The science behind iGRO

iGRO is an interactive tool that can help physicians evaluate growth outcomes in patients receiving growth hormone (GH) treatment. These pages provide an overview of the concepts and scientific basis underlying iGRO.

1. The concept of growth prediction

The change in height velocity induced by GH treatment (the growth response) can vary considerably among children with growth disorders. This variation in growth reflects a broad range of responsiveness to GH and depends upon a patient's baseline characteristics and sensitivity to treatment.[1] If these differences are not accounted for, some patients may receive an insufficient or unnecessarily high dose of GH, they may fail to reach their target mid-parental height (MPH) and concomitant pathologies or poor adherence may go unrecognised.[2]

Deciding on the most effective treatment strategy for each individual can present a considerable challenge to physicians in everyday clinical practice.[1] The application of growth prediction models can assist with making this decision.[2]

Essential terminology

Algorithm: a mathematical description of variables that correlate with growth response.

Response: the change in a parameter induced by treatment; this usually depends on the dosage used and can be quantified in terms of a dose–response curve.

Responsiveness: the innate capacity of an individual to grow in response to GH. This is evaluated by comparing a child's predicted growth response, based on his/her biological characteristics, with his/her actual response to GH. A growth response that is smaller than expected indicates that the patient is less responsive to GH than other children of the same age and with the same biological characteristics.

Target mid-parental height: a child's predicted height based on the height of their parents. The calculation of mid-parental height (MPH) provides an estimate of the normal genetic potential of an individual and is calculated as follows:

target height standard deviation score (SDS) = (father's height SDS + mother's height SDS)/1.61

2. iGRO: the individualised growth response optimisation tool

iGRO uses growth prediction algorithms that are based on data from the largest database of GH-treated children in the world, the KIGS–Pfizer International Growth Database.[3–8] This contains growth data from approximately 83 000 children, collected over a 25-year period.[2] iGRO provides growth predictions using data typically collected in routine clinical practice (**Table 1**). Models currently available include algorithms for prepubertal and pubertal growth in children with idiopathic GH deficiency (IGHD), Turner syndrome and short children born small for gestational age (SGA). The validity of these models has been demonstrated in large patient cohorts and the scientific basis for iGRO is established in the scientific literature.[3–9] Full details of iGRO models and how they were developed and validated can be found below.

Table 1. Baseline dataset and additional variables required for iGRO growth prediction algorithms for the first year of GH therapy.

Minimal set of variables required during prepubertal years[3–5]	
• Birth date	• Parents' heights
• Gender	• Height
• Primary diagnosis	• Weight
• Gestational age	• Age at start of treatment
• Birth weight	• GH dose
Additional variables required during prepubertal years	
• For children with IGHD only (optional)[3] – Maximum GH peak	• For girls with Turner syndrome only[4,7] – Oxandrolone treatment status – Number of injections per week
For total pubertal growth predictions only[6,7]	
• Pubertal status and age of onset • Bone age at puberty onset • Height at puberty onset • Gender	

GH, growth hormone; IGHD, idiopathic GH deficiency.

3. Methodology of algorithm development

Data from patients enrolled in the KIGS database were used for the generation of growth prediction algorithms. The following patient inclusion criteria were used.[3–8]

- Patients received 6–7 injections of recombinant human GH per week.
- IGHD: maximum GH peak below 10 µg/l (in at least two standard tests) and an appropriate size at birth.
- Turner syndrome: diagnosis confirmed by karyotype analysis.
- SGA: birth weight for gestational age SDS below –1.28, gestational age of at least 30 weeks and maximum GH peak over 5 µg/l.

The characteristics of the patients whose data were used in the development of the models can be found in the original publications.[3–8] Patients were defined as pubertal if the mean testes volume was greater than 3 ml for boys, breast development was equal or above stage B2 (Tanner) for girls, or if puberty was pharmacologically induced. Factors correlating with height velocity, or total pubertal height gain, were identified using multiple linear regression.

3.1 IGHD

Growth in prepubertal children with IGHD

Predictive algorithms were constructed using data obtained from 593 prepubertal patients with IGHD.[3]

KIGS first-year prediction algorithm

GH peak, age, body weight and dose of GH at the start of treatment, difference between height SDS and MPH SDS and birth weight were found to be independently correlated with first-year height velocity (**Table 2**). The model explains 61% of the variability of the response (error standard deviation [SD], 1.46 cm). When excluding maximum GH peak, the model still explains 45% of the variability of the response (error SD, 1.72 cm).

KIGS second-, third- and fourth-year prediction algorithms

Treatment was continued for 4 years in at least 180 patients. Data from these patients were used for construction of the prediction algorithms for the second to the fourth year. Age, GH dose, body weight at onset of the growth period and height velocity in the previous year were the variables that correlated with the second-, third- and fourth-year height velocities (**Table 2**). The models for the second to the fourth year of treatment explained 40%, 37% and 30% of the variability in growth response, respectively (error SDs, 1.19 cm, 1.05 cm and 0.95 cm).

There were no statistically significant differences between the predicted and the observed growth when the algorithms were validated using data from three cohorts of patients with IGHD who were treated with GH. These comprised:

- 237 patients enrolled in KIGS but not used in the construction of the algorithms
- 33 patients from a clinic in Tübingen, Germany
- 29 patients enrolled in OZGROW, the Australian National Growth Database.

The fourth-year response model was also shown to give accurate prospective growth predictions for the fifth to the eighth prepubertal year of GH treatment in a subset of KIGS patients (n = 48).

Table 2. Rank of predictors of first-, second-, third- and fourth-year height velocity in patients with IGHD. Adapted from Ranke *et al*.[3] with permission of The Endocrine Society. Permission conveyed through Copyright Clearance Center, Inc.

Parameter	Rank				
	First year (n = 593)		Second year (n = 573)	Third year (n = 335)	Fourth year (n = 180)
	+ Peak GH	– Peak GH			
Maximum GH peak (ln µg/l)	1 (–ve)	–	–	–	–
Age at start of therapy (years)	2 (–ve)	2 (–ve)	3 (–ve)	3 (–ve)	4 (–ve)
Height – MPH (SDS)	3 (–ve)	1 (–ve)	–	–	–
Body weight (SDS)	4 (+ve)	5 (+ve)	2 (+ve)	2 (+ve)	1 (+ve)
GH dose (ln IU/kg/week)	5 (+ve)	4 (+ve)	4 (+ve)	4 (+ve)	3 (+ve)
Birth weight (SDS)	6 (+ve)	3 (+ve)	–	–	–
Height velocity during previous year (cm/year)	–	–	1 (+ve)	1 (+ve)	2 (+ve)

GH, growth hormone; IGHD, idiopathic GH deficiency; ln, natural log; MPH, mid-parental height; SDS, standard deviation score; +ve, variable is positively correlated with growth response; –ve, variable is negatively correlated with growth response.

Total pubertal growth in children with IGHD

The magnitude of growth during puberty accounts for approximately 25% of total postnatal height, and is greater in boys than in girls.[6] Data for the construction of predictive algorithms for total pubertal growth were obtained from 303 patients (180 males, 123 females) with IGHD.[6] All had been treated with GH for at least 5 years, including a minimum of 2 prepubertal years, and a minimum of 2 years during puberty. Total pubertal growth was defined as the difference (in cm) between height at the onset of puberty and height at near-adult stature.

KIGS total pubertal growth prediction algorithm

Gender, age at onset of puberty, the difference between height SDS and MPH SDS and mean GH dose were found to be independently correlated with height velocity during puberty (**Table 3**). The model explains 70% of the variability of the response (error SD, 4.2 cm).

Table 3. Rank of predictors for total pubertal growth in patients with IGHD. Adapted from Ranke *et al.*[6] with permission of The Endocrine Society. Permission conveyed through Copyright Clearance Center, Inc.

Parameter	Rank
Male gender	1 (+ve)
Age at onset of puberty (years)	2 (–ve)
Height – MPH at onset of puberty (SDS)	3 (–ve)
Mean GH dose (mg/kg/day)	4 (+ve)

GH, growth hormone; IGHD, idiopathic GH deficiency; MPH, mid-parental height; SDS, standard deviation score; +ve, variable is positively correlated with growth response; –ve, variable is negatively correlated with growth response.

The algorithms were validated in 36 patients from the University Children's Hospital in Tübingen, Germany. There was no significant difference between predicted growth and actual growth.

Total pubertal growth in patients with IGHD – updated to include bone age

Growth prediction algorithms, incorporating bone age as an independent predictor, were constructed using data obtained from 576 patients (355 males, 221 females) with IGHD.[7] All patients had been treated with GH for a total of at least 5 years, including a minimum of 2 years before the onset of puberty.

KIGS total pubertal growth prediction algorithm

Age at onset of puberty, bone age delay at onset of puberty, the difference between height SDS and MPH SDS at onset of puberty and mean dose of GH during puberty were found to be predictive of total pubertal growth (**Table 4**). There was no difference between the adolescents with or without induced/maintained puberty. Response parameters from the first prepubertal year on GH were not found to be predictive for total pubertal growth. The model explains 66% and 65% of the variability of pubertal growth for males and females, respectively (error SDs, 4.5 cm and 3.8 cm).

Table 4. Rank of predictors for total pubertal growth in patients with IGHD. Adapted from Ranke *et al.*[7] with permission. ©2011, Karger Publishers, Basel, Switzerland.

Parameter	Rank
Age at onset of puberty (years)	1 (–ve)
Bone age delay at onset of puberty (years)	2 (+ve)
Height – MPH at onset of puberty (SDS)	3 (–ve)
Mean GH dose during puberty (mg/kg/day)	4 (+ve)

GH, growth hormone; IGHD, idiopathic GH deficiency; MPH, mid-parental height; SDS, standard deviation score; +ve, variable is positively correlated with growth response; –ve, variable is negatively correlated with growth response.

The algorithms were validated in 63 patients with IGHD (44 males, 19 females) who were enrolled in KIGS.

3.2 Turner syndrome

Growth in prepubertal girls with Turner syndrome

Predictive algorithms were constructed using data obtained from 686 prepubertal patients with Turner syndrome.[4]

KIGS first-year prediction algorithm

GH dose, age at the start of treatment, body weight SDS, oxandrolone therapy, difference between height SDS and MPH SDS and number of weekly injections were found to be independently correlated with first-year height velocity (**Table 5**). This model explains 46% of the variability of the response (error SD, 1.26 cm).

KIGS second-, third- and fourth-year prediction algorithms

Treatment was continued in at least 294 patients for 4 years. Data from these patients were used for construction of the prediction algorithms for the second to the fourth year. Height velocity in the previous year, GH dose, age and weight SDS at the onset of the respective growth period and oxandrolone therapy were the variables that correlated with the second- to the fourth-year height velocity (**Table 5**). The models for the second, third and fourth year of treatment explained 32%, 29% and 30% of the variability in growth response, respectively (error SDs, 1.09 cm, 0.99 cm and 1.01 cm).

There were no statistically significant differences between the predicted and observed growth when the algorithms were validated using data from two cohorts of patients with Turner syndrome who were treated with GH.

Table 5. Rank of predictors for the first-, second-, third- and fourth-year height velocity in patients with Turner syndrome. Adapted from Ranke *et al.*[4] with permission of The Endocrine Society. Permission conveyed through Copyright Clearance Center, Inc.

Parameter	Rank			
	First year (n = 686)	Second year (n = 681)	Third year (n = 293)	Fourth year (n = 291)
GH dose (ln IU/kg/week)	1 (+ve)	2 (+ve)	4 (+ve)	4 (+ve)
Age at start of GH therapy (years)	2 (–ve)	3 (–ve)	5 (–ve)	2 (–ve)
Body weight (SDS)	3 (+ve)	5 (+ve)	3 (+ve)	5 (+ve)
Oxandrolone therapy	4 (+ve)	4 (+ve)	2 (+ve)	3 (+ve)
Height – MPH (SDS)	5 (–ve)	–	–	–
Number of injections per week	6 (+ve)	–	–	–
Height velocity during previous year (cm/year)	–	1 (+ve)	1 (+ve)	1 (+ve)

GH, growth hormone; ln, natural log; MPH, mid-parental height; SDS, standard deviation score; +ve, variable is positively correlated with growth response; –ve, variable is negatively correlated with growth response.

These comprised:

- 76 patients enrolled in KIGS but not used in the construction of the algorithms
- 81 patients from one clinic in Tübingen, Germany.

Total pubertal growth in girls with Turner syndrome

Data obtained from 419 patients with Turner syndrome were used for the construction of predictive algorithms.[7]

KIGS total pubertal growth prediction algorithm

Age at onset of puberty, bone age delay at onset of puberty, the difference between height SDS and MPH SDS at onset of puberty and mean dose of GH during puberty were found to be predictive of total pubertal growth (**Table 6**). There was no difference between the patients with spontaneous or induced puberty. The model explains 68% of the variability of pubertal growth (error SD, 2.9 cm).

Table 6. Rank of predictors for total pubertal growth in patients with Turner syndrome. Adapted from Ranke *et al.*[7] with permission. ©2011, Karger Publishers, Basel, Switzerland.

Parameter	Rank
Age at onset of puberty (years)	1 (–ve)
Bone age delay at onset of puberty (years)	2 (+ve)
Height – MPH at onset of puberty (SDS)	3 (–ve)
Mean GH dose during puberty (mg/kg/day)	4 (+ve)

GH, growth hormone; MPH, mid-parental height; SDS, standard deviation score; +ve, variable is positively correlated with growth response; –ve, variable is negatively correlated with growth response.

The algorithms were validated in 44 patients with Turner syndrome who were enrolled in KIGS.

3.3 SGA

Growth in short prepubertal children born SGA

Predictive algorithms were constructed using data obtained from 613 prepubertal patients (408 males, 205 females) who were born SGA.[5]

KIGS first-year prediction algorithm

GH dose, age at start, weight SDS at start and MPH SDS were found to be independently correlated with first-year height velocity (**Table 7**). The model explains 52% of the variability of the response (error SD, 1.3 cm).

KIGS second-year prediction algorithms

Data from 385 of the patients who were treated longitudinally for 2 years were used to construct two prediction models for the second year of treatment. Model A is based on the same four predictors as the first-year model, while model B is a three-parameter model that includes height velocity in the previous year of treatment. For model A, age at the start of treatment, GH dose, weight SDS after 1 year of GH and MPH SDS were the variables that correlated with the second-year height velocity (**Table 7**). This model explained 30% of the variability in growth response (error SD, 1.1 cm). For model B, height velocity during the first year of treatment, age at the start of treatment and GH dose correlated with second-year height velocity (**Table 7**). This model explained 34% of the variability in growth response (error SD, 1.1 cm).

Table 7. Rank of predictors of first- and second-year height velocity in children born SGA. Adapted from Ranke *et al*.[5] with permission of The Endocrine Society. Permission conveyed through Copyright Clearance Center, Inc.

Parameter	Rank		
	First year (n = 613)	Second year (n = 385)	
		Model A	Model B
Age at start of treatment (years)	2 (–ve)	1 (–ve)	2 (–ve)
GH dose (mg/kg/day)	1 (+ve)	2 (+ve)	3 (+ve)
Body weight (SDS)	3 (+ve)	3 (+ve)	–
MPH (SDS)	4 (+ve)	4 (+ve)	–
Height velocity during previous year (cm/year)	–	–	1 (+ve)

GH, growth hormone; MPH, mid-parental height; SDS, standard deviation score; SGA, small for gestational age; +ve, variable is positively correlated with growth response; –ve, variable is negatively correlated with growth response.

The algorithms were validated in a group of patients (68 for the first-year model and 43 for the second-year model) enrolled in KIGS but not used in the construction of the algorithms. There were no statistically significant differences between the predicted and observed growth responses.

Total pubertal growth in short patients born SGA

A total of 59 short patients who were born SGA (35 males, 24 females) qualified for the analysis.[7] The numbers were too small for a predictive algorithm to be developed, but the characteristics at the time points investigated were very similar to those in IGHD. In addition, the total pubertal growth observed in short patients born SGA was highly correlated with that predicted using the model for IGHD. Therefore the models for IGHD can be applied for short adolescents born SGA.

Total growth in short patients born SGA

Although growth prediction models have already been developed for the first 2 prepubertal years in short patients born SGA,[5] models are required that allow the prediction of growth up until final height. Data obtained from 317 short children born SGA (72% males) were used to construct a new prediction model for the third prepubertal year.[8]

KIGS third-year prediction algorithm

Height velocity in the previous year, age at start of treatment, body weight, MPH and GH dose were found to correlate with the growth response during the third year of treatment (**Table 8**). This model explains 33% of the variability of the response (error SD, 1.0 cm).

The model was validated using data from 34 patients who were enrolled in KIGS but not used in the construction of the algorithms.

KIGS fourth-year prediction algorithm

Treatment was continued for a full fourth year in 182 patients (62% males), but the numbers were too small for a predictive algorithm to be developed for the fourth prepubertal year on GH therapy. However, the fourth-year prediction model for children with IGHD that was previously developed was applied to these patients born SGA.[3,8] There was no significant difference between observed and predicted growth using this model, indicating that it can be applied to short patients born SGA.

KIGS total pubertal growth algorithm

A total of 59 short patients who were born SGA (35 males, 24 females) and who were treated for a total of at least 5 years, and at least 2 years before puberty onset, were included in the analysis of total pubertal growth.[8] The numbers were too small for the development of a predictive algorithm, however the model previously devised for total pubertal growth in children with IGHD was employed. There was no significant difference between the observed and predicted growth using this model, indicating that it can be applied to short patients born SGA.

Table 8. Rank of predictors for third-year growth in short patients born SGA. Adapted from Ranke *et al*.[8] with permission. ©2011, licensed by BioMed Central.

Parameter	Rank
Height velocity during previous year (cm/year)	1 (+ve)
Age at start of GH therapy (years)	2 (–ve)
Weight at start of GH therapy (SDS)	3 (+ve)
MPH (SDS)	4 (+ve)
GH dose (mg/kg/day)	5 (+ve)

GH, growth hormone; MPH, mid-parental height; SDS, standard deviation score; SGA, small for gestational age; +ve, variable is positively correlated with growth response; –ve, variable is negatively correlated with growth response.

4. References

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Pfizer

iGRO Individual Growth Response Optimisation

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