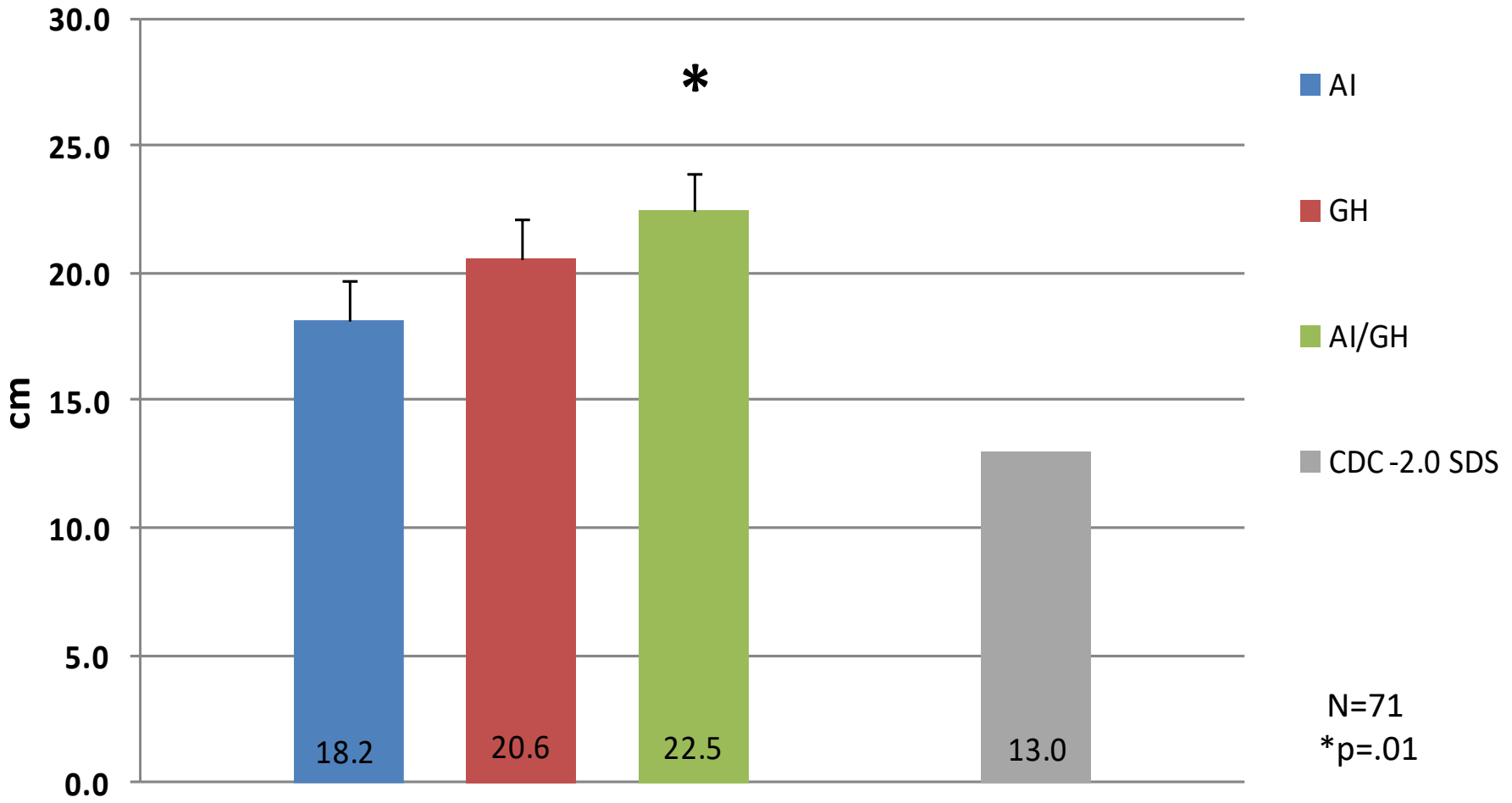
Mauras, et al. JCEM 2016

NEAR FINAL HEIGHT



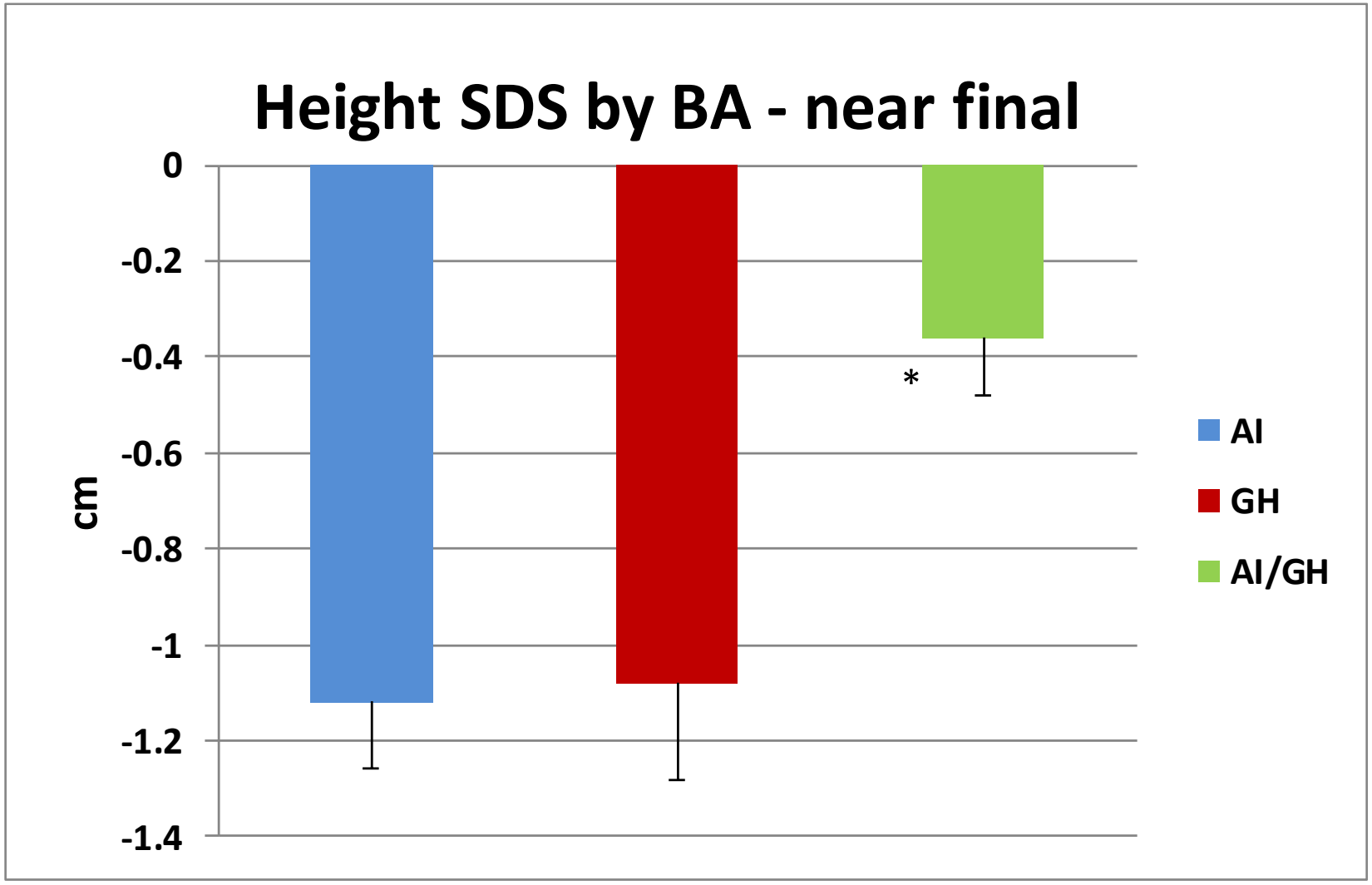
Mauras, et al. JCEM 2016

NET GAIN IN HEIGHT



Mauras, et al. JCEM 2016

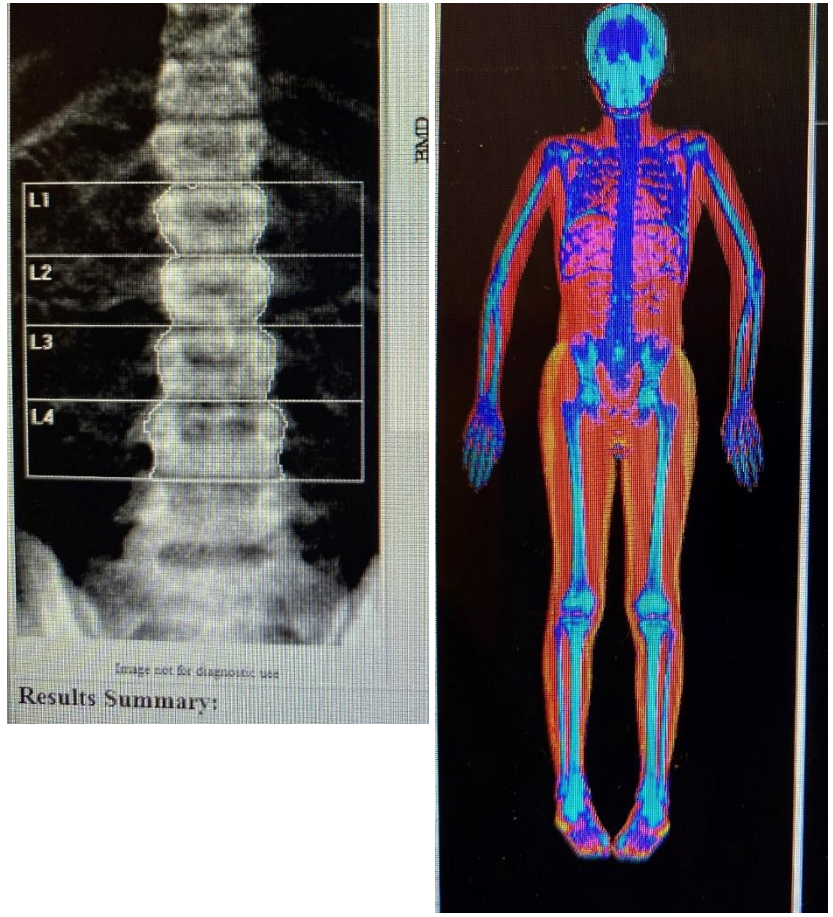
HEIGHT SDS BY BA – NEAR FINAL



Mauras, et al. JCEM 2016

BONE ASSESSMENTS

DEXA

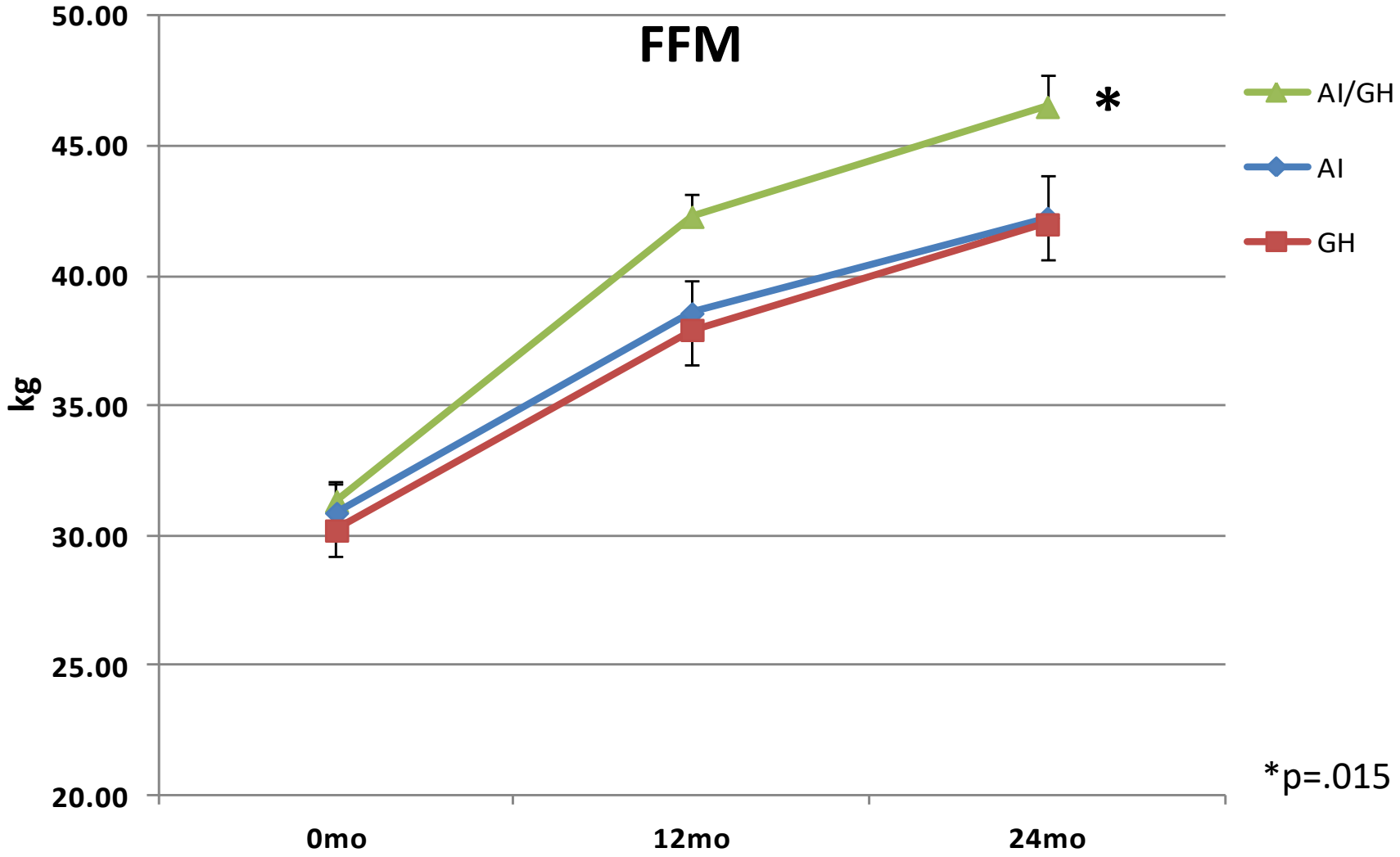


Vertebral Changes

- Space narrowing
- Compression
- Irregularity
- Wedging

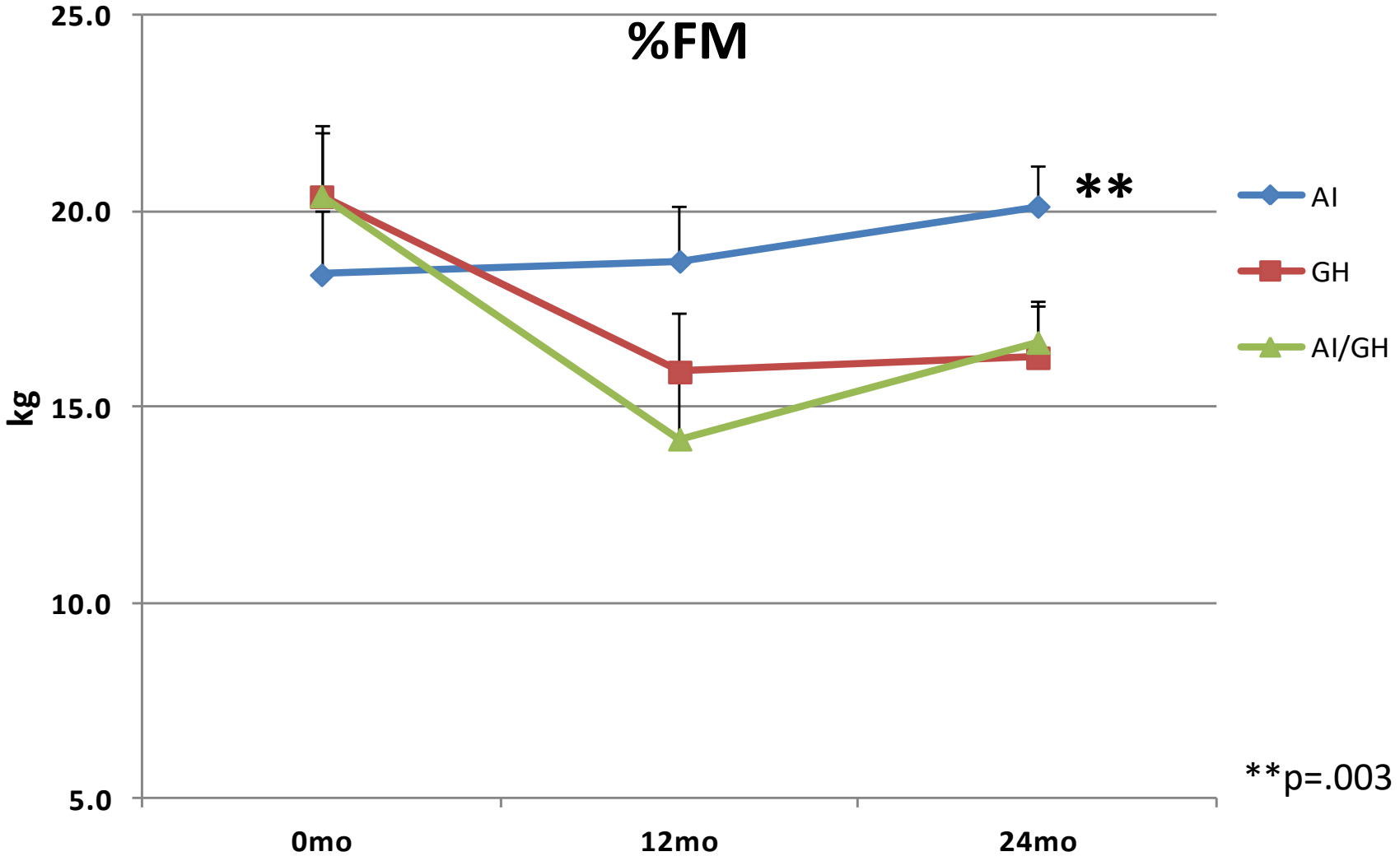
Bone Pain Questionnaires

FFM



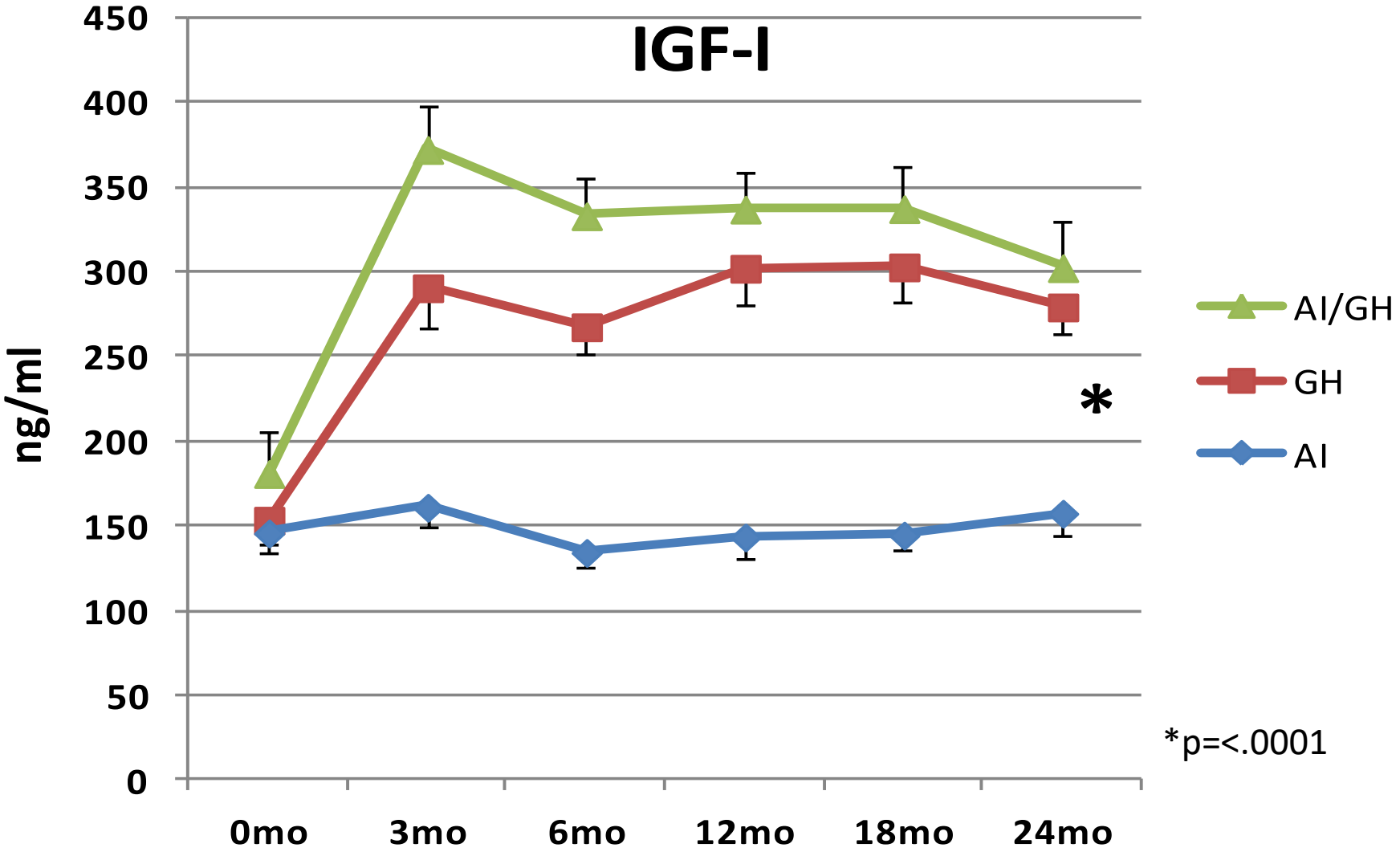
Mauras, et al. JCEM 2016

%FM



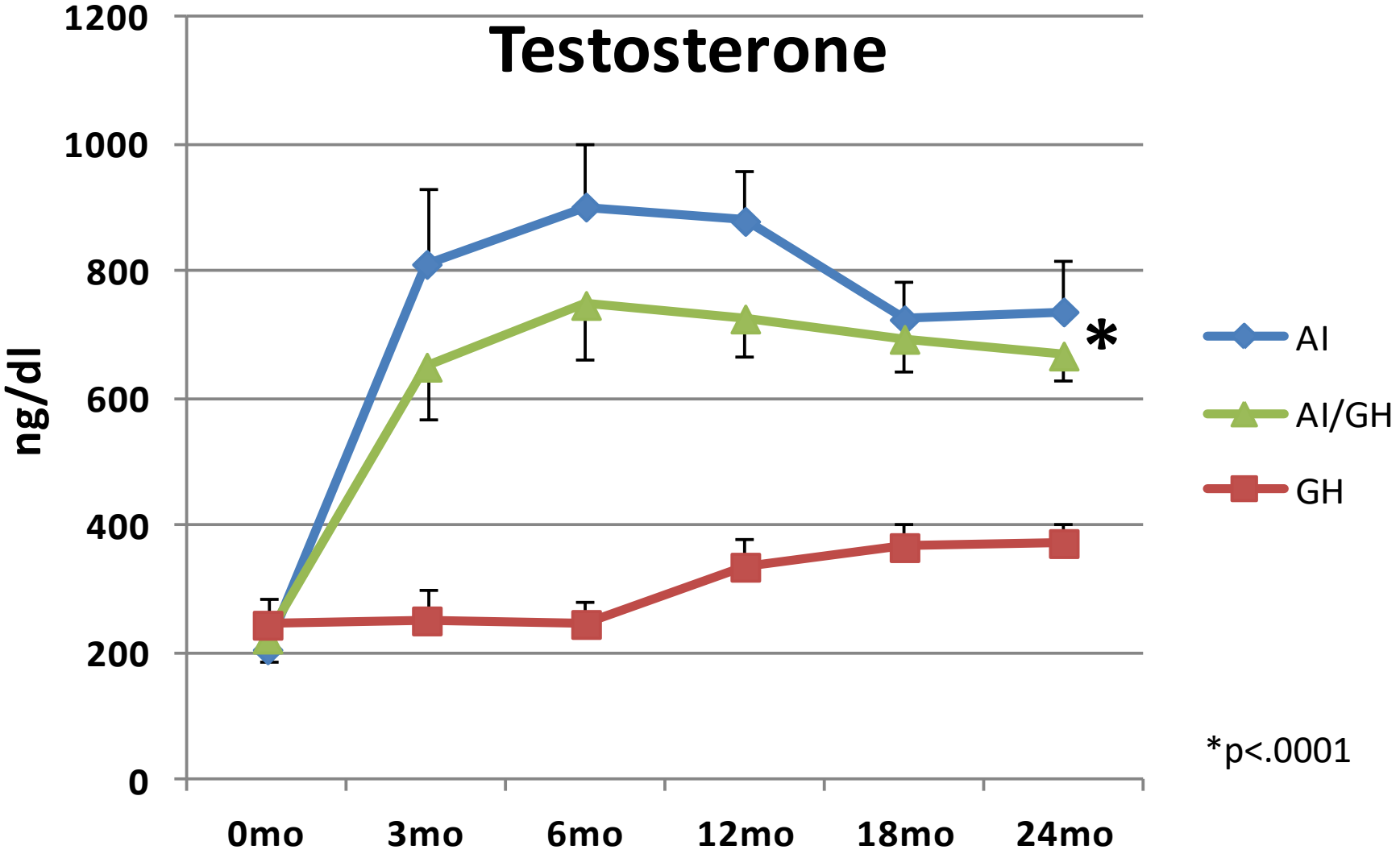
Mauras, et al. JCEM 2016

IGF-I



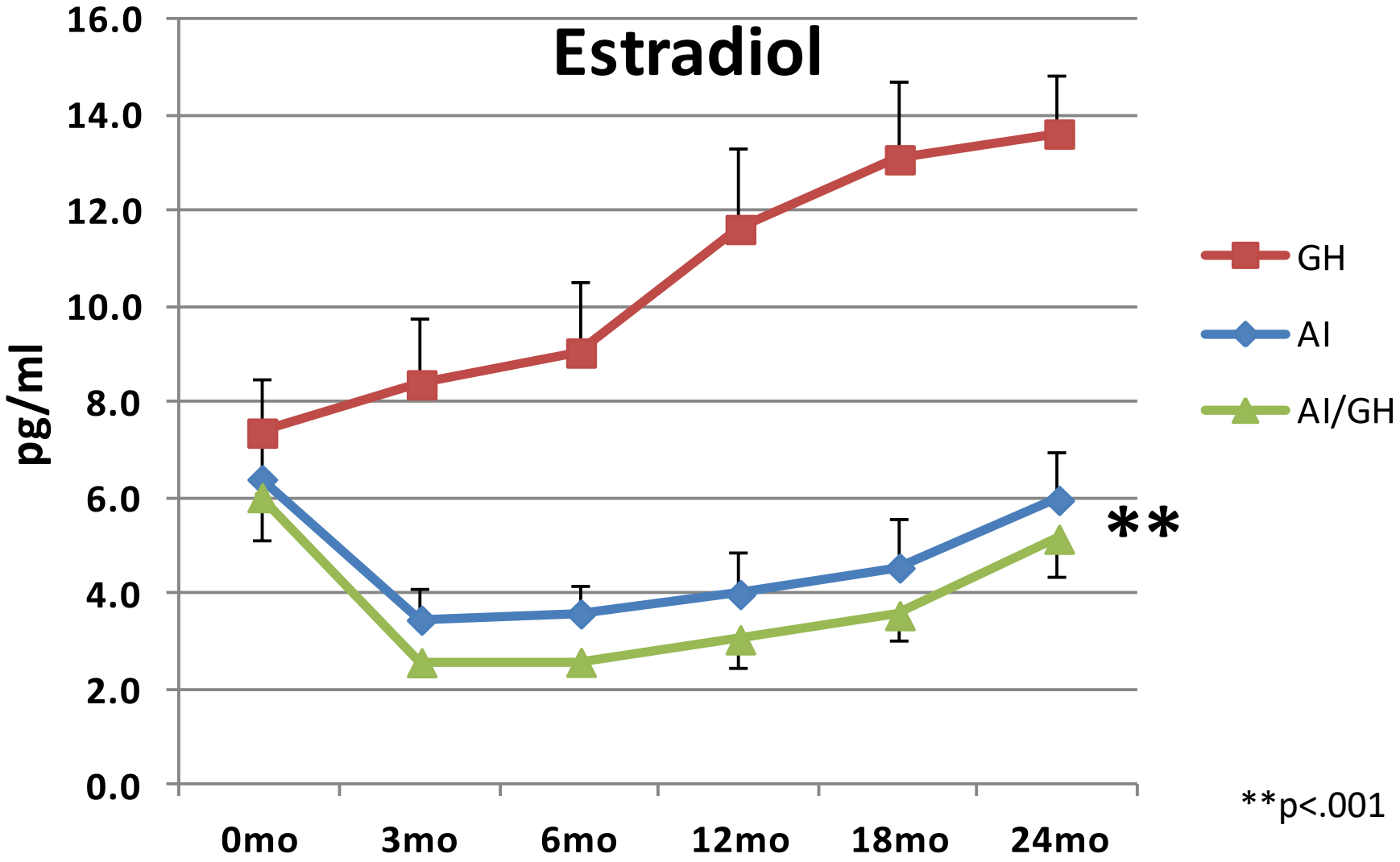
Mauras, et al. JCEM 2016

TESTOSTERONE



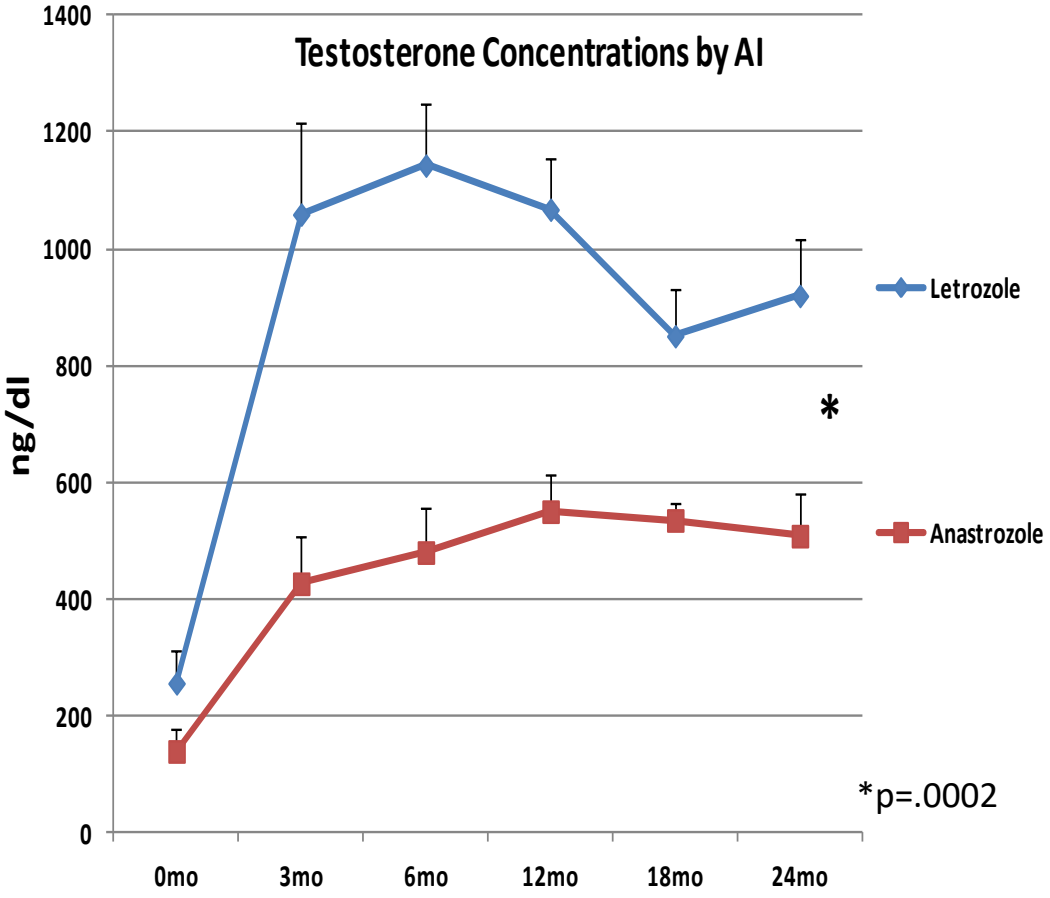
Mauras, et al. JCEM 2016

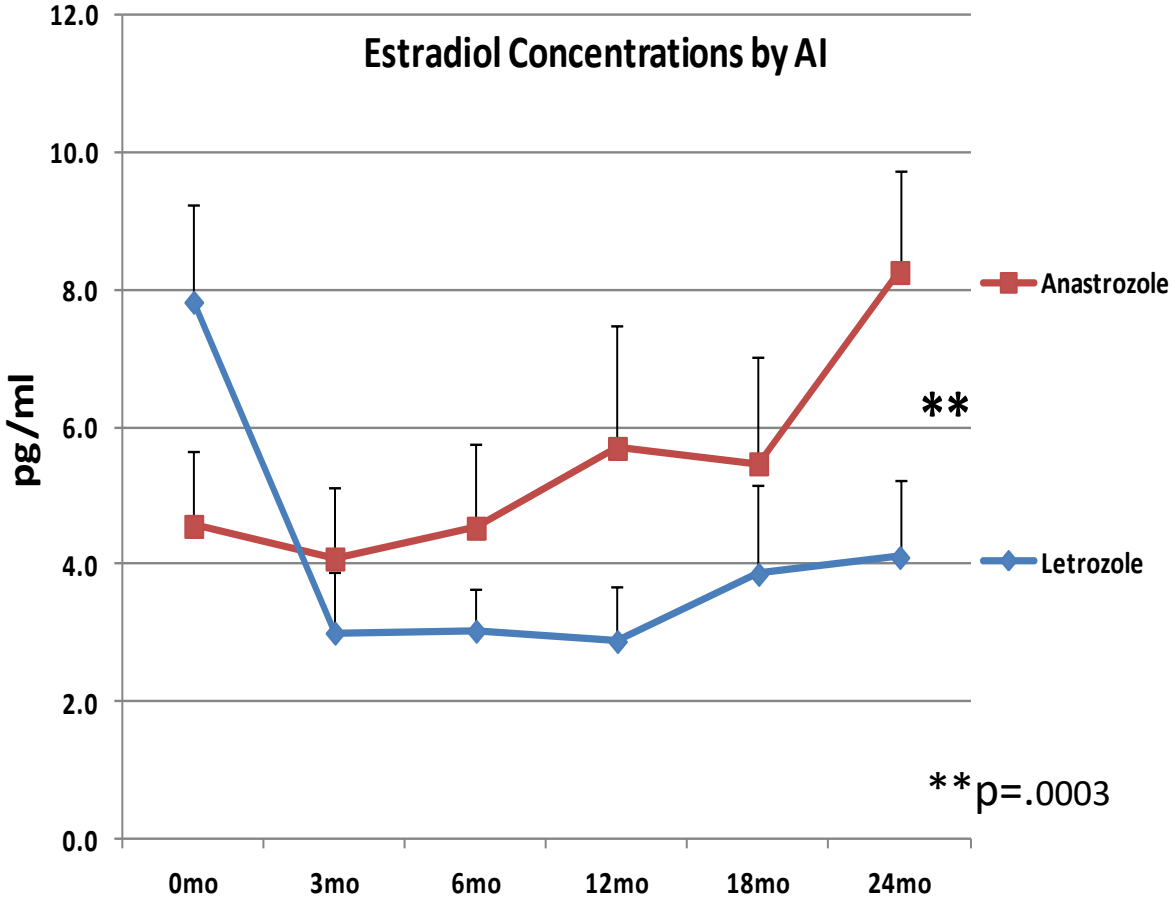
ESTRADIOL



Mauras, et al. JCEM 2016

TESTOSTERONE CONCENTRATIONS BY AI





Mauras, et al. JCEM 2016

SUMMARY OF ADVERSE EVENTS

Summary of Adverse Events				
	ALL	AI	GH	AI/GH
All events	382	118	114	150
Head & Neck	36	10	11	15
Respiratory	56	19	24	13
Skin	50	20	9	21
Lab	90	28	28	34
Neurological	28	9	7	12
Gastrointestinal	21	4	8	9
Musculoskeletal	79	22	18	39
Genitourinary	15	3	7	5
Cardiovascular	5	3	1	1
Psychological	2	0	1	1

8 SAE: 3 AI, 2 GH, 3 GH/AI, 1 possibly related (SCFE)

Mauras, et al. JCEM 2016

SUMMARY – IN GROWTH-RETARDED ADOLESCENTS WITH ISS

- **All 3 treatment modalities increased height at 24 months**
  AI/GH> GH >AI
  - +8.7cm
  - +6.9 cm
  - +3.8 cm above CDC reference data
- **Near final height gain (CA 17.3 yr, BA 15.3 yr)**
  AI/GH> GH >AI
  - +9.4 cm
  - +7.0 cm
  - +4.3 cm above CDC reference data

  Many of these subjects had residual height potential
- The combination of GH and AI was more anabolic enhancing FFM accrual than each compound alone
- Safety profile for all programs was very good

Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr
DOI: 10.1159/000496353
February 28, 2019

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Quality of Life in Adolescent Boys with Idiopathic Short Stature: Positive Impact of Growth Hormone and Aromatase Inhibitors

Monika Bullinger[a] Janika Bloemeke[a] Veronica Mericq[b] Rachel Sommer[a]
Xiemena Gaete[b] Judith L. Ross[c] Y. Miles Yu[d] Joseph Permuy[e]
Priscila Gagliardi[e] Y. Ligeia Damaso[e] Nelly Mauras[e]

QoL scores higher (better) than baseline

- GH and GH/AI groups – participants' report
- AI, GH, GH/AI groups – parental report

A randomized pilot trial of growth hormone with anastrozole versus growth hormone alone, starting at the very end of puberty in adolescents with idiopathic short stature

Anya Rothenbuhler, Agnès Linglart and Pierre Bougnères*

Int J Pediatr Endo 2015

N=24 randomized to GH/AI vs. GH

N=17 historical controls

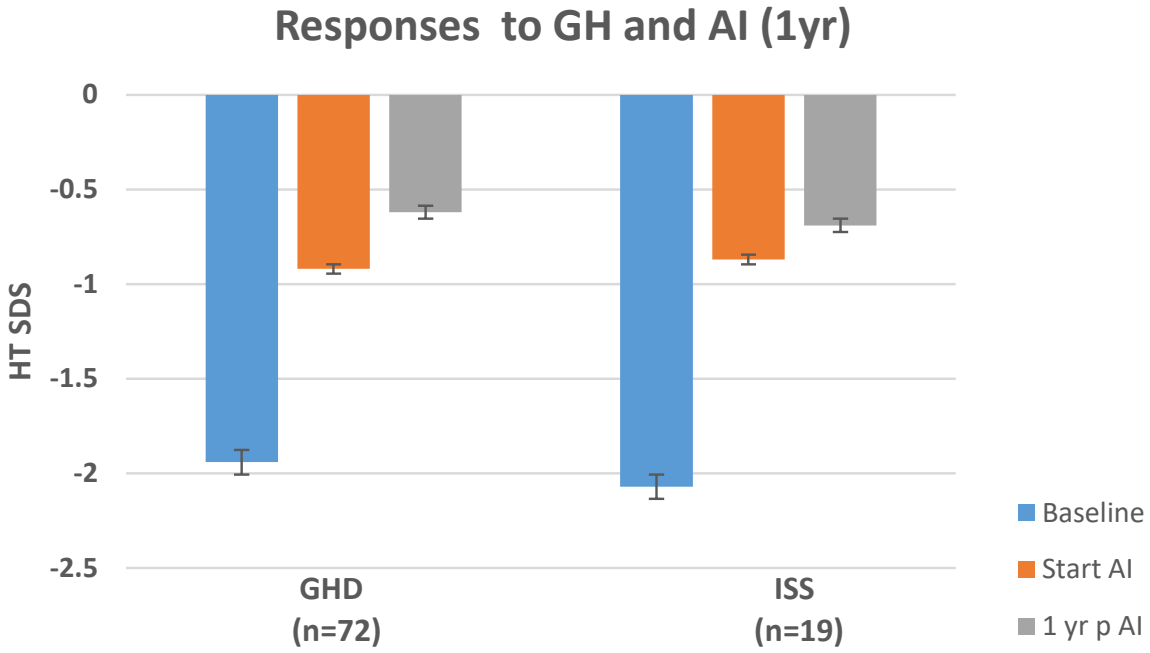
Age: 15.2 ± 1.2 yrs

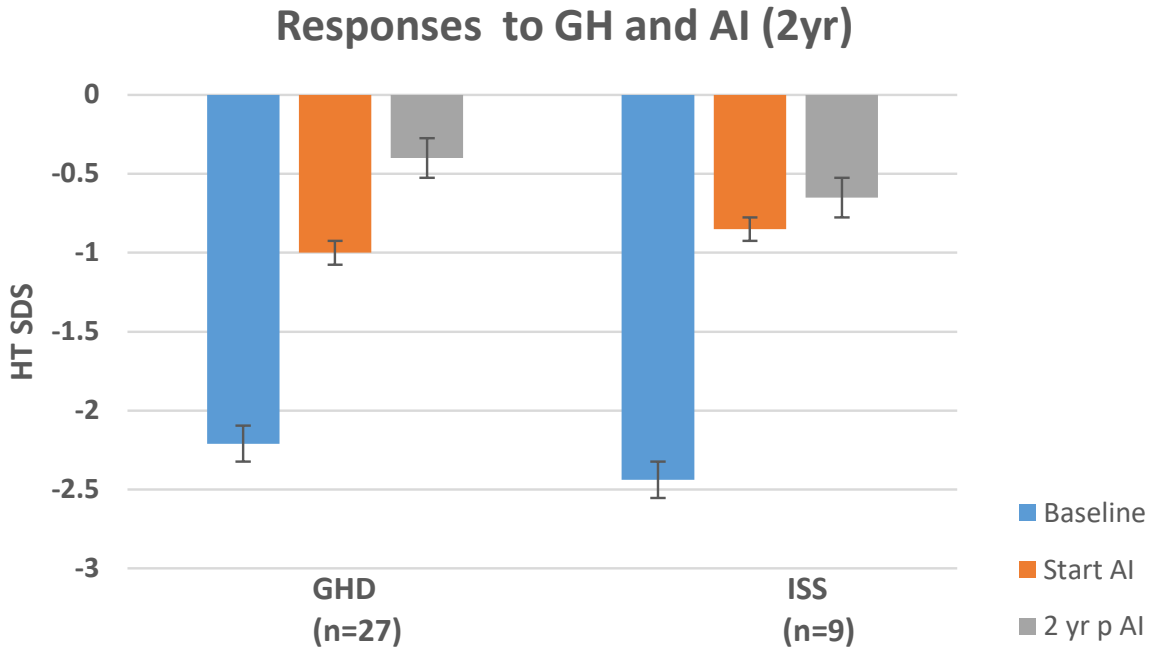
Bone Age: 14.5 ± 0.7 yrs

HT SDS: -1.7 ± 0.7 (PAH <-2.5)

Results: 168.5 ± 2.6 cm – GH/AI (19mo)
164.2 ± 5.6 cm – GH (11.5mo)
160.1 ± 2.8 cm – historical controls

HEIGHT OUTCOMES IN CHILDREN WITH GHD, ISS TREATED WITH GH AND AI: ANSWER PROGRAM

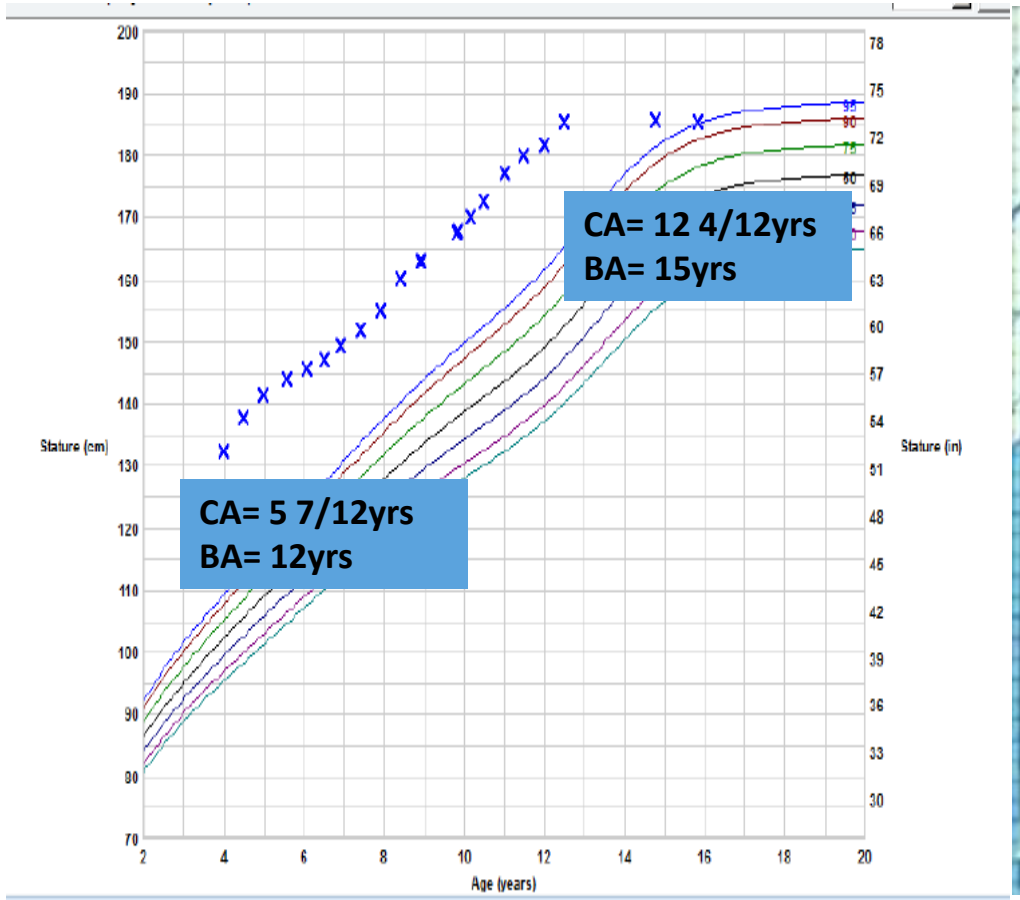


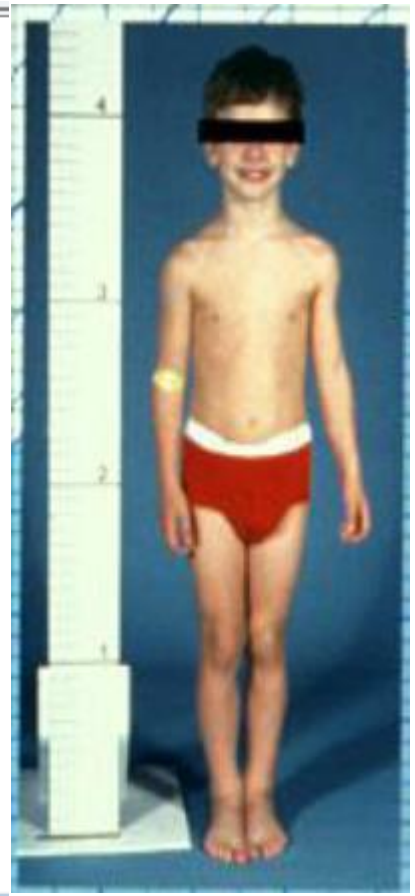


	GH start	AI start
GHD –	12.1 yrs	14.7 yrs
ISS –	10.8 yrs	13.8 yrs

Miller at al, Int J Ped Endo 2020

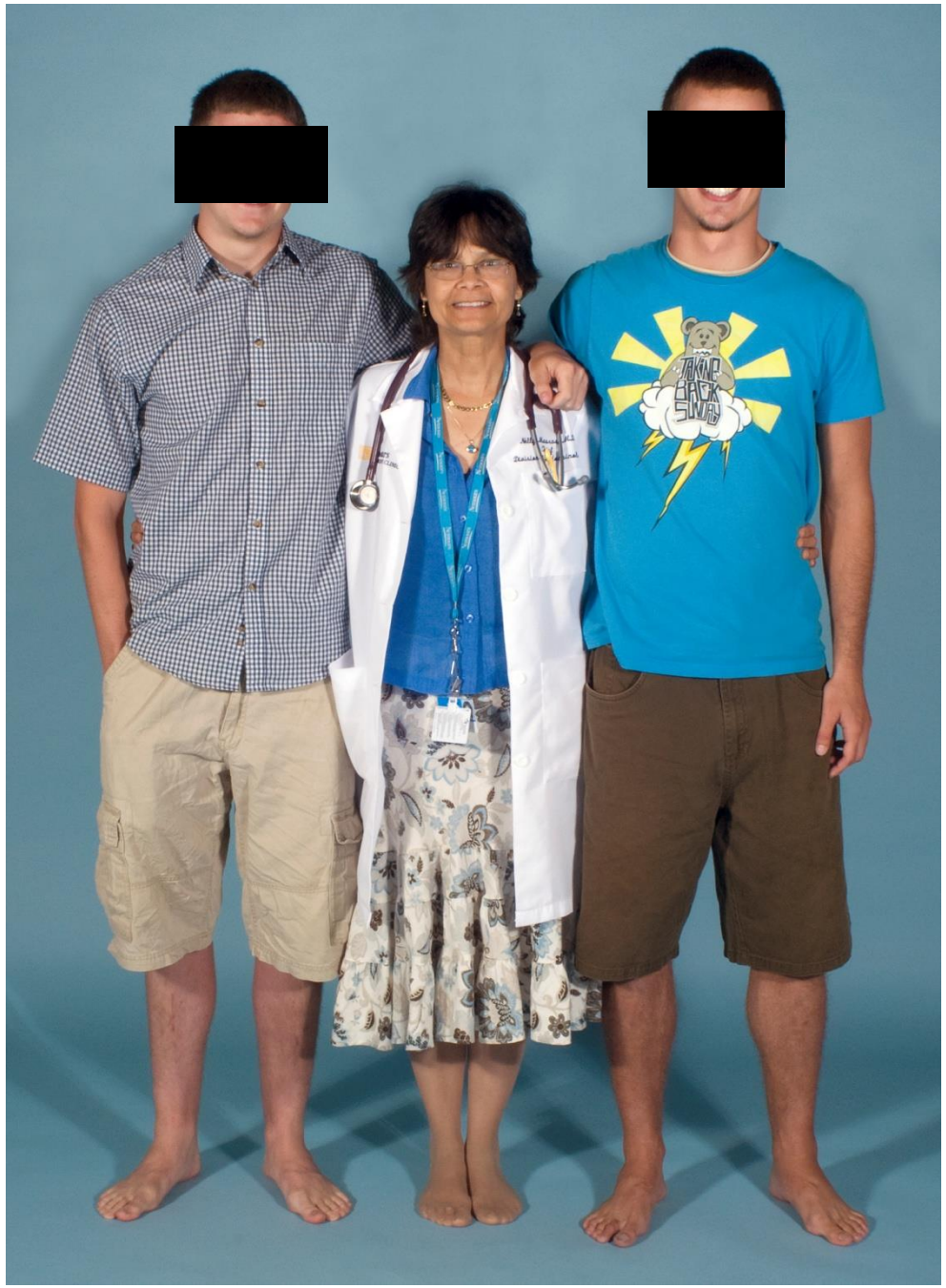
GIP/FMPP





Initial Testosterone:
185ng/dl
(16.8nmol/L)

Photo shown with permission



Adult HT	MPH	Dad's HT
1) 186.5cm (73.4")	179cm (70.5")	188cm (74")
2) 183.6cm (72.3")		
3) 168cm (65.3")	167.6cm (66")	165cm (65")

Photo shown with permission

THE JOURNAL OF PEDIATRICS • www.jpeds.com 2017

ORIGINAL ARTICLES

Effect of Antiandrogen, Aromatase Inhibitor, and Gonadotropin-releasing Hormone Analog on Adult Height in Familial Male Precocious Puberty

Ellen Werber Leschek, MD[1], Armando C. Flor, MD[2], Joy C. Bryant, RN[3], Janet V. Jones, RN[4], Kevin M. Barnes, PhD[5], and Gordon B. Cutler, Jr, MD[6]

N=28

Age at treatment onset = 4.9 ± 1.5 years

Rx: testolactone/anastrozole, spironolactone

Adult height = 173.6 ± 6.8 cm (-0.4SDS)

BICALUTAMIDE PLUS ANASTROZOLE FOR THE TREATMENT OF GIP IN BOYS REITER, ET. AL. J PED ENDO METAB 23; 2010

Aromatase inhibitors for male infertility

Peter N. Schlegel, M.D.

Fert Ster 2012

Successful testicular sperm retrieval in adolescents with Klinefelter syndrome treated with at least 1 year of topical testosterone and aromatase inhibitor

Mehta A, et al. Fert & Ster 2013 (N=10, 14-22yrs)

Ejaculatory sperm production in non-obstructive azoospermic patients with a history of negative testicular biopsy after the administration of an aromatase inhibitor: report of two cases

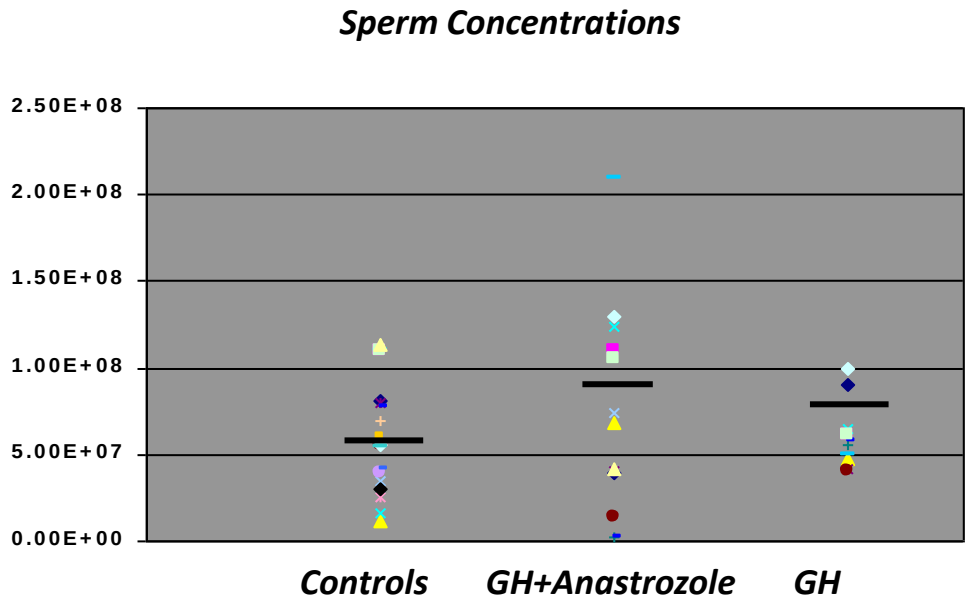
Kyrou D, et al. Eur J Ob Gyn & Rep Biol 173:120, 2014

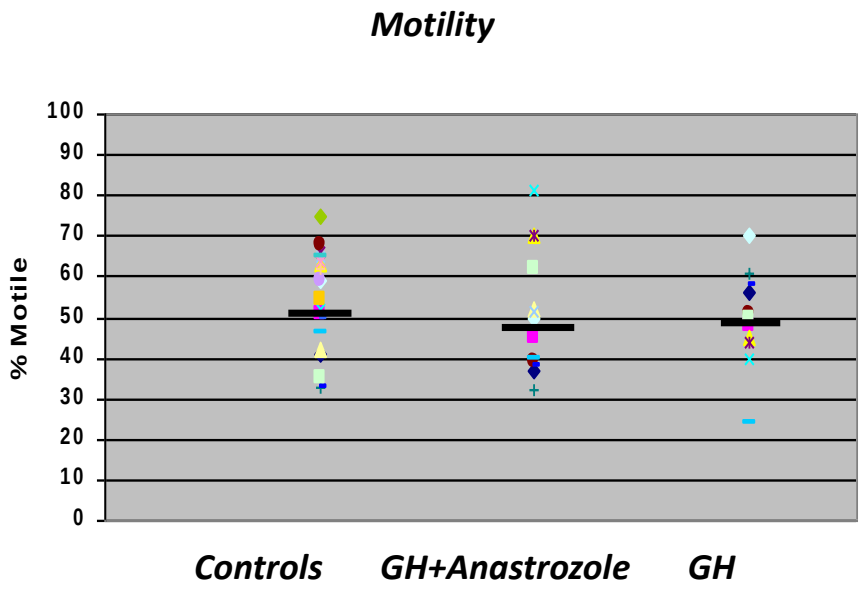
Aromatase inhibitors in the treatment of oligozoospermic or azoospermic men: a systematic review of randomized controlled trials

JBRA Assisted Reprod 2016

Mariana A. Ribeiro[1], Luís F. O. Gameiro[2], Wellerson R. Scarano[1], Christine Briton-Jones[3], Anil Kapoor[4,5], Mauro B. Rosa[6], Regina El Dib[5,7]

SPERM ANALYSIS IN GROWTH HORMONE-DEFICIENT ADOLESCENTS PREVIOUSLY TREATED WITH AN AROMATASE INHIBITOR: COMPARISON WITH NORMAL CONTROLS





Mauras N, et al, Fertility & Sterility 2005

WHAT ABOUT GIRLS?

Long-term outcomes of letrozole treatment for precocious puberty in girls with McCune–Albright syndrome

Andrea Estrada[1,2,3,*], Alison M Boyce[1,2,3,*], Beth A Brillante[1], Lori C Guthrie[1], Rachel I Gafni[1] and Michael T Collins[1]

EJE 2016

The use of aromatase inhibitors for ovulation induction

Curr Opin Obst Gynecol 2015

Anat Hershko Klement[a,b] *and Robert F. Casper*[a,b]

Anastrozole plus leuprorelin in early maturing girls with compromised growth: the "GAIL" study

D. T. Papadimitriou[1,2] · E. Dermitzaki[2] · M. Papagianni[3] · G. Papaioannou[4] · V. Papaevangelou[2] · A. Papadimitriou[2]

J Endocrinol Invest 2016

N=40 with early puberty

Age: 7.5 – 9 yrs

Bone age: +1.8 yrs

Randomized to: Leuprorelin IM/q mo vs.
Leuprorelin + anastrozole

Rx x 2yrs or until age 10 yrs

PAH at 24 months: +1.21 ± 0.45 SDS (7.51cm) Leuprorelin/AI
+0.31 ± 0.37 (1.92 cm), p=0.001 Leuprorelin

CONCLUSIONS

Aromatase inhibitors in boys

- Have been studied over 20y in gynecomastia, testotoxicosis, CDGM, GH deficiency and ISS with a slowdown of bone maturation and increased height potential
- **Judicious use of AIs** combined with GH, for 2-3 years, offer an alternative to the treatment of pubertal males with ISS with an excellent safety profile
- Measures of quality of life were improved with GH and AI/GH
- Testosterone, IGF-I and bone densitometry should be monitored
- Anastrozole is better than letrozole avoiding excessive increase in testosterone
- Rx in physiologic puberty should be limited to 2-3 years

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Ravinder Singh, PhD

University of Hamburg:
Monika Bullinger, PhD; Janika Blömeke, PhD

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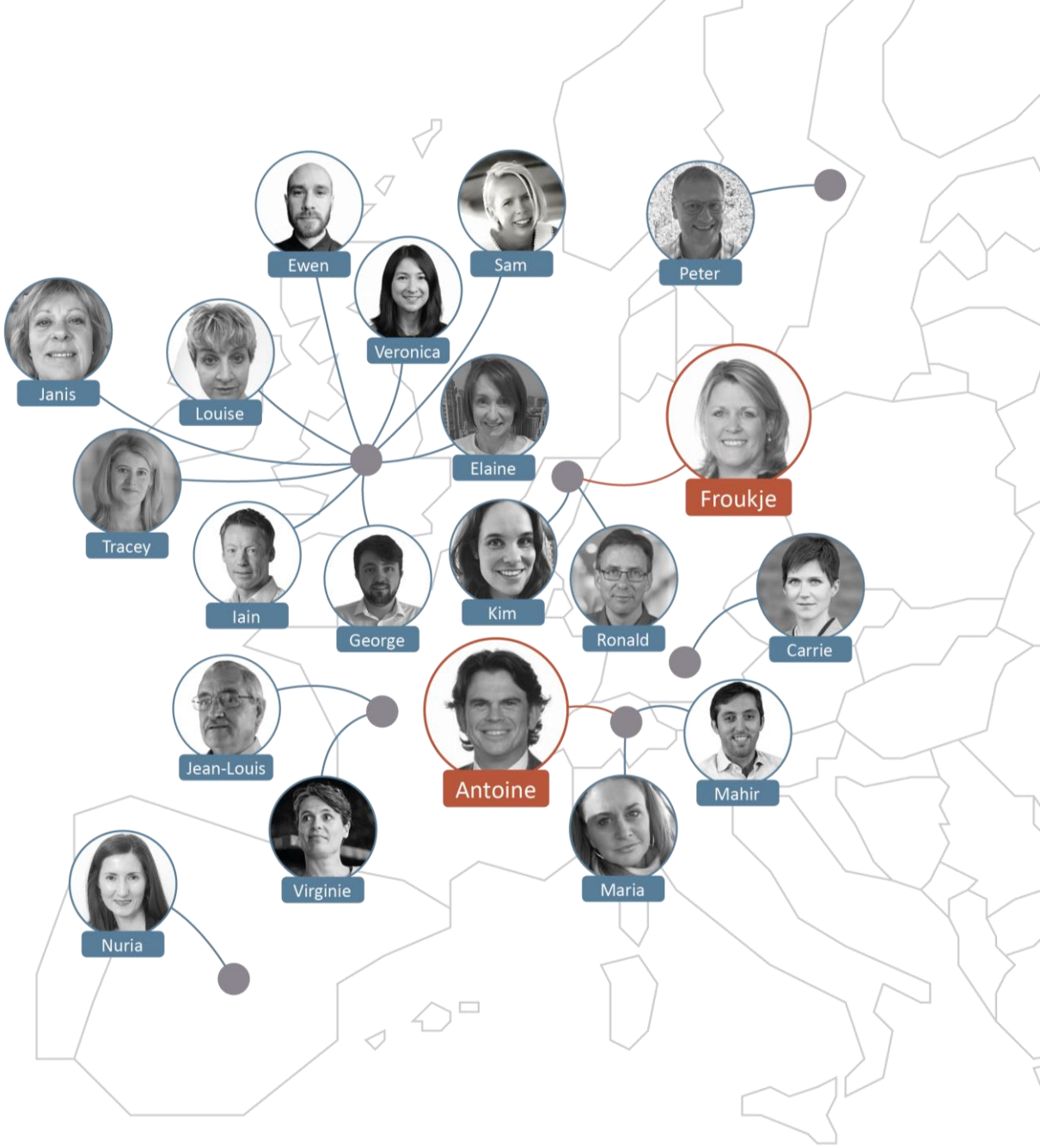

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