A National Study of Physician Recommendations to Initiate and Discontinue Growth Hormone for Short Stature

WHAT'S KNOWN ON THIS SUBJECT: Almost 500 000 US children are potential candidates for GH therapy. Overall use of GH for ISS depends on physician decisions to both initiate and continue treatment. However, the determinants of both critical decisions are not known.

WHAT THIS STUDY ADDS: This is the first study to examine physician recommendations for both initiation and continuation of a treatment. The data underscore powerful nonphysiologic influences (including physician attitudes and previous decisions, and family preferences) that underlie variation in decisions and drive GH use.

abstract

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OBJECTIVES: Overall growth hormone (GH) use depends on decisions to both initiate treatment and continue treatment. The determinants of both are unclear. We studied how physicians decided to begin GH in idiopathic short stature and how, after an initial course of treatment, they decided to continue, intensify (increase the dose), or terminate treatment.

METHODS: We used a national census study of 727 pediatric endocrinologists involving a structured questionnaires with a factorial experimental design. Main outcome measures were GH recommendations for previously untreated children and those children who were treated with GH for 1 year.

RESULTS: The response rate was 90%. In previously untreated children, recommendations to initiate GH were consistent with guidelines and also influenced by family preferences and physician attitudes ($P <$ .001). In children treated with GH, recommendations on whether to continue GH were influenced by the growth response to therapy ($P <$ .01) but were divided regarding course of action. With identical growth responses to treatment, physician decisions diverged (intensify versus discontinue GH) and were driven by independent, nonphysiologic, and contextual factors (eg, physician attitudes, family preferences, and GH-initiation recommendation; each $P <$ .001). Together, attitudinal and contextual factors exerted more influence on continuation decisions than did the growth response to therapy.

CONCLUSIONS: Physician decisions to initiate GH are largely consistent with evidence-based medicine. However, decisions about continuing GH vary and are strongly influenced by factors other than response to treatment. With a potential market of 500 000 US children and costs exceeding $10 billion per year, changes in GH use may depend on potentially modifiable physician attitudes and family preferences as much as physiologic evidence. *Pediatrics* 2010;126:468–476

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KEY WORDS

growth hormone, children, physician decision-making, short stature, medication use

ABBREVIATIONS

GH—growth hormone
ISS—idiopathic short stature
FDA—Food and Drug Administration
PAH—predicted adult height

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Physicians influence the overall use of pharmaceuticals through initiation decisions on the basis of patient assessments and, subsequently, decisions to continue unchanged, intensify, or discontinue medication contingent on the patient's response to treatment. This sequential initiation and continuation process determines drug use and costs. Yet, the factors that influence initiation are only partially understood, and the determinants of continuation decisions are unknown.

Growth hormone (GH) decisions for short stature of unknown cause (idiopathic short stature [ISS]) provide an opportunity to understand the dynamics of this sequential process for an expensive drug with observable patient response (growth), a single decision-maker (pediatric endocrinologist) and definitive patient preferences (family wishes). Although the US Food and Drug Administration (FDA) has provided guidelines for GH treatment initiation,[1,2] guidelines for continuation decisions are less clear, and controversies about the goals and assessment of treatment persist. GH is managed almost exclusively by pediatric endocrinologists for children largely referred by primary care pediatricians.[3] GH use is growing, with >500 000 potential US children with ISS and the corresponding market potential exceeding $10 billion per year.[3–6] GH is an example of the fastest growing class of pharmaceuticals: expensive biological specialty drugs, many with controversial indications and unclear end points for treating chronic conditions.[6–10]

This study addresses current gaps in the literature by systematically investigating endocrinologists' recommendations for GH treatment of ISS, and assesses (1) the relative influence of guidelines, patient preferences, and physician beliefs on recommendations to initiate GH, and (2) the determinants of physician decisions to continue GH unchanged, intensify GH (increase mg/kg dose), or terminate GH in children after a course of treatment, including the roles of treatment response, family wishes, pretreatment factors, attitudes, and contextual factors.

METHODS

Design

A structured, experimentally designed questionnaire was developed on the basis of the literature, interviews with 10 pediatric endocrinologists in 5 states, FDA guidelines, and pretesting. The results of interviews and the literature suggested that, for GH initiation in children with ISS, endocrinologists consider the child's height, growth velocity (eg, paralleling or deviating from the growth curve), predicted adult height (PAH) based on the child's height and bone age,[11,12] and family preferences.[13,14] FDA guidelines for GH initiation are based primarily on the child's height, with consideration of projected growth.[1,2] Although there is no FDA guidance for follow-up decisions, traditional recommendations in the literature indicate that a child's growth response to 6 to 12 months of GH serve as the basis for subsequent decisions. An increment in growth velocity of ≥2 to 3 cm/year above baseline is suggested an adequate response to 6 to 12 months of GH.[15–20] Increments of ≤2[15,17] or 3[20] cm/year have been suggested inadequate, as have growth velocities lower than −1 SD for children treated with GH (increments of <2–2.5 cm/year for 10-year-olds).[21] Both the physician interviews and traditional recommendations suggest that GH be discontinued for inadequate response to treatment[15,17] although an article raised the possibility of increasing the GH dose.[20] Use of insulin-like growth factor 1 levels as a primary guide to GH dosing is controversial.[22,23] The literature on physician decision-making in general suggests potential roles for patient gender, age, treatment price, insurance, family preferences, and physician characteristics in treatment decisions.[24–27]

The resulting questionnaire experimentally varied cases on the basis of the identified influential experimental and controlled variables (Fig 1). Initiation decisions were assessed by presenting each endocrinologist with 4 cases, with factors experimentally varied (1) within physicians (child's baseline height, PAH, GH price, and family preferences) in a balanced 2^4 factorial block design, and (^{2}) across physicians (growth velocity and child gender) in a 2 × 2 factorial design. All factors had 2 levels carefully chosen to bracket the appropriate decision space. A height of 2.25 SDs below the mean is the FDA eligibility threshold for GH treatment of ISS[1,2]; thus, the child's baseline height was designated as either 2 or 3 SDs below the mean. Similarly, levels for PAH were set at 2 or 3 SDs below the mean. Growth velocity, corresponding with growth patterns parallel or "deviating from" the growth curve, was −1 or −3 SDs (also presented to physicians as cm/year). The family was specified as either wanting treatment or neutral. The price of GH was $22 000 (current) or ~60% less ($9000), reflecting market entry of new competitors and/or generics.[28,29] Endocrinologists were randomly assigned cases. For each case, endocrinologists indicated their likelihood of initiating GH at a dose consistent with their usual practice on a 5-point scale that ranged from "very unlikely" to "very likely."

Respondents also were asked for follow-up treatment decisions in each case after the child received 1 year of GH (initiated by themselves or other physicians). For each case, they were given follow-up scenarios in a 2 × 2 full factorial design with differing

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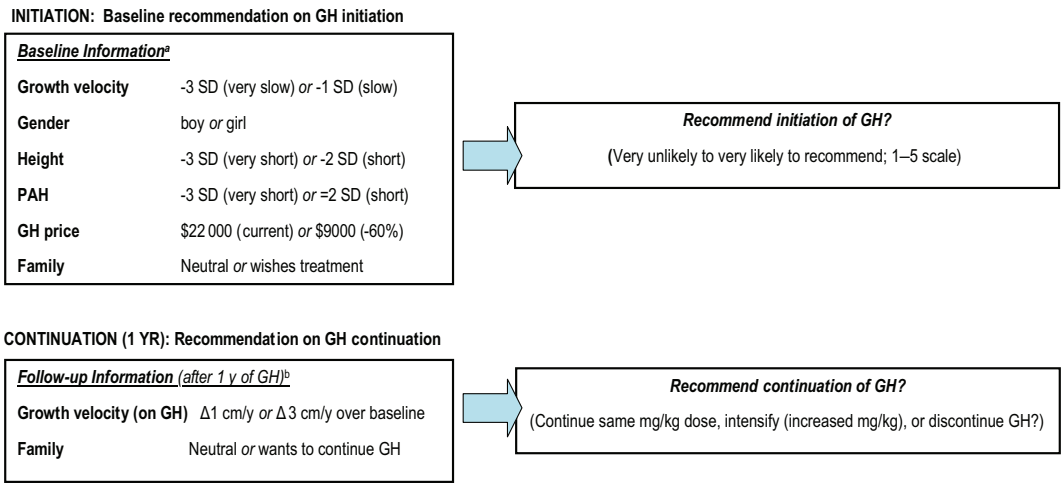

FIGURE 1

Decision task: physician recommendations for initiating GH at baseline and continuing GH at follow-up. [a] Child was described as 10 years old and followed by the physician for short stature for 2 years. The child was well with no other medical problems. Past medical history was unremarkable, with normal birth weight and length. Review of systems was negative. Results of all laboratory studies were normal, including GH (peak: 15 ng/mL), insulin-like growth factor I (IGF-I), and IGF-BP3 levels, complete blood count, chemistry, and all other tests the physician ordered. The bone age was somewhat delayed to somewhat advanced, as reflected in the PAH. The child was prepubertal with weight at the 3rd to 5th percentile, and the physical examination was normal. The mother's height was −2 SDs and the father's height was −1 SD, which, together, suggest the diagnosis of ISS. [b] After 1 year of GH treatment (started by the respondent or another physician in doses standard for the practice), the child's growth velocity increased by 1 or 3 cm/year over baseline. The family now wishes to continue GH or is neutral about continuing GH. The child remains well and prepubertal, IGF-I and IGF-BP3 levels are normal for age, bone age has advanced 1 year, the price of GH is unchanged, and the family is adherent to treatment.

growth velocity (+3 or +1 cm/year over baseline, representing growth responses of more or less successful trials, respectively[15–21]) and family preferences (neutral or wish to continue GH), with other variables held constant. For each case, endocrinologists were asked whether they would recommend continuing the GH dose unchanged (same mg/kg), intensifying it (increased mg/kg), or discontinuing it. Each endocrinologist evaluated 16 cases (ie, 4 initiation cases with 4 follow-up scenarios each).

The questionnaire also included sections that measured physician beliefs about short stature, attitudes about practice, and demographics using well-established procedures,[30] and pretested to ensure clarity, interest, realism, and application to practice.

Sample

The questionnaire was mailed to all eligible US members of the Pediatric Endocrine Society (a major professional society for pediatric endocrinologists) and the endocrine section of the American Academy of Pediatrics, to capture the highest possible number of US pediatric endocrinologists. Eligibility criteria were that the doctor is board-eligible or certified in pediatric endocrinology and is currently practicing pediatric endocrinology. Exclusion criteria were trainee status, industry or government employment, retirement, unverifiable contact information, or participation in survey development. The final sample consisted of a census of 727 eligible US pediatric endocrinologists. Those who had not managed short stature within 5 years were asked to return the questionnaire uncompleted.

Analyses

First, the determinants of endocrinologists' recommendations for GH initiation were analyzed by using a random-parameters regression model,[31] and the dependent variable was the likelihood of GH initiation. Independent variables were experimental (child's height, PAH, growth velocity, gender, family preferences, and GH price) and measured (physician beliefs about stature, attitudes about practice, and demographic factors). This model was used to account for the nested structure of the data and to estimate appropriately across- and within-endocrinologist effects based on a maximum-likelihood method.[31]

Second, independent determinants of endocrinologists' continuation decisions (whether to continue GH unchanged, intensify GH, or discontinue GH) were analyzed with a random-parameters logit model to jointly account for the nested structure of the data and the dichotomous dependent variable (ie, yes-or-no decision).[31] Variables included those varying within endocrinologists (baseline height, PAH, family preferences, price, posttreatment follow-up growth velocity, and family preferences) and across endocrinologists (child's gender and baseline growth velocity), physician at-

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titudes, and demographic characteristics, and an instrumental variable (orthogonal to the predictors of initiation recommendation to avoid bias) that represented the strength of the GH initiation decision at baseline.[31]

RESULTS

The response rate was 90% ($n = 656$), suggesting highly representative data. More than 96% reported that the cases reflected prescribing decisions made in practice. Respondents were 46.5% female, had practiced for 17.6 ± 0.5 years primarily (87.1%) in medical school or university settings, and in large (52.5%) or small (43.5%) metropolitan areas.

Physician Beliefs About Short Stature and Attitudes About Practice

More than 25% of respondents believed that the emotional well-being of children and adults with heights below the third percentile is often or always impaired, and >50% believed that it is sometimes impaired (Tables 1). More than 28% believed that GH positively impacts children with ISS, even if there is no major gain in adult height. Respondents overwhelmingly reported using the results of individual patient-specific trials of GH as a basis for follow-up decisions (88% somewhat or fully agree). However, fewer reported having actually ended GH when ineffective (31% never or seldom vs 22% often or always).

Recommendations to Initiate GH

GH-initiation decisions are shown in Fig 2. At one extreme (top bar), for the very short child with very low PAH, very slow growth velocity (all −3 SDs), and a family wishing treatment, almost all physicians (93%) initiated GH ("likely" or "very likely" to initiate). On the other extreme (bottom bar), 74% would not initiate GH ("unlikely" or "very unlikely") for the child when growth parameters were less impaired (PAH and

TABLE 1 Physician Beliefs About Short Stature and Attitudes About Practice

	Never, %	Seldom, %	Sometimes, %	Often, %	Always, %	1-to-5 Scale, Mean (SE)
Beliefs about short stature						
How often does height impair emotional well-being						
If children are in the <3rd percentile?	—	13.7	57.9	27.1	1.3	3.15 (0.03)
If adults are in the <3rd percentile?	—	19.9	54.1	23.8	2.2	3.08 (0.03)
	Very Unlikely, %	Unlikely, %	Unsure, %	Likely, %	Very Likely, %	Mean (SE)
How likely is GH to have a positive impact on emotional well-being of children with ISS even if it does not have a major impact on adult height?	6.7	30.8	34.4	25.5	2.6	2.86 (0.04)
	≤2.5 cm (≤1.0 in), %	2.5–5.1 cm (1.1–2.0 in), %	5.2–7.6 cm (2.1–3.0 in), %	7.7–10.2 cm (3.1–4.0 in), %	>10.2 cm (>4.0 in), %	Mean (SE)
How much gain in adult height would you expect in a prepubertal 10-y-old with ISS treated with 0.24–0.35 mg/kg GH weekly?	3.9	46.0	43.4	6.0	0.7	2.54 (0.03)
	Disagree, %	Somewhat Disagree, %	Neutral, %	Somewhat Agree, %	Agree, %	1-to-5 Scale, Mean (SE)
Attitudes regarding practice style in GH management						
I generally consider trying GH in children with ISS who are very short, and base subsequent decisions on the results.	2.0	3.6	6.0	38.7	49.7	4.31 (0.04)
GH treatment for children with ISS is unlikely to have long-term health risks.	3.1	13.1	15.8	38.3	29.7	3.78 (0.05)
Drug companies provide useful information about growth problems and growth treatments.	8.4	22.5	29.0	35.2	4.9	3.06 (0.04)
	Never, %	Seldom, %	Sometimes, %	Often, %	Always, %	Mean (SE)
How often have you ended GH treatment for a child with ISS after 1–2 y because it was not effective enough?	6.70	24.00	47.50	18.50	3.30	2.88 (0.04)

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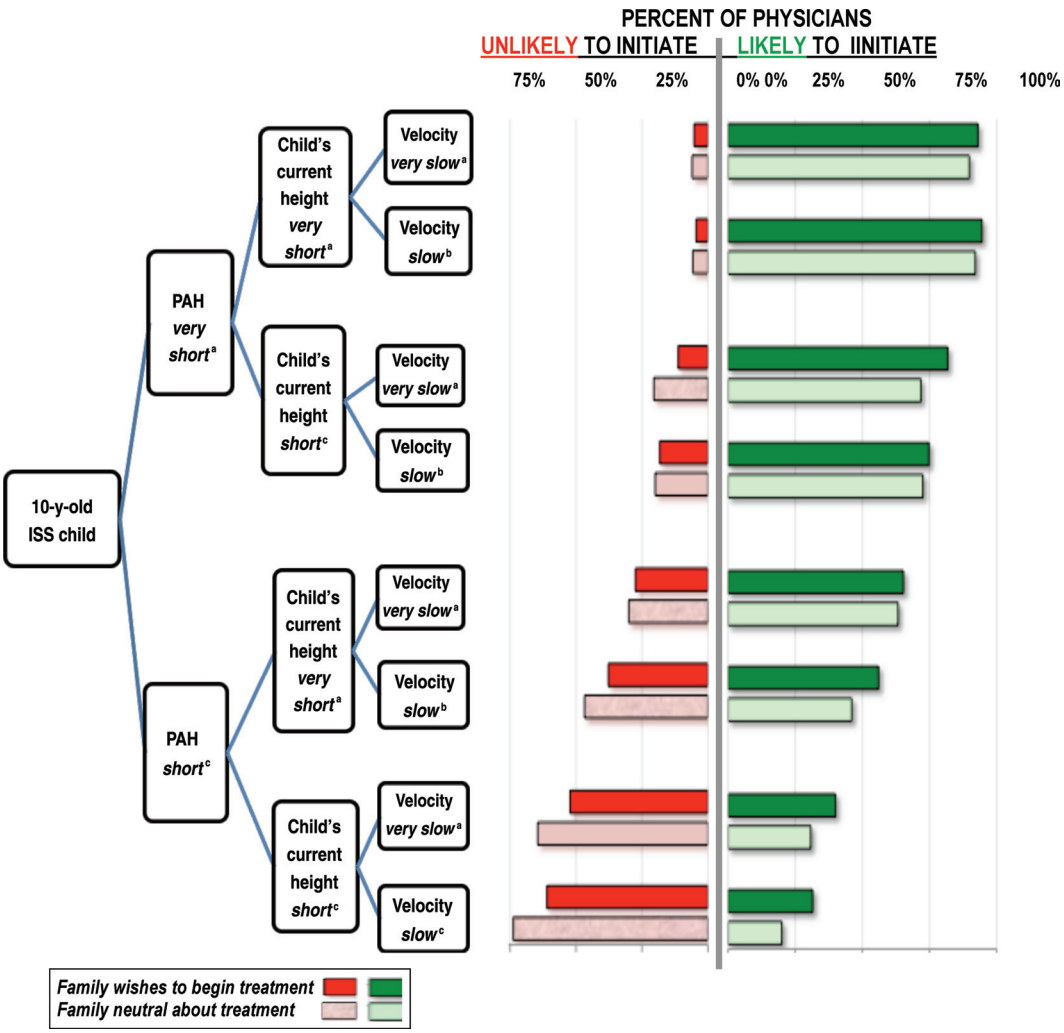

FIGURE 2

Physician recommendations on initiating GH for children with ISS. Very short: 3 SDs below the mean; short: 2 SDs below the mean; very slow: 3 SDs below the mean; slow: 2 SDs below the mean. For cases in which the family wanted GH, the red and dark-green bars indicate the percentage of physicians who were unlikely ("unlikely" or "very unlikely") and likely ("likely" or "very likely"), respectively, to recommend GH. For cases in which the family was neutral about GH, the pink and light-green bars indicate the percentage of physicians who were unlikely ("unlikely" or "very unlikely") and likely ("likely" or "very likely"), respectively, to recommend GH. [a] −3 SDs below the mean; [b] −1 SD below the mean; [c] −2 SDs below the mean.

current height −2 SDs, growth velocity −1 SD) and the family was neutral about treatment.

The independent contribution of each factor to physicians' recommendations to initiate GH is shown by regression coefficients in Table 2 ("initiation of GH"). The most important determinant was PAH, followed by baseline height and growth velocity (each $P < .001$); lower levels of each independently increased physicians' decisions to initiate GH. Family preference had almost as strong an influence as growth velocity; physicians were more likely to initiate GH if the family wanted treatment rather than if the family was neutral ($P < .001$).

In addition, physicians who believed that shortness impacts emotional well-being were more likely to initiate GH ($P < .001$), as were those who considered its risks low ($P < .001$). Physicians who believed in individualized trials of GH were more likely to initiate treatment ($P < .001$), as were those who believed drug companies provide useful information on growth ($P < .001$). GH initiation was higher for boys and when the GH price was lower. Physicians' demographic characteristics had little impact.

Recommendations on Whether to Continue Unchanged, Intensify, or Terminate GH

Overall, physicians demonstrated a preference for continuation (47.3% of cases) and intensification (36.7%) versus discontinuing GH (16%). In the cases where growth response to GH was low (+1 cm/year above baseline), physicians recommended intensifying

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TABLE 2 Independent Influences on Physician GH Treatment Recommendations: Multivariate Analysis

Variables	Initiation of GH,Recommend GH (1–5)		Continuation of GH			
			Discontinue GH (0,1)		Increase GH Dose (0,1)	
	Coefficient	SE	Coefficient	SE	Coefficient	SE
Impact of baseline pretreatment factors (year 0)						
Child's height: short (0), very short (1)	0.749	0.012[a]	−0.695	0.066[a]	0.575	0.059[a]
Child's growth velocity: slow (0), very slow (1)	0.251	0.014[a]	−0.089	0.065[b]	0.636	0.051[a]
Child's predicted adult height: short (0), very short (1)	1.334	0.011[a]	−1.210	0.073[a]	0.947	0.054[a]
Family treatment preference: neutral (0), wishes treatment (1)	0.231	0.011[a]	−0.247	0.079[c]	0.064	0.073[b]
Impact of physician recommendation to initiate GH						
Strength of GH recommendation (instrumental variable: mean, 0; variable, 1)	—	—	−0.619	0.048[a]	0.535	0.045[a]
Impact of follow-up formation (after 1 y of GH)						
Child's growth velocity: Δ3 cm/y (0), Δ1 cm/y (1) over baseline	—	—	2.403	0.089[a]	2.911	0.084[a]
Family treatment preference: neutral regarding GH treatment (0), wishes to continue GH treatment (1)	—	—	−1.567	0.082[a]	0.909	0.071[a]
Interaction: follow-up growth velocity × follow-up family preference	—	—	0.042	0.154[b]	0.693	0.145[a]
Impact of other factors						
Physician's beliefs about short stature (5-point scale)						
How often does height impair emotional well-being?						
If the child is in the <3rd percentile in height	0.036	0.015[d]	−0.171	0.067[c]	0.488	0.055[a]
If the adult is in the <3rd percentile in height	0.192	0.013[a]	−0.594	0.064[a]	0.561	0.050[a]
Likelihood that GH has a positive impact on the emotional well-being of the child	0.137	0.009[a]	−0.308	0.042[a]	0.409	0.034[a]
Likely gain in adult height at 0.24–0.35 mg of GH (kg/wk)	0.067	0.010[a]	0.025	0.047[b]	−0.079	0.038[d]
Physician's attitudes about practice (5-point scale)						
I consider a trial of GH for children with ISS who are very short	0.282	0.009[a]	−0.262	0.040[a]	0.164	0.032[a]
GH treatment for children with ISS is unlikely to have long-term health risks	0.141	0.007[a]	−0.122	0.030[a]	0.182	0.026[a]
Drug companies give useful information regarding growth problems and treatments	0.038	0.007[a]	−0.108	0.034[c]	0.034	0.027[b]
I have ended GH treatment if not effective after 1 to 2 y	0.022	0.008[c]	0.351	0.039[a]	−0.319	0.031[a]
Physician demographics						
Gender: male (0), female (1)	0.024	0.015[b]	−0.475	0.070[a]	−0.231	0.056[a]
Age, y	0.0003	0.001[b]	0.006	0.003[b]	−0.005	0.002[d]
Standardized height in SDs (mean: 0; SD: 1)	0.022	0.015[b]	−0.021	0.072[b]	0.003	0.055[b]
Hours/week of direct patient care	0.005	0.001[a]	0.001	0.003[b]	−0.009	0.002[a]
Gender and price						
Child's gender: girl (0), boy (1)	0.118	0.015[a]	0.133	0.068[d]	−0.141	0.054[c]
Price of growth hormone: current (0), 60% lower (1)	0.132	0.010[a]	−0.190	0.081[d]	0.118	0.073[b]

[a] $P < .001$.
[b] Nonsignificant coefficient.
[c] $P < .01$.
[d] $P < .05$.

the GH dose in 60.3% of cases, whereas they recommended discontinuing GH in 26% and no change in GH in 13.8% of cases. The data in Table 2 offer insights into these recommendations.

Growth velocity in response to GH had by far the largest impact on both increasing dose (coefficient: 2.911, $P < .001$) and discontinuing GH (coefficient: 2.403, $P < .001$), with a lower growth rate enhancing both the likelihood of increasing dose and discontinuing treatment. Poor results stimulated change in treatment, but the path was bifurcated and influenced strongly by factors other than physiologic response to treatment. For example, if the family wished to continue treatment (versus neutral), physicians were far more likely to intensify (0.909, $P < .001$) and less likely to end GH (−1.567, $P < .001$), all else being equal. The combination of family preference to continue GH and a low growth response to treatment was particularly powerful in increasing dose (interaction effect: 0.693, $P < .001$). Moreover, physicians with stronger recommendations to initiate GH at baseline were more likely to intensify GH (0.535, $P < .001$) and less likely to discontinue (−0.619, $P < .001$) than were other physicians, regardless of the child's response to treatment.

The factors present at GH initiation continued to significantly influence continuation decisions independent of the child's response to treatment. For example, physicians were more likely to recommend discontinuing GH at follow-up if the child's baseline (pretreatment) PAH was only moderately

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short (−2 SDs; coefficient: −1.210, $P < .001$) and more likely to recommend increasing the GH dose if the baseline PAH was very short (−3 SDs; coefficient: 0.947, $P < .001$). The effect of pretreatment predicted height on follow-up decisions was similar in magnitude to its influence on initiation decisions. Likewise, other pretreatment factors (child's height, growth velocity, and family preference) continued to significantly influence follow-up decisions independent of changes in these variables and independent of the child's response to treatment.

Physicians' beliefs and attitudes also were powerful influences on continuation decisions. Concerns about emotional well-being and belief in the use of individualized GH trials independently increased the likelihood of intensifying GH and reduced the likelihood of discontinuing GH ($P < .001$). Those who reported having ended GH if it was not effective were more likely to discontinue (0.351, $P < .001$) and about growth were less likely to increase the dose (−0.319, $P < .001$). Those who believed that drug companies provide useful information were less likely to discontinue GH ($P < .001$). Female physicians were less likely than male physicians to recommend a change (increase dose or terminate GH; $P < .001$). Lower GH price reduced the likelihood of discontinuing treatment.

The combined impact (the sum of absolute value of coefficients) of baseline factors, strength of initial recommendation, and contextual/attitudinal factors exceeded the influence of the child's actual response to GH (growth rate and family wishes after treatment) on decisions to discontinue GH (5.49 vs 3.97) and to intensify GH (5.14 vs 3.82).

DISCUSSION

This is the first study, to our knowledge, to examine physician recommendations for the continuation of GH or any other ongoing medication. Evidence-based medicine (using scientific studies/guidelines and incorporating patient preferences, reflecting response to treatment[32,33]), together with respondents' self-reported statements, suggest that the results of patient-specific trials of medications such as GH should be a primary basis for continuation decisions.[34,35] However, the results reveal divergence in recommendations on whether to intensify, discontinue, or continue GH unchanged for children with identical physiologic characteristics, which suggests differences among physicians' interpretation of treatment response and/or significant influence by factors distinct from response to treatment.

Three-quarters of the physicians continued or increased GH in the face of poor growth responses to standard doses. Yet, the stated purpose of "therapeutic trials" of GH by 88% of respondents was to determine the need for long-term treatment.[15–20] Of course, trials may be to test GH dose rather than the need for GH itself.[36] However, the fact that poorer growth response increased the likelihood of both increasing and ending treatment makes this explanation less plausible, and underscores significant variation among physicians even after controlling for patients' clinical characteristics.

On the other hand, recommendations to initiate GH were generally consistent with the Institute of Medicine's[33] recommended evidence-based approach that uses scientifically derived guidelines and patient preferences.[32,33] Growth parameters along with family preferences dominated other factors, with practice style ("consider a trial"), perceived risk, perceived behavioral impact, and price playing lesser roles.

The seeming difference in the centrality of classic evidence (relevant physiologic characteristics and patient preferences) between recommendations to initiate GH and recommendations on whether to continue GH is unexplained. The particularly strong role of factors other than response to GH in decisions to intensify or discontinue GH may reflect lack of clear guidance from the FDA or professional groups, as well as uncertainty about appropriate management for inadequate growth response.

Physicians' recommendations on whether to intensify or discontinue GH were strongly and independently affected by baseline pretreatment factors (eg, height and predicted height) that do not themselves indicate whether the actual treatment was effective. This is particularly striking because their influence persisted even after new evidence on growth response and family preference was known. This suggests that physicians may continue to be influenced by perceived disability associated with short stature, rather than guided primarily by evidence of the child's response to treatment, an interpretation consistent with the significant influence of physician attitudes on follow-up decisions. Another possible explanation is that physicians might share known bias found in other fields based on the starting point for a decision process; in this case, baseline characteristics.[37–40] Experimental psychology and management studies demonstrate that the initial situation often provides an anchor from which incremental revisions are made,[41–45] and the anchor casts excessive influence on subsequent decisions. In this case, pretreatment factors may serve as the anchor, unduly influencing the ensuing adjustment (ie, change in treatment) relative to the influence of new information provided by follow-up growth velocity and family wishes.

The way a decision is framed has major influence on what course is subse-

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quently chosen by consumers and patients.[38,40] The current data suggest this applies to physicians' decisions as well, in this case contributing to the large impact of the initial commitment to GH treatment on continuation decisions. Those with strong initiation recommendations were more likely to intensify the dose subsequently, whereas weaker initiation recommendations were more likely to lead to discontinuation, controlling for the child's growth parameters. With a strong initial commitment to GH initiation, a relatively poor growth response could suggest an insufficient dose. However, if the initial recommendation for GH was more equivocal, the same poor result might be seen as confirmation of initial hesitation to treat. The same response to treatment results in different decisions depending on the initial commitment to treatment.

Physicians' beliefs about short stature and attitudes about practice also strongly influenced their choices among divergent approaches (intensify versus discontinue GH). Beliefs and attitudes, together with persistent influence of baseline factors and strength of commitment to GH initiation, had more influence on these decisions than did the actual growth response to treatment.

Overall, in continuation decisions for GH, the use of evidence regarding the response to treatment is tempered by other factors that produced a tendency to favor intensifying rather than discontinuing treatment.

There are limitations to this study, including the use of case scenarios and potential response bias. However, the cases were based on real situations derived from discussions and pretests with physicians, and respondents agreed that they reflected their practice. In addition, the response rate to this national census study was high. Taken together, we believe within reason that the results can be generalized. Although results are always contingent on variables selected, those studied captured endocrinologists' bases for GH decisions as assessed by extensive pretesting and were confirmed by respondents' agreement.

If applicable to other conditions, the findings have profound implications for our understanding of medication management, especially for chronic conditions treated with drugs that have unclear therapeutic end points, such as many emerging biologicals. Even when guidelines and patient preferences appropriately serve as the primary determinants of medication initiation, evidence-based care may break down as therapy progresses. Commitment to initial decisions and persistent influence of pretreatment factors may contribute to growing pharmaceutical use and cost and are difficult to change. The attitudes of both physicians and families also significantly influence continuation decisions; these may be modified by many forces, potentially driving drug use up or down.

The implications of these results for policy and practice are substantial. At a minimum, the results underscore the need for more emphasis and guidance on criteria for discontinuing GH and perhaps other similar medications. The high likelihood of intensification calls for careful evaluation of higher doses. Comparative-effectiveness analyses may be needed not only across alternative treatments, but also across each treatment's life cycle. Otherwise, we may have little chance to optimize treatment and manage the explosion of the costs of pharmaceuticals.

REFERENCES

1. US Food and Drug Administration. Approval letter for application number NDA 19-640/S-033: Humatrope; July 25, 2003. Available at: www.accessdata.fda.gov/drugsatfda_docs/appletter/2003/19640se1-033ltr.pdf. Accessed July 26, 2010
2. Cuttler L, Silvers JB. Growth hormone treatment for idiopathic short stature: implications for practice and policy. *Arch Pediatr Adolesc Med*. 2004;158(2):108–110
3. Cuttler L, Marinova D, Mercer MB, Connors A, Meehan R, Silvers JB. Patient, physician, and consumer drivers: referrals for short stature and access to specialty drugs. *Med Care*. 2009;47(8):858–865
4. Finkelstein BS, Imperiale TF, Speroff T, Marrero U, Radcliffe DJ, Cuttler L. Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. *Arch Pediatr Adolesc Med*. 2002;156(3):230–240
5. Lee JM, Davis MM, Clark SJ, Hofer TP, Kemper AR. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *Arch Pediatr Adolesc Med*. 2006;160(3):263–269
6. Kelly CJ, Mir FA. Economics of biological therapies. *BMJ*. 2009;339:b3276
7. Goldman DP, Joyce GF, Lawless G, Crown WH, Willey V. Benefit design and specialty drug use. *Health Aff (Millwood)*. 2006;25(5):1319–1331
8. Golenski JD. Specialist discretion for managing specialty pharmaceuticals: the ethics argument for discretion. *Am J Manag Care*. 2004;10(suppl 8):S240–S241
9. Lee TH, Emanuel EJ. Tier 4 drugs and the fraying of the social compact. *N Engl J Med*. 2008;359(4):333–335
10. Mullins CD, DeVries AR, Hsu VD, Meng F, Palumbo FB. Variability and growth in spending for outpatient specialty pharmaceuticals. *Health Aff (Millwood)*. 2005;24(4):1117–1127
11. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. *J Pediatr*. 1952;40(4):423–441
12. Greulich W, Pyle S. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. 2nd ed. Palo Alto, CA: Stanford University Press; 1959
13. Cuttler L, Silvers JB, Singh J, et al. Short stature and growth hormone therapy: a national study of physician recommendation patterns. *JAMA*. 1996;276(7):531–537

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14. Wyatt DT, Mark D, Slyper A. Survey of growth hormone treatment practices by 251 pediatric endocrinologists. *J Clin Endocrinol Metab*. 1995;80(11):3292–3297
15. Alter C. Growth hormone for idiopathic short stature: whether and when to treat. *Endocrine News*. 2006;October:12–15
16. Bercu BB. The growing conundrum; growth hormone treatment of the nongrowth hormone-deficient child. *JAMA*. 1996;276(7):567–568
17. Frasier SD. An attempt at synthesis. *J Clin Endocrinol Metab*. 1994;79(5):1246–1248
18. Lee MM. Idiopathic short stature. *N Engl J Med*. 2006;354(24):2576–2582
19. Underwood LE. Growth hormone therapy for short stature: yes or no? *Hosp Pract (Off Ed)*. 1992;27(4):192–196, 198
20. Cohen P, Rogol AD, Deal CL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab*. 2008;93(11):4210–4217
21. Bakker B, Frane J, Anhalt H, Lippe B, Rosenfeld RG. Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. *J Clin Endocrinol Metab*. 2008; 93(2):352–357
22. Cohen P, Rogol AD, Howard CP, et al. Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. *J Clin Endocrinol Metab*. 2007;92(7):2480–2486
23. Baron J. Growth hormone therapy in childhood: titration versus weight-based dosing? *J Clin Endocrinol Metab*. 2007;92(7):2436–2438
24. André M, Hedin K, Hakansson A, Molstad S, Rodhe N, Petersson C. More physician consultations and antibiotic prescriptions in families with high concern about infectious illness: adequate response to infection-prone child or self-fulfilling prophecy? *Fam Pract*. 2007;24(4):302–307
25. Epstein AM, Read JL, Winickoff R. Physician beliefs, attitudes, and prescribing behavior for anti-inflammatory drugs. *Am J Med*. 1984;77(2):313–318
26. Feldman HA, McKinlay JB, Potter DA, et al. Nonmedical influences on medical decision making: an experimental technique using videotapes, factorial design, and survey sampling. *Health Serv Res*. 1997;32(3): 343–366
27. Yu SM, Bellamy HA, Kogan MD, Dunbar JL, Schwalberg RH, Schuster MA. Factors that influence receipt of recommended preventive pediatric health and dental care. *Pediatrics*. 2002;110(6). Available at: www.pediatrics.org/cgi/content/full/110/6/e73
28. Ferrándiz JM. The impact of generic goods in the pharmaceutical industry. *Health Econ*. 1999;8(7):599–612
29. Saha A, Grabowski H, Birnbaum H, Greenberg P, Bizan O. Generic competition in the US pharmaceutical industry. *Int J Econ Bus*. 2006;13:15–38
30. Dillman DA. *Mail and Internet Surveys: The Tailored Design Method*. 2nd ed. Hoboken, NJ: John Wiley and Sons; 2006
31. Greene WH. *Econometric Analysis*. 6th ed: Upper Saddle River, NJ: Prentice Hall; 2008
32. Bergeson SC, Dean JD. A systems approach to patient-centered care. *JAMA*. 2006; 296(23):2848–2851
33. Institute of Medicine Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press; 2001
34. Miser WF. An introduction to evidence-based medicine. *Prim Care*. 2006;33(4):811–829
35. Institute of Medicine. *The Learning Healthcare System: Workshop Summary*. Olsen L, Aisner D, McGinnis JM, eds. Washington, DC: National Academies Press; 2007
36. Cohen P, Bright GM, Rogol AD, Kappelgaard AM, Rosenfeld RG. Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: implications for efficacy and safety. *J Clin Endocrinol Metab*. 2002;87(1):90–98
37. Harvey N. Use of heuristics: insights from forecasting research. *Think Reason*. 2007; 13:5–24
38. Kahneman D, Tversky A. Prospect theory: an analysis of decision under risk. *Econometrica*. 1979;47(2):263–291
39. Montgomery H. The psychology of economic forecasting: a possibility for cooperation between judgment and decision making and naturalistic decision-making theories? In: Montgomery H, Brehmer, B, eds. *How Professionals Make Decisions*. Mahwah, NJ: Lawrence Erlbaum; 2005: 119–122
40. Tversky A, Kahneman D. The framing of decisions and the psychology of choice. *Science*. 1981;211(4481):453–458
41. Epley N, Gilovich T. The anchoring-and-adjustment heuristic: why the adjustments are insufficient. *Psychol Sci*. 2006;17(4): 311–318
42. Hammond JS, Keeney RL, Raiffa H. The hidden traps in decision making. *Harv Bus Rev*. 1998;76(5):47–48, 50, 52 passim
43. Knecht S, Reinholz J, Kenning P. The spread of obesity in a social network. *N Engl J Med*. 2007;357(18):1866–1867; author reply 1867–1868
44. Senay I, Kaphingst KA. Anchoring-and-adjustment bias in communication of disease risk. *Med Decis Making*. 2009;29(2): 193–201
45. Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. *Science*. 1974;185(4157):1124–1131

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