

# Future Directions: Growth Prediction Models

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## Key Words

Prediction model · Growth hormone

## Abstract

**Background:** One strategy for optimizing growth hormone (GH) treatment is to develop mathematical models based on clinical data from the large numbers of subjects in the KIGS (Pfizer International Growth Study Database) and to compare the observed versus predicted growth responses in subjects with short stature secondary to idiopathic GH deficiency (GHD), Turner syndrome, small birth size and idiopathic causes of short stature. **Mathematical Models:** Variables employed in derived regression equations include those related to birth status, genetic potential, current clinical status, laboratory data and GH treatment schedule. These models can provide an accurate estimate of potential growth on GH therapy and the tools to optimize and individualize GH therapy to obtain maximum height with the least risk and the lowest cost. Current prediction models explain around 58% of GH responsiveness in subjects with GHD, 46% in subjects with Turner syndrome and 52% in those born small for gestational age. **Future Considerations:** The predictive value of these models could be improved by the inclusion of extended anthropometric variables and biological parameters such as insulin-like growth factor I levels. However, recent reports that common polymorphisms of the GH receptor (GHR) gene may be associated with variations in response to GH suggest that, in the future, molecular

genetics may provide an additional tool for refining growth prediction models. This possibility is being explored in a pilot study examining the effects of candidate genes in a targeted KIGS population to determine whether the *GHR* gene or other gene variants contribute to growth response over the first year of GH treatment. Copyright © 2007 S. Karger AG, Basel

## Introduction

The goals of growth hormone (GH) therapy should be to select candidate subjects according to country-specific registered indications using doses that normalize height as quickly as possible with the least risk and at the lowest cost. The various strategies to optimize GH treatment by temporal order of development are: (1) using dosage paradigms that closely mimic physiology (e.g., higher GH doses during puberty in children with GH deficiency [GHD]) [1]; (2) matching GH doses to yield physiological concentrations of GH surrogates (e.g., insulin-like growth factor I [IGF-I]-based dosing in children with GHD) [2]; (3) developing mathematical models that can be used to compare observed versus predicted growth responses in subjects receiving GH treatment for various causes of growth failure [3], and (4) applying genomics as it relates to differences in GH sensitivity for various causes of growth failure [4]. This article focuses on the application of mathematical modelling to growth prediction using

data from KIGS (Pfizer International Growth Study Database), an international registry developed with the main objective of documenting long-term outcomes and safety of recombinant human GH products (Somatorm® and Genotropin®, Pfizer, Inc.). The database was initiated in 1987 and contains data on ~50,000 subjects treated with GH for various indications.

### Growth Prediction Models: General Aspects

A growth prediction model [5] is a derived algorithm (multiple regression equation) containing variables (established before initiation of GH treatment) that influence growth responses to GH therapy in a defined group of subjects over a defined period of time such that:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \dots + b_pX_p + \varepsilon$$

where:

Y = dependent variable (e.g., growth velocity),  
 X = independent variable (e.g., mid-parental target height),  
 b = parameter to be estimated,  
 p = index indicator, and  
 ε = error term.

Growth prediction models can be used: (1) to determine the GH dose needed to achieve a child's target height as rapidly as possible; (2) to identify poor responders (e.g., secondary to noncompliance, incorrect diagnosis, unrecognized secondary diagnosis and concomitant GH resistance); (3) to provide realistic expectations about growth response; (4) to individualize treatment thereby achieving target height range as quickly as possible and appropriate final adult height with minimal side effects, and (5) to foster development of dosing strategies using the lowest possible cumulative GH dose – perhaps with the highest doses administered early in the treatment course – to maximize response and limit overall costs.

Growth prediction models are considered reliable if they are retrospectively developed from a large population (preferably with at least several hundred subjects); use a well-defined cohort of subjects with a specific disorder; can accommodate heterogeneous clinical characteristics; include easily determined, standardized and reproducible variables; and are easily adapted for simple-to-use (hand-held) computer programs. Ideally, growth prediction models should employ simple linear correlations to identify potentially important variables such as GH dose; describe a high percentage of the observed variation in growth response (i.e., have a high R<sup>2</sup>); have a low margin of error (i.e., a low error SD); be based on a longi-

**Table 1.** Practical predictive variables

General class	Specific parameters
Birth status	Weight, length, and gender
Genetic potential	Parents' heights
Current clinical status	Age, puberty and height
Current laboratory data <sup>a</sup>	Peak GH levels
GH treatment schedule	Dose, frequency and duration

<sup>a</sup> Bone age and IGF-I levels are not included here due to insufficient data and because bone age apparently does not add any additional information beyond that of chronological age, and IGF-I does not add additional information beyond peak stimulated GH level.

tudinal series of algorithms for sequential time periods (including puberty) and on validated, easily accessible predictors; be robust; be validated against an independent population; and be regularly updated to reflect changes in clinical characteristics and GH treatment practices.

The difference between observed and predicted growth responses can be expressed in terms of a Studentized residual [6]:

$$\text{Studentized residual} = \frac{\text{Observed} - \text{predicted height velocity}}{\text{SE calculated for each subject}}$$

The Studentized residual is a calculation comparable to that of a standard deviation score (SDS). It is an index of responsiveness to GH, with values within ±2 SD (or close to 0 SDS) indicative of better response to GH. The calculation shows the accuracy of the height prediction growth rate as it relates to the actual growth rate for each subject, determines linearity, and helps to identify 'outliers'.

### Growth Prediction Models: Specific Aspects

The practical variables considered in the development of growth prediction models are summarized in table 1. Using the KIGS database, prediction models have been developed for three groups of children with IGHD according to age: the very young (birth to 3 years) [7], childhood (first to eighth years of prepubertal treatment) [6] and total pubertal growth [8]. In addition, models have been developed for girls with Turner syndrome for the first to eighth years of prepubertal treatment [9]; for children born small for gestational age (SGA) (defined as more than -1.28 SD or less than ~10th percentile for

birth weight corrected for gestational age, greater than 30 weeks' gestation and persistent postnatal short stature, with normal GH testing) during the first and second prepubertal years of treatment [10]; and for children with idiopathic short stature (defined by individual investigators but including a peak stimulated GH level >10 mg/l and a birth weight greater than -2.0 SD) for the first prepubertal year of treatment [11].

As an example, this is the derived equation for the predicted height velocity (PdHV) in cm/year for prepubertal children with idiopathic GHD in the first year of treatment:

$$\begin{aligned} \text{PdHV} = & 14.55 + \\ & [-1.37 \times \text{maximum stimulated GH response (ln; ng/ml)}] + \\ & [-0.32 \times \text{age at onset (years)}] + \\ & [0.32 \times \text{birth weight SDS}] + \\ & [1.62 \times \text{GH dose (ln; IU/kg/week)}] + \\ & [-0.4 \times (\text{height SDS} - \text{midparental height SDS})] + \\ & [0.29 \times \text{weight SDS}] \end{aligned}$$

This model explains 61% of the variability of the observed growth response with an SD error of 1.46 cm. The order of predictive factors and their clinical ramifications from most to least important are:

- 1 maximum natural log GH response to stimulation (the lower the GH peak, the better the growth),
- 2 age at onset (the younger the child at GH initiation, the better the growth),
- 3 difference between subject height and midparental height (the larger the gap, the better the growth),
- 4 body weight (the heavier the child at the start of GH treatment, the better the growth),
- 5 GH dose (higher doses yield better growth), and
- 6 birth weight (the heavier the child at birth, the greater the growth).

In most cases, the above findings are consistent with long-standing clinical observations. The least logical associations may be those related to weight, which could reflect the need for better nutritional status, both at the time of GH initiation and at birth, to ensure the best height outcome.

Table 2 depicts the hierarchy of predictive values influencing growth response in the first year of GH treatment for prepubertal children with Turner syndrome and SGA compared with idiopathic GHD children. For subjects with Turner syndrome and SGA, the most important predictor is GH dose. Because neither of these conditions is intrinsically associated with GHD, it is not surprising that the cardinal predictor differs from that seen in idiopathic GHD, for which the primary predictor is the degree of GHD. In all three conditions, a young age at

**Table 2.** Hierarchy of predictive values for the first-year growth response for prepubertal children with idiopathic GHD, Turner syndrome (TS), and those born small for gestational age

Characteristic	IGHD	TS	SGA
<i>Population</i>			
N	593	686	682
R <sup>2</sup>	0.61	0.46	0.52
Error SD, cm/year	1.5	1.3	1.3
<i>Predictor</i>			
Degree of GH deficiency	1	-	-
GH dose	5	1	1
Young age at start of treatment, years	2	2	2
Height - midparental height SDS	3	5	-
Midparental height SDS	-	-	4
Weight SDS	4	3	3
Birth weight SDS	6	-	-
Other	-	4 (oxandrolone use)	-

initiation of treatment is the second best prognosticator of growth response. Again, this is probably not surprising since naturally higher growth rates are observed in children who are younger at the start of treatment compared with those who are older. Although not shown, the best predictor of growth response in the second through fourth years of treatment is the growth velocity of the previous year (i.e., good initial growth begets better later growth).

### Utility of Growth Prediction Models

KIGS prediction models can be used to accurately estimate potential growth on GH therapy and to optimize and individualize GH therapy. In the United States, a dose of ~0.3 mg/kg/week GH is the approved starting dose for treating prepubertal subjects with GHD to capitalize on maximal growth potential during the first year of treatment. Thereafter, subsequent GH dosing can be altered according to desired objectives, costs and observed response to GH. If prepubertal growth in response to GH provides expected catch-up, upward adjustment of GH dose during puberty should not be necessary; alternatively, if catch-up is incomplete during the prepubertal years, higher doses of GH can be considered during the pubertal age range. Although physicians need to prescribe GH in adherence to national guidelines, it would be helpful if they were granted some flexibility to respond

to individual subject variation. To balance dosing and to maximize height achievement at the least cost, higher GH doses given to younger, lighter children may allow the most economical efficacy.

In the future, KIGS models may allow prediction of both the safety and efficacy of GH treatment. In addition to predicting height, these models may be used for assessing metabolic benefits, e.g., improvements in body composition, and improving overall quantification of explained variability (by as much as 80%) with the lowest possible error; they may be adapted for use of additional parameters (e.g., extended anthropometry, other biochemical markers and molecular genomic markers); and, finally, they may be made more easily available to investigators. At present, they can be found at: [www.growth-predictions.org](http://www.growth-predictions.org).

### Growth Prediction Models and Genetics

Genetic defects in the GH receptor gene (*GHR*) are associated with GH insensitivity and Laron dwarfism [12]. However, in 2006 Dos Santos et al. [13] reported that a common polymorphism of the *GHR* was associated with increased responsiveness to GH therapy. In the normal population there are two isoforms of *GHR*: the full-length isoform and the isoform lacking exon 3 (d3-*GHR*), which is lost during splicing [14]. It has been calculated that around 50% of Europeans are either heterozygous or homozygous for the d3-*GHR* isoform [13], and it has been proposed that the d3-*GHR* isoform may be dominant over the full-length isoform [13]. Dos Santos et al. [13] studied two cohorts of 76 and 96 children of European descent with idiopathic short stature and short stature related to low birth weight, respectively. The growth rate over the first year of GH therapy was greater for subjects with one or two copies of the d3-*GHR* isoform [13]. The biological significance of the exon 3 deletion is uncertain as preliminary crystallography study does not indicate that it is within the binding or signalling domain of the receptor. Nevertheless, Dos Santos et al. were able to demonstrate differences in the in vitro bioactivity of the full-length and d3-*GHR* isoforms [13].

Further study of these two isoforms gives a rather mixed picture. Two studies of children with GHD failed to show any difference between d3-*GHR* and *GHR* in response to GH treatment [4, 15]. A study from Spain of children born SGA also found no difference between the isoforms in response to GH [16]. However, a study from Brazil of patients with GHD showed patients who are ho-

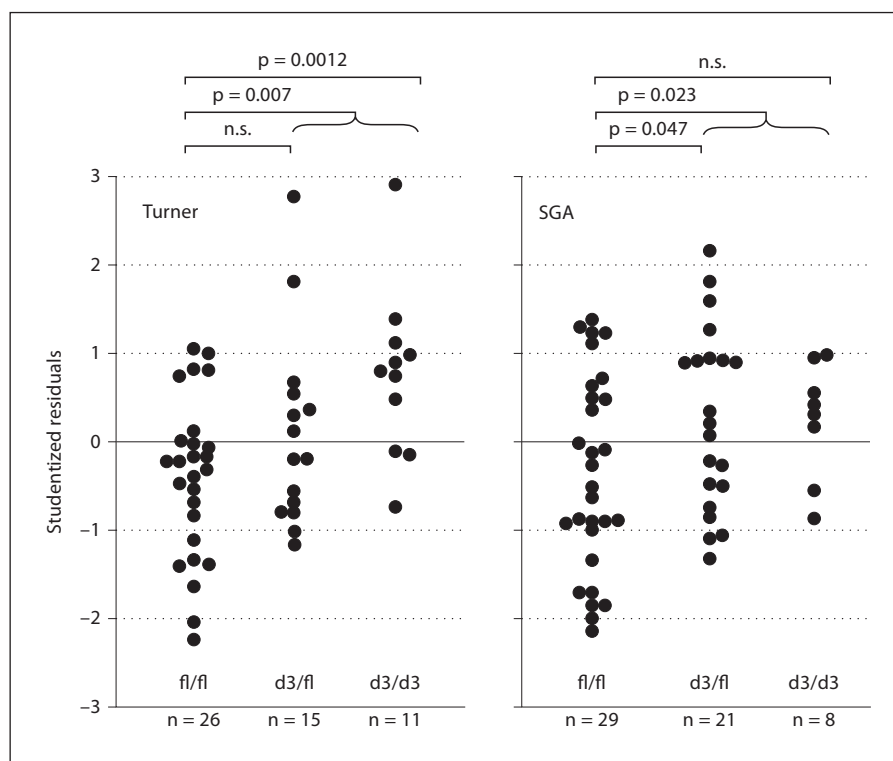
mozygous for *GHR* exon 3 full-length were *less* responsive to short- and long-term human GH therapy (i.e., d3GH3 cohort was more responsive) [17]. Of particular interest, Binder et al. [18] applied the KIGS prediction models to data from subjects with Turner syndrome and short children born SGA and found a trend towards improved response to GH in the first year of treatment among subjects with one or two copies of the d3-*GHR* isoform (fig. 1).

Despite the inconsistency of these preliminary observations, they introduced the important concept that common variation in genes regulating the GH/IGF-I axis may play a role in predicting response to GH therapy. They might include functional variation in the GH receptor, the *IGF-I* gene, the IGF-I receptor and the IGF-I postreceptor signalling mechanisms. There are precedents for this concept. Studies of knockout animals and rare genetic mutations in humans suggest that subtle variation at any of these sites could affect GH response [19]. Furthermore, the growth prediction models derived from KIGS suggest that birth weight may be an important indicator of response to GH in subjects with GHD and that body weight at the start of treatment is a significant predictor of response in subjects with GHD, Turner syndrome and children born SGA [3]. Insulin plays a pivotal role in the regulation of the GH/IGF-I axis [20], and variation in  $\beta$ -cell function and insulin-receptor signalling could significantly influence GH response. Variation in putative satiety genes that regulate weight gain could also have an effect on statural growth and, thus, potentially on GH response. Children with MC4 receptor deficiency exhibit reduced satiety, hyperphagia, increased weight gain and increased height gain during infancy [21]. There is also a spectrum of response relating to whether genetic defects are partial or complete. Thus, the pool of potential candidate genes that could have an effect on GH response is already very large. The recent finding of the *FTO* gene that affects weight gain during childhood [22] suggests there will be other genes involved in as-yet unidentified physiological pathways that could impact the growth response.

### The KIGS Genetic Project

A study group within KIGS is using the database to carry out a pilot study of the effects of common genetic polymorphisms on GH response. A total of 1,000 children with either isolated GHD or multiple pituitary hormone deficiencies will be selected from the KIGS data-

**Fig. 1.** Individual deviations from the growth prediction for the first year of high-dose recombinant human GH therapy according to the model of Ranke et al. [9, 10]. This model incorporates the factors of GH dose, age and weight at start of therapy as well as gender-adjusted midparental height for SGA subjects or the distance to midparental height (for Turner syndrome subjects). Positive Studentized residuals indicate growth that exceeded the prediction and negative values indicate less growth than predicted. A Studentized residual of +1.0 is equivalent to 1.26 cm more growth in Turner syndrome and 1.30 cm more growth in short SGA children compared with the predicted values. Each circle represents one child. No prediction was possible for three subjects because midparental height was unknown. In both Turner syndrome and SGA, height velocity of carriers of the d3-*GHR* allele exceeded the predicted mean. (Reprinted with permission from Binder et al. [18].)



base and recruited for study if all variables are available for first-year prediction modelling, if they remained prepubertal and if they had one visit 10–14 months from the start of treatment. For practical reasons, they will be recruited from large centres from many different countries and study procedures will be kept as simple as possible. Mouthwash kits will be used to collect DNA samples, and the extracted DNA will be used for high through-put genotyping. Currently, the plan is to focus attention on nonsynonymous single-nucleotide polymorphisms (SNPs), haplotype-tagging SNPs and SNPs in the regulatory regions of 87 genes. Data analysis will be carried out by KIGS statisticians using the KIGS prediction models. Custodians of the data will be the KIGS Advisory Board and the consultants contributing to the KIGS database.

## Conclusions

Over its 20-year history, the KIGS database has been invaluable for producing robust data concerning the safety of GH therapy. It has also made a major contribution by enabling development of various prediction models. These models allow the pediatrician to determine if an individ-

ual subject is responding as expected over the first year of GH treatment in relation to the responses of the large number of subjects in the KIGS database. A good or a poor response may be explained by identifiable variables already in the prediction model. Alternatively, it may contribute to identification of one of the many other possible factors relating to nutrition or common genetic variants affecting the GH response and lead to refinements in the prediction models. KIGS provides an opportunity to explore some of these factors and improve the predictive value of the models, and, thus, their utility in determining clinical response, optimal GH dose and the long-term prospects for successful outcome of GH therapy.

## Disclosure Statement

M.E.G. has a relevant financial relationship with a commercial interest. He is an independent contractor of Lilly, Pfizer and LG Biopartners, speaking and teaching at Lilly, Genentech, Serono, Pfizer and TAP, is a member of the Advisory Committee/Review Panel of Genentech and Pfizer, and an Advisory Board member of Pfizer, Serono, Genentech, Lilly and TAP. Honoraria have been received from all of these companies. D.B.D. has a relevant financial relationship with a commercial interest. He has been speaking/teaching for Rusmed and is a Board member of Pfizer.

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