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 behind 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 this decision-making process.[2]

Essential terminology

Algorithm: a mathematical description of variables that correlate with growth response.[3]

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.[3]

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.[3]

Index of responsiveness (IoR): the measure of an individual's ability to respond to GH.[3]

$$\text{IoR} = \frac{\text{(Actual height velocity} - \text{Predicted height velocity)}}{\text{Error standard deviation (SD) of predicted response}}$$

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[4]

2. iGRO: the individualised growth response optimisation tool

iGRO uses validated growth prediction algorithms that are based on data from the largest database of GH-treated children in the world, KIGS—Pfizer International Growth Database.[5–11] KIGS contains growth data from approximately 83 000 children, collected over a 25-year period.[2] iGRO provides growth predictions using patient characteristics typically recorded in routine clinical practice (**Table 1**). Models currently available include those 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 treated with recombinant GH and the scientific basis for iGRO is established in the scientific literature.[5–12] 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[5–8]

- Birth date
- Gender
- Primary diagnosis
- Birth weight
- Parents' heights
- Height
- Weight
- Age at start of treatment
- GH dose

Additional variables required during prepubertal years

- For children with IGHD only (optional)[5,8]
  - Maximum GH peak
  - Gestational age
- For girls with Turner syndrome only[6,10]
  - Oxandrolone treatment status
  - Number of injections per week

For total pubertal growth predictions only[9,10]

- 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.[5–11]

- 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 algorithims can be found in the original publications.[5–11] Patients were defined as pubertal if 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.[5]

KIGS first-year prediction algorithm

GH peak, age, body weight and dose of GH at the start of treatment, difference between height and MPH, and birth weight were found to be independently correlated with first-year height velocity (**Table 2**). The model explained 61% of the variability of the response (error standard deviation [SD], 1.46 cm). When maximum GH peak was excluded, the model still explained 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 to construct the prediction algorithms for the second, third and fourth years of treatment. Age, GH dose, body weight at onset of the growth period and height velocity in the previous year were the variables that correlated with height velocity in the second, third and fourth years (**Table 2**). The models for the second, third and fourth years 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 predicted and observed growth when the algorithms were validated using data from three cohorts of prepubertal 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.[13]

The fourth-year response model was also shown to give accurate growth predictions for the fifth to eighth prepubertal years of GH treatment in a subset of patients enrolled in the KIGS database (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*.[5] with permission. 1999, © The Endocrine Society.

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.

Growth in very young prepubertal children with IGHD

The response to GH in the first year of treatment is typically greater in younger patients (< 3 years of age) than in older patients.[8] Therefore, predictive algorithms were also developed for very young patients using data obtained from 265 children (180 males, 85 females) with IGHD who were aged between 0 and 3 years.[8]

KIGS first-year prediction algorithm

Two prediction models were constructed for the first year of treatment. For model A, the difference between height and MPH, age, body weight, birth weight and GH dose were found to correlate with first-year height velocity (**Table 3**). This model explained 45% of the variability of the response (error SD, 2.3 cm). Model B was based on the same parameters as model A, but also included maximum GH peak as a predictor (**Table 3**). This model explained 54% of the variability of the response (error SD, 2.1 cm). While the predictors in models A and B were the same as in other prediction models for prepubertal children with IGHD, the order of their importance differed; in particular, the contribution of GH dose was higher in this younger group.

Table 3. Rank of predictors of first-year height velocity (HV) in patients with idiopathic growth hormone (GH) deficiency. Adapted from Ranke *et al.*[8] with permission of The Endocrine Society. Permission conveyed through Copyright Clearance Center, Inc.

Parameter	Rank	
	Model A	Model B
Age at start of treatment (years)	1 (–ve)	1 (–ve)
GH dose (log IU/kg/week)	2 (+ve)	3 (+ve)
Birth weight (SDS)	3 (+ve)	6 (+ve)
Height – MPH (SDS)	4 (–ve)	5 (–ve)
Body weight (SDS)	5 (+ve)	4 (+ve)
Maximum GH peak (log µg/l)	–	2 (–ve)

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.[9] Data for the construction of predictive algorithms for total pubertal growth were obtained from 303 patients (180 males, 123 females) with IGHD.[8] 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 and MPH, and mean GH dose during puberty were found to be independently correlated with height velocity during puberty (**Table 4**). The model explained 70% of the variability of the response (error SD, 4.2 cm).

Table 4. Rank of predictors for total pubertal growth in patients with IGHD. Adapted from Ranke *et al.*[9] 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 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 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.[10] All patients had been treated with GH for 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 and MPH at onset of puberty, and mean dose of GH during puberty were found to be predictive of total pubertal growth (**Table 5**). There was no difference between 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 explained 66% and 65% of the variability of pubertal growth for males and females, respectively (error SDs, 4.5 cm and 3.8 cm).

Table 5. Rank of predictors for total pubertal growth in patients with IGHD. Adapted from Ranke *et al.*[10] 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.[6]

KIGS first-year prediction algorithm

GH dose, age at the start of treatment, body weight SDS, use of oxandrolone therapy, difference between height and MPH, and number of weekly injections were found to be independently correlated with first-year height velocity (**Table 6**). This model explained 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 to construct prediction algorithms for the second, third and fourth years of treatment. 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 height velocity in the second, third and fourth years (**Table 6**). The models for the second, third and fourth years 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 predicted and observed growth when the algorithms were validated using data from two cohorts of patients with Turner syndrome who were treated with GH. These comprised:

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

The following response model was also shown to give accurate growth predictions for the fifth to eighth prepubertal years of GH treatment in a subset of patients enrolled in the KIGS database (n = 291).[3]

Total pubertal growth in girls with Turner syndrome

Data obtained from 419 patients with Turner syndrome were used for the construction of predictive algorithms.[10]

KIGS total pubertal growth prediction algorithm

Age at onset of puberty, bone age delay at onset of puberty, the difference between height and MPH at onset of puberty, and mean dose of GH during puberty were found to be predictive of total pubertal growth (**Table 7**). There was no difference between patients with spontaneous or induced puberty. The model explained 68% of the variability of pubertal growth (error SD, 2.9 cm).

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.[7]

Table 6. Rank of predictors for the first-, second-, third- and fourth-year height velocity in patients with Turner syndrome. Adapted from Ranke *et al*.[6] 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.

Table 7. Rank of predictors for total pubertal growth in patients with Turner syndrome. Adapted from Ranke *et al.*[10] 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.

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 8**). The model explained 52% of the variability of the response (error SD, 1.3 cm).

KIGS second-year prediction algorithms

Data from 385 patients who were treated longitudinally for 2 years were used to construct two prediction models for the second year of treatment. Model A was based on the same four predictors as the first-year model, while model B was a three-parameter model that included 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 8**). 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 8**). This model explained 34% of the variability in growth response (error SD, 1.1 cm).

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 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,[7] 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.[11]

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 9**). This model explained 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, when the fourth-year prediction model for children with IGHD was applied to these patients born SGA,[5,11] 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 an analysis of total pubertal growth.[11] The

Table 8. Rank of predictors of first- and second-year height velocity in children born SGA. Adapted from Ranke *et al.*[7] 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.

Table 9. Rank of predictors for third-year growth in short patients born SGA. Adapted from Ranke *et al.*[11] 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.

number of patients was too small for the development of a predictive algorithm, so the model previously devised for total pubertal growth in children with IGHD was employed. There was no significant difference between observed and predicted growth using this model, indicating that it can be applied to short patients born SGA.

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