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Prediction of Response to Growth Hormone Treatment in Short Children Born Small for Gestational Age: Analysis of Data from KIGS (Pharmacia International Growth Database)

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A model was developed that allows physicians to individualize GH treatment in children born short for gestational age (SGA) who fail to show spontaneous catch-up growth. Data from children (n = 613) in a large pharmacoepidemiological survey, the KIGS (Pharmacia International Growth Database), or who had participated in clinical trials were used to develop the model. Another group of similar children (n = 68) from KIGS was used for validation. In the first year of GH treatment, the growth response correlated positively with GH dose, weight at the start of GH treatment, and midparental height SD score and negatively with age at treatment start. Using this model, 52% of the variability of the growth response could be explained, with a mean error SD of 1.3 cm. GH dose was the most important response predictor (35% of variability), followed by age at treatment start. The second year growth response was best predicted by a three-parameter model (height velocity in yr 1 of treatment, age at start of treatment, and GH dose), which accounted for 34% of the variability, with an error SD of 1.1 cm. The first year response to GH treatment was the most important predictor of the second year response, accounting for 29% of the variability. No statistically significant differences between the predicted and observed growth responses were found when the models were applied to the validation groups. In conclusion, using simple variables, we have developed a model that can be used in clinical practice to adjust the GH dose to achieve the desired growth response in patients born SGA. Furthermore, this model can be used to provide patients with a realistic expectation of treatment and may help to identify compliance problems or other underlying causes of treatment failure. (*J Clin Endocrinol Metab* 88: 125–131, 2003)

SMALL FOR GESTATIONAL age (SGA) is a working diagnostic term used to describe fetuses or newborn infants who have a lower weight and/or length than is normal (*e.g.* >10th percentile) for their gestational age in the absence of any other specific diagnosis or reason for their small stature (1).

The majority of children born SGA experience catch-up growth by 2 yr of age. In about 10%, however, catch-up growth does not occur. Without treatment, these children remain short and constitute some 20–25% of adults whose final height is below –2 SD scores (2). Although these individuals are not GH deficient, recent long-term studies have shown that treatment with recombinant human GH is successful in promoting catch-up growth (3).

Treatment with GH is effective in increasing height velocity in children with a variety of conditions resulting in short stature, although individual patient responsiveness varies. Prediction models have therefore been developed for children with idiopathic GH deficiency (4) and Turner syndrome (5) and for short children with a range of GH secretory capacities (6) as tools for optimizing GH therapy in individual patients. These prediction models enable physicians to calculate expected height velocities, to determine putative treatment modalities, to identify discrepancies between observed and predicted height velocities, and to provide the rationale for continuation or discontinuation of treatment. Most importantly, they enable a rational discussion between physicians and patients or parents based on a realistic expectation of the benefits of treatment.

The aim of the present study was to develop and validate a model with which to predict individual responsiveness to GH therapy of short children born SGA.

Subjects and Methods

Patients

The patients included in this analysis were receiving recombinant human GH (Genotropin, Pharmacia Corporation) during follow-up in

Abbreviations: MPH, Midparental height; SGA, short for gestational age.

TABLE 1. Demographic characteristics at birth and at the start of GH therapy, and the first-year response to GH treatment in children born SGA in the KIGS cohort (408 boys, 205 girls) used to analyze predictors of the first-year growth response

Variable	n	Median	10th–90th percentile	Mean	SD
Before GH treatment					
Birth weight SD score	613	−2.5	−4.0 to −1.6	−2.7	1.0
Birth length SD score	465	−2.7	−4.5 to −1.0	−2.7	1.3
Maximum GH peak (ng/ml)	613	17.0	9.1 to 36.0	20.8	13.3
MPH SD score	607	−0.9	−2.4 to 0.7	−0.9	1.2
Age (yr)	613	6.4	3.3 to 10.1	6.6	2.5
Bone age (yr)	399	4.0	2.0 to 7.7	4.6	2.2
Height SD score	613	−2.7	−4.0 to −1.9	−2.8	0.9
Weight SD score	613	−3.1	−5.4 to −1.9	−3.4	1.6
Height velocity (cm/yr)	276	4.8	3.2 to 6.7	4.9	1.5
GH dose (mg/kg · d)	613	0.04	0.02 to 0.07	0.04	0.02
First-year growth response					
Height velocity (cm/yr)	613	8.4	6.2 to 11.2	8.6	1.9
Change in height SD score	613	0.6	0.27 to 1.2	0.7	0.4

TABLE 2. Demographic characteristics at birth and at the start of GH therapy, and the first- and second-year responses to GH treatment in children born SGA in the KIGS cohort (259 boys, 126 girls) used to analyze predictors of the second-year growth response

Variable	n	Median	10th–90th percentile	Mean	SD
Before GH treatment					
Birth weight SD score	385	−2.4	−4.0 to −1.5	−2.6	1.0
Birth length SD score	295	−2.7	−4.5 to −1.0	−2.7	1.3
Maximum GH peak (ng/ml)	385	17.0	9.0 to 39.0	20.9	13.6
MPH SD score	379	−0.8	−2.3 to 0.9	−0.8	1.2
Age (yr)	385	6.1	3.3 to 9.2	6.3	2.2
Bone age (yr)	257	4.0	2.1 to 7.3	4.4	2.0
Height SD score	385	−2.7	−4.0 to −1.8	−2.8	0.9
Weight SD score	385	−3.1	−5.6 to −1.6	−3.4	1.6
Height velocity (cm/yr)	183	5.0	3.6 to 6.9	5.1	1.4
GH dose (mg/kg · d)	385	0.04	0.02 to 0.07	0.04	0.02
First-year growth response					
Height velocity (cm/yr)	385	8.4	6.7 to 11.1	8.7	1.8
Change in height SD score	385	0.6	0.3 to 1.2	0.7	0.3
Second-year growth response					
Height velocity (cm/yr)	385	6.9	5.4 to 8.9	7.0	1.4
Change in height SD score	385	0.3	0.1 to 0.6	0.3	0.2

a large pharmacoepidemiological survey, the KIGS (Pharmacia International Growth Database), or had participated in clinical trials to evaluate the safety and efficacy of Genotropin in patients born SGA (3).

Diagnosis was made according to the KIGS etiology classification list: codes 3.1 (idiopathic short stature), 3.4 (intrauterine growth retardation with persisting short stature without stigma), and 3.5 (intrauterine growth retardation with persisting short stature with minor dysmorphic stigma) (7).

Additional inclusion criteria for both the patients in KIGS and those included from the clinical trials were a birth weight for gestational age below –1.28 SD score (approximately equal to the 10th percentile) and a gestational age of at least 30 wk. Furthermore, the maximum GH response to one to three GH stimulation tests had to be over 5 μg/liter to exclude patients with additional severe GH deficiency, and the patients had to be prepubertal (mean testes volume, ≤3 ml; Tanner breast stage B1) at the onset of GH treatment and less than 12 and 10 yr of age at the end of the analyzed treatment period for boys and girls, respectively. Patients also had to be receiving 6 or 7 injections of GH per week. Those patients (accounting for 8% of the original cohort) who missed GH injections for a total of more than 14 d during the first year of treatment were not included in the analysis. Only 6 of these patients (1%) were excluded because of unscheduled breaks in treatment. These inclusion criteria resulted in an original cohort of 682 patients (448 from KIGS and 234 from clinical trials). Height measurements, recorded at intervals of 9–15 months, were used to calculate height velocity (centimeters per year).

Data were available for 613 patients (408 boys) treated for 1 yr. Of these, about 10% (n = 68; 42 boys) were randomly assigned to the validation group, as were about 10% (n = 43; 26 boys) of the 432 patients treated longitudinally for 2 yr. All patients for these validation groups were from the KIGS cohort.

Development of the prediction model

Growth responses (annualized height velocities) during the initial 2 yr of GH therapy were correlated, by multiple regression analysis, with potentially relevant variables. These variables are reported as the median and range as well as the mean ± SD.

The variables tested were 1) status at birth: sex, weight SD score, length SD score, ponderal index, mode of delivery, and Apgar score; 2) genetic background: height SD score of the mother, height SD score of the father, and midparental height (MPH) SD score; 3) treatment modality: GH dose [per kilogram of body weight and per kilogram of ideal body weight (weight for height)], frequency of GH injections, and accumulated years of GH treatment; 4) patient variables at the beginning of the treatment period: age, bone age, height SD score, weight SD score, height SD score minus MPH SD score, and the peak serum GH concentration during stimulation testing. SD scores were calculated as follows: SD score = (patient value – mean value for age- and sex-matched normal subjects) ÷ SD of the value for age- and sex-matched normal subjects. Predictive growth models based on the above variables were derived from the analysis for each of the initial 2 yr of therapy.

To be consistent with previous similar analyses (4, 5), the height standards used for normal children were those of Tanner *et al.* (8), and the weight standards were those of Freeman *et al.* (9). Birth weight for gestational age was transformed to an SD score based on the standards of Niklasson *et al.* (10). The MPH SD score was calculated as: (father's height SD score + mother's height SD score) ÷ 1.61 (8, 11). Bone ages,

calculated according to the method of Greulich and Pyle (12), were determined by the treating physician.

Statistical analysis

The prediction models were developed by means of multiple linear regression analysis fitted by least squares and the REG procedure in the SAS computer program (version 6.12, SAS Institute, Inc., Cary, NC) A hierarchy of predictive factors was derived by the all-possible regression approach, using Mallow's C(p) criterion for ordering predictive factors, as described previously (13, 14). Differences between observed and predicted height velocities were expressed in terms of Studentized residuals. The residual is calculated as the observed height velocity minus the predicted height velocity for each observation, and the Studentized residual is the residual divided by its SE.

Validation of the model

From the group of patients in KIGS originally identified for inclusion in the study, approximately 10% were randomly assigned to a validation group and were not used to construct the prediction model. The actual growth responses over 1 and 2 yr of GH treatment in this validation group were then compared with the growth responses predicted from the model.

Results

Demographic characteristics of the patients used to construct the prediction models

The characteristics at the start of GH treatment for the 613 children treated for 1 yr are given in Table 1. The corresponding data for the 385 children who were treated longitudinally for 2 yr are shown in Table 2. The children were typical for short children born SGA and started GH treatment at a mean age of 6.6 yr after failing to achieve spontaneous catch-up growth (all were ≥2 SD below the mean for height). The mean maximum GH peak during a stimulation test exceeded 9 μg/liter, indicating that these children were not GH deficient.

Mean height velocity was 8.7 and 7.0 cm/yr, corresponding to a height increment of 0.7 and 0.3 SD scores, in the first and second year of GH treatment, respectively.

TABLE 3. Regression equation variables for predicting the first-year growth response (cm/yr) to GH therapy in 613 children born SGA

	Parameter estimate	Rank	Partial R^2
Intercept (constant)	9.4		
Age at start (yr)	−0.31	2	0.11
Weight SD score at start	0.30	3	0.05
GH dose (mg/kg · d)	56.51	1	0.35
MPH SD score	0.11	4	0.01
R^2	0.52		
Error SD (cm)	1.3		

Prediction models

The variables found by multiple linear regression analysis to be predictive of the growth response over 1 and 2 yr are given in Tables 3 and 4. These also give the rank order of importance of the variables as predictors, the overall correlation coefficients of the prediction models (R^2), the contribution of each variable to R^2 (partial R^2), and the error SD of the prediction in centimeters. Two models have been constructed for the second year growth response (Table 4). Model A is based on the same four predictors as the first year model, whereas model B is a three-parameter model that includes height velocity in the previous year of treatment, age at the start of treatment, and GH dose. All single predictors were significant ($P < 0.0001$).

The equation describing the predicted height velocity (PHV) for the first year of GH therapy (from Table 3) is as follows: PHV (cm/yr) = 8.0 + [−0.31 × age at start (years)] + [0.30 × weight SD score at start] + [56.51 × GH dose (mg/kg·d)] + [0.11 × MPH SD score] ± 1.3.

Using this simple four-parameter model, 52% of the variability of the growth response could be explained, with an error SD of 1.3 cm. The dose of GH was the most important predictor of the four identified in the first year model, accounting for 35% of the variability, followed by age (11%), weight SD score (5%), and MPH SD score (1%). Height SD score was not included in the model because it was highly correlated with weight SD score ($R^2 = 0.93$; $P < 0.0001$) and was of less predictive value. The GH dose, weight SD score, and MPH SD score were positively correlated, and age was negatively correlated with the response to treatment. Thus, the greatest first year response to treatment occurs in younger children on higher doses of GH. The positive linear correlation between the GH dose and height velocity is shown in Fig. 1.

In the four-parameter, second year prediction model (model A), age at the start of treatment was the most important predictor of the second year response, followed by GH dose, weight SD score after 1 yr, and MPH SD score. This model could explain 30% of the variability in growth response, with an error SD of 1.1 cm. When height velocity in the previous year was included in a three-parameter model (model B), 34% of the variability could be explained, with an error SD of 1.1 cm. The contribution of the first year response in this model was 29% of the total variability.

TABLE 4. Regression equation variables for predicting the second-year growth response (cm/yr) to GH therapy in 385 children born SGA, using a four-parameter model (model A) and a three-parameter model (model B)

	Model A			Model B		
	Parameter estimate	Rank	Partial R^2	Parameter estimate	Rank	Partial R^2
Intercept (constant)	8.0			4.7		
Age at start (yr)	−0.20	1	0.15	−0.11	2	0.03
Weight SD score after 1 yr	0.19	3	0.06			
GH dose (mg/kg · d)	27.48	2	0.09	13.46	3	0.02
MPH SD score	0.16	4	0.01			
Height velocity in first year (cm/yr)				0.30	1	0.29
R^2	0.30			0.34		
Error SD (cm)	1.1			1.1		

Validation of prediction models

The children used to validate the prediction models were not used in model development, but were taken at random from the original KIGS cohort. The demographic characteristics of the model and validation groups were therefore similar (Tables 5 and 6). There were no statistically significant differences between the predicted and observed growth responses for the validation groups in either the first or second year models. This was demonstrated by the fact that the Studentized residual values are not significantly different from zero (Tables 5 and 6).

A plot of Studentized residuals (see *Subjects and Methods*) *vs.* the predicted response for the cohort used to develop the first year response model is shown in Fig. 2A. Studentized residual plots are used to identify outliers, nonlinearity, and nonconstant error variance in prediction models and are a part of their mathematical validation. The random distribution indicates that there is no heterogeneity in the group with respect to the relative importance of the different predictors.

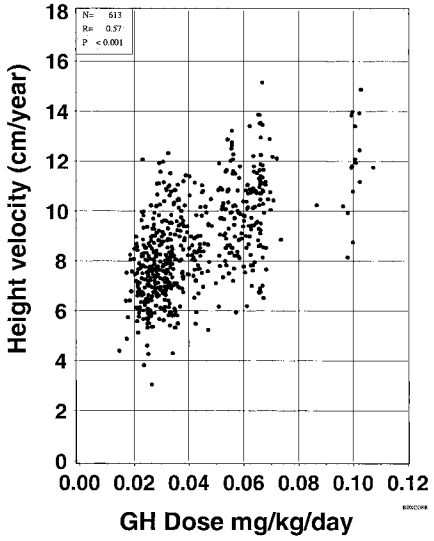

FIG. 1. Linear correlation between height velocity during the first year of GH treatment and the dose of GH in 613 children born SGA ($R = 0.57$; $P < 0.001$).

Importantly, the corresponding plot of the KIGS cohort used to validate the model shows a similar random distribution of values (Fig. 2B). The same concordance between the original model-generation cohorts and validation groups was found for the two second year growth response models (Fig. 3, A–D).

Discussion

The present study demonstrates how simple mathematical models can be used to predict the response to GH treatment in short patients born SGA who have not undergone spontaneous catch-up growth. Using data from a large cohort of children in KIGS, we have developed a model that fulfils the criteria required of any such model intended for routine use (Table 7). Thus, 52% of the variation in the first year response was explained by the present model. At the same time, the error SD (degree of accuracy) was only 1.3 cm. This level of predictive accuracy was based on the readily available variables of dose of GH, age, weight SD score, and MPH SD score, making the model suitable for use in clinical practice. In addition to providing an accurate prediction of treatment outcome, by including the GH dose as a variable, the model has an important role in individualizing treatment to achieve the required target height.

In the present model the growth response was linearly correlated with the GH dose over a wide dose range. This contrasts with the authors' previous prediction models for Turner syndrome (5) and idiopathic GHD (4), in which the growth response was correlated with the natural logarithm of the GH dose. This is probably due to the wider GH dose range in SGA (Fig. 1).

In the second year models, although the R^2 values (predictive power) were lower than in the first year model, explaining between 30–35% of the variation in response, the degrees of accuracy were higher. This may indicate a stabilization of the growth response after initial catch-up growth in a group of heterogeneous patients born SGA due to various causes. Similar trends in R^2 and error SD values after the first year of treatment have also been found in previous prediction models for children with idiopathic GHD (4) and girls with Turner syndrome (5). As with these two previous studies, height velocity during the first year of treatment in

TABLE 5. Demographic characteristics at birth and at the start of GH therapy, and the first-year responses to GH treatment in children born SGA in the KIGS cohort (42 boys, 26 girls) used for validation of the first-year growth prediction model

Variable	n	Median	10th–90th percentile	Mean	SD
Before GH treatment					
Birth weight SD score	68	−2.7	−4.0 to −1.7	−2.8	0.9
Birth length SD score	51	−2.7	−3.9 to −1.0	−2.5	1.3
Maximum GH peak (ng/ml)	68	17.4	9.4 to 46.9	20.8	13.2
MPH SD score	68	−0.7	−2.2 to 1.0	−0.7	1.1
Age (yr)	68	6.6	3.2 to 10.2	6.6	2.4
Bone age (yr)	44	4.8	2.4 to 8.5	5.2	2.5
Height SD score	68	−2.4	−3.9 to −1.7	−2.7	0.9
Weight SD score	68	−3.0	−5.2 to −1.2	−3.1	1.6
Height velocity (cm/yr)	25	4.7	3.7 to 7.6	5.2	1.5
GH dose (mg/kg · d)	68	0.03	0.02 to 0.07	0.04	0.02
First-year growth response					
Height velocity (cm/yr)	68	8.2	6.1 to 11.2	8.5	2.1
Predicted height velocity (cm/yr)	68	8.4	6.9 to 10.8	8.8	1.5
Studentized residual	68	−0.2	−1.6 to 1.0	−0.2	1.0
Change in height SD score	68	0.6	0.3 to 1.2	0.7	0.4

TABLE 6. Demographic characteristics at birth and at the start of GH therapy, and the first- and second-year responses to GH treatment in children born SGA in the KIGS cohort (26 boys, 17 girls) used for validation of first- and second-year growth prediction models

Variable	n	Median	10th–90th percentile	Mean	SD
Before GH treatment					
Birth weight SD score	43	−2.4	−4.0 to −1.5	−2.6	1.0
Birth length SD score	32	−2.6	−5.1 to −0.7	−2.6	1.0
Maximum GH peak (ng/ml)	43	16.5	9.0 to 37.6	20.5	11.5
MPH SD score	43	−0.9	−1.7 to 0.4	−0.8	1.0
Age (yr)	43	5.2	3.2 to 9.7	5.8	2.5
Bone age (yr)	31	3.6	1.8 to 6.0	3.8	1.8
Height SD score	43	−2.8	−4.5 to −1.9	−3.1	1.1
Weight SD score	43	−3.5	−6.9 to −2.1	−4.0	1.8
Height velocity (cm/yr)	14	4.9	3.4 to 7.5	5.3	1.7
GH dose (mg/kg · d)	43	0.04	0.03 to 0.06	0.04	0.02
First-year growth response					
Height velocity (cm/yr)	43	8.6	7.0 to 11.4	8.8	1.8
Height SD score	43	−2.3	−3.6 to −1.1	−2.4	1.1
Change in height SD score	43	0.7	0.3 to 1.2	0.7	0.4
Second-year growth response					
Height velocity (cm/yr)	43	6.6	6.0 to 9.2	7.2	1.3
Predicted height velocity (cm/yr)[a]	43	7.1	6.1 to 8.3	7.1	0.8
Studentized residual[a]	43	0.2	−1.1 to 1.4	0.1	1.0
Predicted height velocity (cm/yr)[b]	43	7.1	6.3 to 8.2	7.1	0.8
Studentized residual[b]	43	0.1	−1.1 to 1.5	0.1	0.9
Change in height SD score	43	0.4	0.1 to 0.7	0.4	0.3

[a] Not using height velocity in previous year as a predictor (model A in Table 4).
[b] Using height velocity in previous year as a predictor (model B in Table 4).

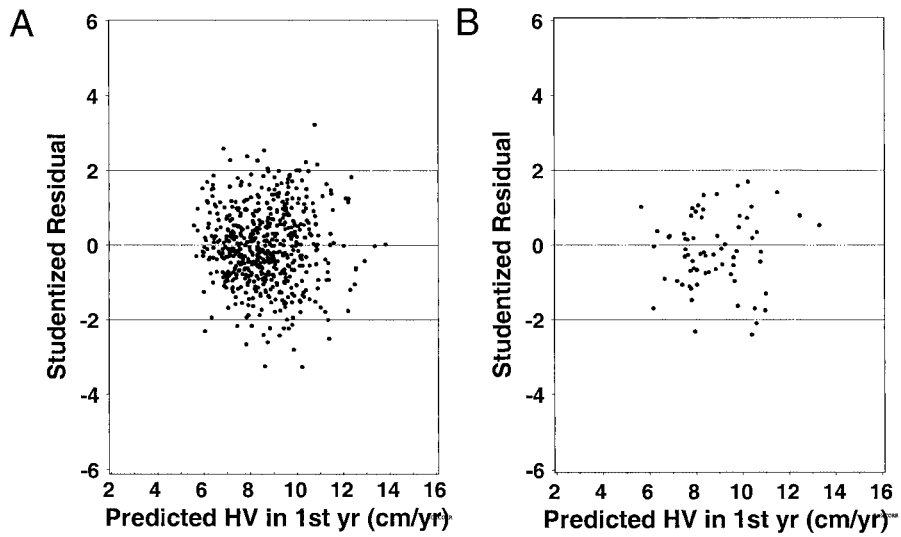

FIG. 2. Studentized residuals *vs.* predicted height velocity in the first year of GH treatment in children born SGA for the cohort used to develop the prediction model (A) and the validation group (B).

the present model was the most important predictor of subsequent growth, suggesting that the final height outcome may be indicated by the initial response to GH.

In the only previous prediction model for children born SGA (n = 135) from KIGS with different inclusion criteria, several variables were used that did not feature in the present model (15). These included birth weight SD score, number of GH injections per week, and target height SD score minus height SD score, contributing to a predictive power of 23% and an error SD of 1.6 cm. In the present model, birth weight SD score was not found to be a predictive variable, nor was target height SD score minus height SD score. With regard to birth weight SD score, this is probably because one of the inclusion criteria in the present study was a gestational age at birth of at least 30 wk , thereby reducing the variability of birth weights and excluding cases with less certain gestational ages. The frequency of injections is also no longer predictive, as GH treatment is now standardized at six or seven injections per week. MPH SD score and weight SD score in the present model mirror, to a certain extent, target height SD score minus height SD score.

In the present study the prediction model was validated using random samples of patients from KIGS. The lack of a significant difference between the predicted and actual growth responses in these groups supports the validity of the prediction equations.

It is clear that simple, robust, and accurate prediction models, which enable treatment to be tailored to an individual patient's requirements, will become increasingly important in the era of evidence-based medicine. The present study shows how the dose of GH can be calculated and adjusted to obtain the optimum balance between efficacy and

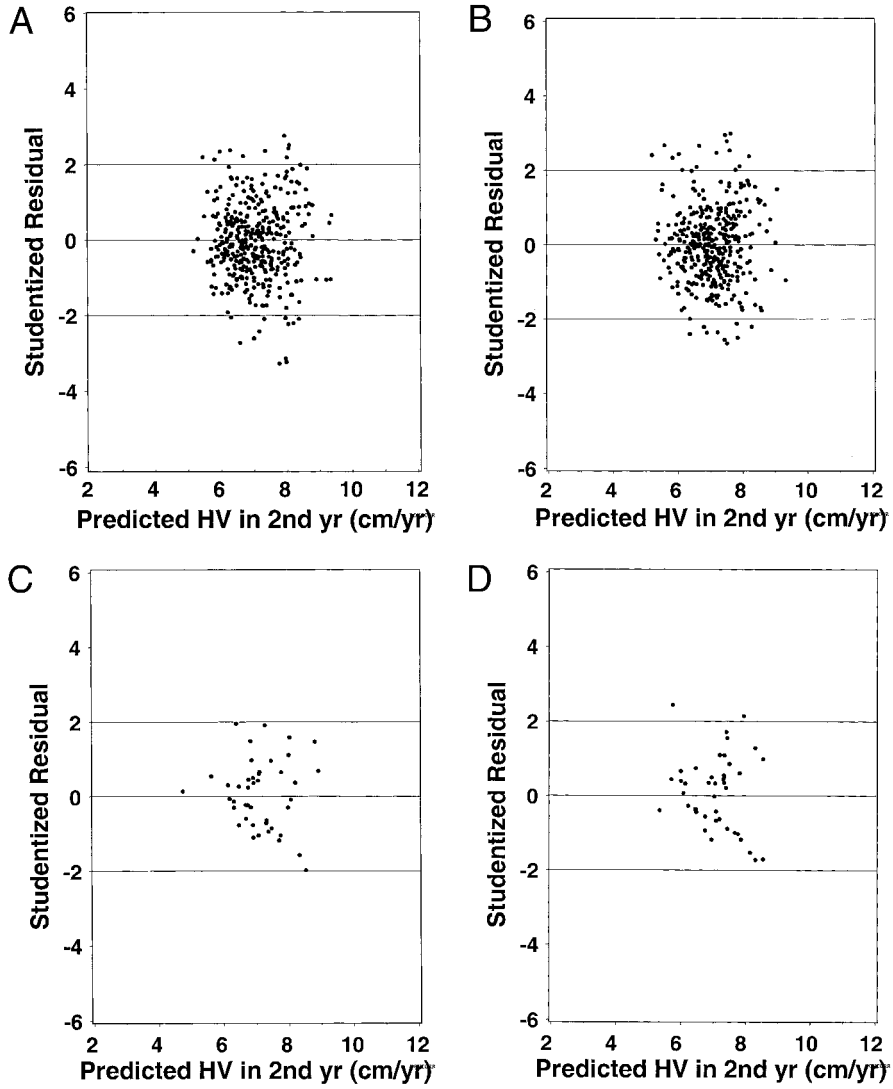

FIG. 3. Studentized residuals *vs.* predicted height velocity in the second year of GH treatment in children born SGA. The plots are for the cohort used to develop the prediction models without (A) and with (B) height velocity in the first year of treatment as a predictor and corresponding plots (C and D) for the validation group.

TABLE 7. Requirements for clinically relevant prediction models

An ideal prediction model should:
• Explain as much as possible of the variability in treatment response in an exactly defined group of patients
• Have a small prediction error
• Be validated using an independent cohort of the same group of patients
• Be based on readily available and standardized variables
• Include treatment modalities as variables
• Be based on biological principles
• Be easy to use in clinical practice

cost of treatment. This may have implications beyond the normalization of stature, as intrauterine growth retardation is thought to produce a permanent resetting of normal development (16) and is possibly predictive of a range of conditions in later life, including hypertension, coronary heart disease, stroke, and type 2 diabetes (17, 18). It is currently not known whether GH treatment, whether effective or not in terms of growth promotion, will ameliorate any of the long-term sequelae of intrauterine growth retardation.

In conclusion, we have developed an accurate model that can be used in normal clinical practice to predict the response to GH treatment in individual short patients born SGA. Such a model could provide the basis for a rational discussion between the treating physician and the patient and/or guardian concerning the expectation of treatment. In addition, it would alert physicians to differences between predicted and expected outcomes and may help to identify compliance problems or other underlying causes of treatment failure. Most importantly, this model will assist physicians in tailoring GH therapy to individual patients.

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