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.

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abstract

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

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.
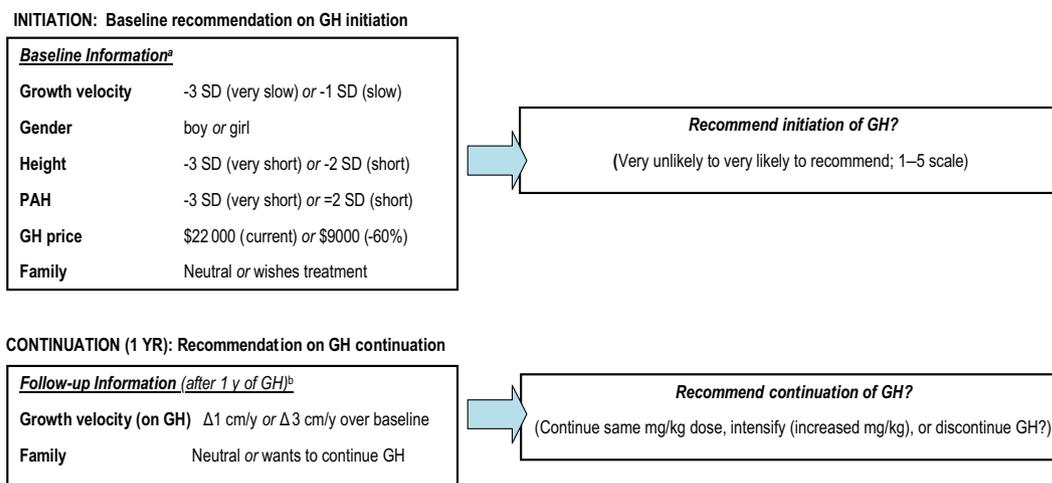
METHODS

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 contro-

versial.[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

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-

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)
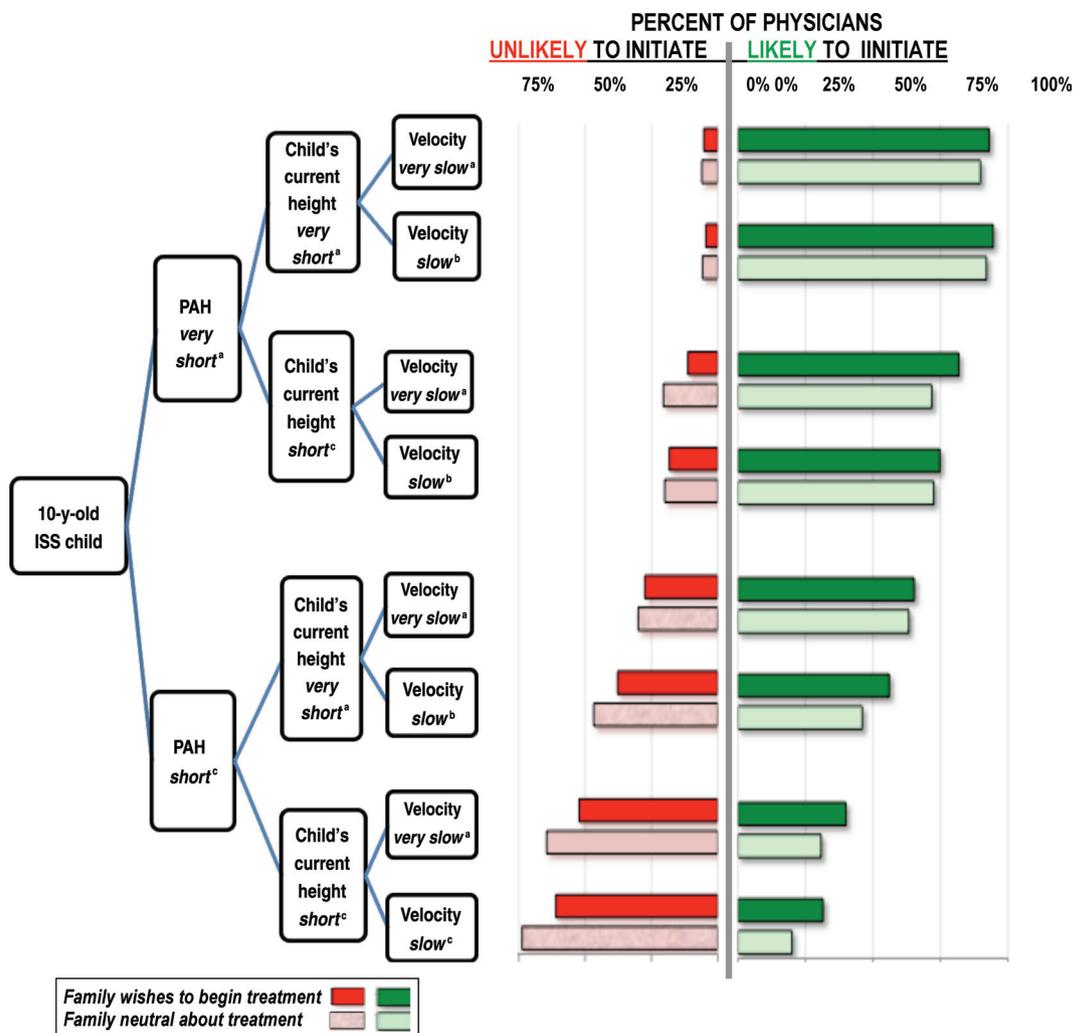
FIGURE 2
Physician recommendations on initiating GH for children with ISS. Very short: 3 SDs below the mean; short: 2 SDs below the mean; very slow: 3 SDs below the mean; slow: 2 SDs below the mean. For cases in which the family wanted GH, the red and dark-green bars indicate the percentage of physicians 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

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

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 recommen-

dations 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 physi-

ologic 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-

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 deci-

sions 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.

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Pediatrics originally published online August 30, 2010;

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