Physician Decisions to Discontinue Long-Term Medications Using a Two-Stage Framework

The Case of Growth Hormone Therapy

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Background: Physician decisions to discontinue prescription medications for chronic conditions are fundamental determinants of drug use but have been inadequately studied. The decision to stop growth hormone (GH) therapy is an important example because of high cost (approximately $26,000/y for a 48-kg child), complexity of treatment options, and expansion of patient populations.

Aim: The aim of this study was to identify the factors that influence physician recommendations in the process of discontinuing therapy.

Design: A random sample of half of U.S. pediatric endocrinologists (n = 265) was mailed a survey that included case scenarios of GH-deficient adolescents. Decision options involved a 2-stage framework to 1) initiate change in ongoing GH therapy (by discussing discontinuing GH with the family but not yet stopping treatment), and 2) take action to discontinue ongoing GH therapy (by terminating GH or reducing the dose to adult maintenance level).

Main Outcome Measure: Physician recommendations.

Results: The response rate was 83.8%. Physiological indices of growth potential (growth velocity, bone age) significantly influenced discontinuation decisions (both $P < 0.001$). However, family preference, child's height, and physician attitudes exerted independent effects (each $P < 0.05$). Treatment price had little influence. Together, these variables accounted for 60% to 70% of the variation in recommendations. Their relative influence differed by stage in the discontinuation process.

Conclusion: The variables in our framework substantially explain discontinuation decisions. The data demonstrate the importance of both physiological and nonphysiological factors. The results suggest that physicians value even small gains as final height approaches, although an additional 20% expenditure may be needed to gain the last 1% to 3% of adult height.

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Most previous studies of physician decisions about prescription medicines have focused on recommendations to initiate therapy[1–6] with little attention to the issue of decisions to discontinue medications. Yet, physician recommendations to discontinue medications are fundamental determinants of overall prescription drug utilization and costs, the most influential driver of national healthcare inflation.[7] Chronic medical conditions[8,9] are the fastest growing segment of health disorders, accounting for over three fourths of U.S. health expenditures and 88% of prescription medications filled.[9] Decisions to stop chronic drug treatments are especially critical for medications with clear *initial* indications but unclear *termination* criteria and those that primarily address quality rather than quantity of life.

The literature in psychology and management has addressed decisions that involve some form of discontinuation (eg, changing service, downgrading, or demarketing). This literature suggests that discontinuation decisions involve a process with multiple stages of increasing withdrawal.[10–13] Although it is likely that discontinuation of medical treatments would similarly involve a process of multiple interrelated decisions, these phenomena have not been systematically studied. This article focuses on physician decisions to discontinue growth hormone (GH) therapy as one such process.

GH therapy is well suited to the study of discontinuation decisions.[14–18] Concern about GH use and its impact on U.S. children is widespread.[19–23] Approximately 1 of 3500 U.S. children has classic GH deficiency.[24] Controversies in diagnostic criteria, together with recent changes in U.S. Food and Drug Administration (FDA) guidelines for GH use, have expanded the population of potential GH recipients and make 400,000 to 900,000 U.S. children potentially eligible for GH at annual costs exceeding $8 billion.[25]

Most previous work on GH has focused on identifying appropriate candidates to begin treatment.[20,21,26] Yet, overall GH utilization and cost will be determined by decisions about when to stop therapy, because these define the duration of

treatment. Moreover, 3 aspects of GH treatment of GH deficiency are particularly relevant for the study of discontinuation decisions: 1) *high cost* ($26,000 or more per year for a 48-kg GH-deficient child,[27,28] typically multiyear treatment often accumulating to well over $100,000 per patient[29]), 2) *professional uncertainty* (unclear criteria and procedures for stopping treatment or defining attainment of adult height[14,15,17,19,21,30]), and 3) *complexity* (multiple options, including low-dose GH treatment to promote metabolic functions even after cessation of growth as an alternative to complete termination of treatment[15,29,31,32]). As applications for GH therapy expand under recent FDA policy,[33] discontinuation decisions will be increasingly important. This study was designed to address the following specific questions: What physiological, attitudinal, and demographic factors influence physician recommendations in the process of discontinuing GH treatment? Is there consensus among expert physicians concerning these transition decisions? Do the influences on decisions differ according to the stage of the discontinuation process?

METHODS

A Conceptual Framework for Physician Recommendations to Discontinue Long-Term Growth Hormone Treatment

Many long-term treatments show efficacy followed by declining effectiveness, which may signal the need to consider changes in the treatment regimen (eg, oral agents for diabetes, GH). For a GH-deficient child, GH therapy would usually have begun primarily to treat/prevent functional and psychosocial consequences of severe growth stunting and, sometimes, to treat hypoglycemia. A GH-deficient child who has received GH for several years typically shows gradual tapering of growth during mid to late adolescence, signaling decreasing potential for growth. Figure 1 depicts a conceptual framework for physician decisions regarding discontinuation of long-term medications, adapted from the literature in psychology and management and applied to the clinical setting of GH therapy. The framework involves 2 thresholds for discontinuation decisions that usually occur sequentially. The first decision threshold involves choosing between continuing growth-promoting efforts unchanged or *initiating change* in the ongoing regimen (eg, by discussing a change or considering alternative treatment options). The second threshold involves *taking action*—either recommending termination of GH or modifying the regimen by reducing the GH dose to levels that promote metabolic function but not linear growth. Factors that potentially influence these decisions are noted in Figure 1; although these variables have been influential in physician decisions to initiate some medications[2,5,6,34–36] (including GH[26]), their role in decisions to end drug therapy is not known.

Survey Design and Development

To identify factors that expert physicians use in GH discontinuation decisions for inclusion in a national survey instrument, we first conducted interviews with 15 pediatric endocrinologists experienced in GH use practicing in 5 geographically dispersed states and located in either academic hospital/university (73%) or private practice (27%). The interviews indicated that pediatric endocrinologists' thinking about GH and prescribing behavior was consistent with Figure 1.

Guided by our initial interviews, we developed a structured questionnaire administered as a national mail survey[37] to collect data on GH discontinuation decisions. The questionnaire included a decision task that presented cases using the key factors identified in our interviews, permitted modeling disparate decision choices and multiple determinants, and ex-

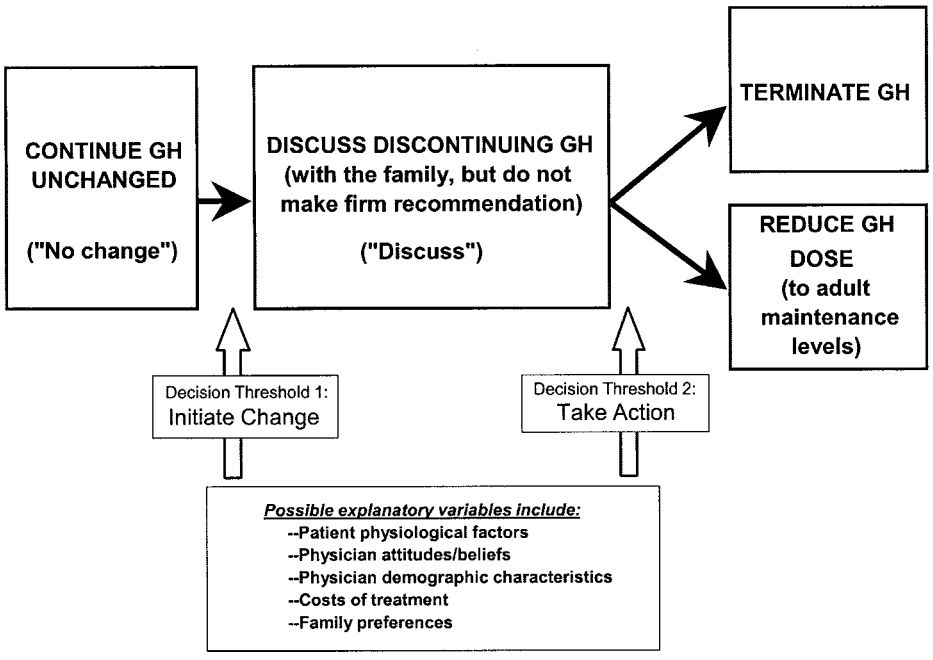


FIGURE 1. A two-stage framework for physician decisions to discontinue ongoing medications (applied to growth hormone therapy).

perimentally manipulated pertinent variables in a full fractional design.[3,26,35,38] Specifically, the cases involved GH-deficient adolescent boys, treated with GH, who were approaching the end of growth to varying degrees. Physiological potential for growth is indicated by the bone age, which assesses maturation of the growth plates (epiphyses) and the growth velocity. The ability of GH to promote growth ends when the growth plates fuse, a process accompanied by slowing of the growth rate. The cases differed experimentally (±1–2 standard deviations [SDs]) according to physiological characteristics (current height, growth velocity, bone age) as well as treatment price and family preferences (Table 1; Fig. 2A). The patient was described in sufficient detail to control for other potentially confounding variables (Table 1). For each case, the physician was asked to choose 1 of 4 possible decisions: 1) continue GH unchanged ("no change"); 2) discuss possible discontinuation of GH with the family but without a firm recommendation to do so ("discuss"); 3) recommend terminating GH completely ("terminate"); or 4) recommend reducing the dose of GH to adult maintenance levels (directly, after GH retesting, or by referral to an adult endocrinologist; "reduce").

The questionnaire also included sections to measure physician attitudes regarding height and GH, the importance of various factors in their GH decisions, and ratings of the degree to which the cases presented matched their experience (all using Likert scales) as well as physicians' demographic characteristics. The questionnaire was pretested to ensure clarity, interest, feasibility of completion, realism of cases, and applicability to practice.

Sampling and Field Procedures

Pediatric endocrinologists are the primary prescribers of GH for children,[18,19] and therefore constituted the target group of expert physicians. To obtain a large, nationally representative sample, we identified all members of the major professional organization of U.S. pediatric endocrinologists—the Lawson Wilkins Pediatric Endocrine Society—and crosschecked this list with the endocrine section of the American Academy of Pediatrics. Pharmaceutical/governmental employees, physicians residing outside the United States or with unconfirmed addresses, and physicians involved in survey development were excluded, resulting in a total of 529 eligible participants nationally. Using a table of randomly generated numbers, we selected 50% of all eligible physicians (n = 265) for study. Anonymity was assured and 2 waves of mailings were sent to secure high participation. The protocol was approved by the Institutional Review Board.

Statistical Analysis

The main outcome variables were physician recommendations for the case scenarios. Additional variables of interest were physician attitudes and demographic/practice characteristics. All analyses were conducted using the Stata statistical software package (version 8).

To determine whether decisions to discontinue GH generally involve a stepwise process with distinct decision thresholds (like in Fig. 1), we initially modeled the physicians' treatment decisions as an ordinal dependent variable with 3 categories: continue GH therapy unchanged, discuss discontinuing growth-promoting dose of GH, or discontinue growth-promoting efforts (by reducing dose or by terminating GH). We used a generalized linear latent and mixed model to

TABLE 1. Decision Task: Case Description and Variable Specification

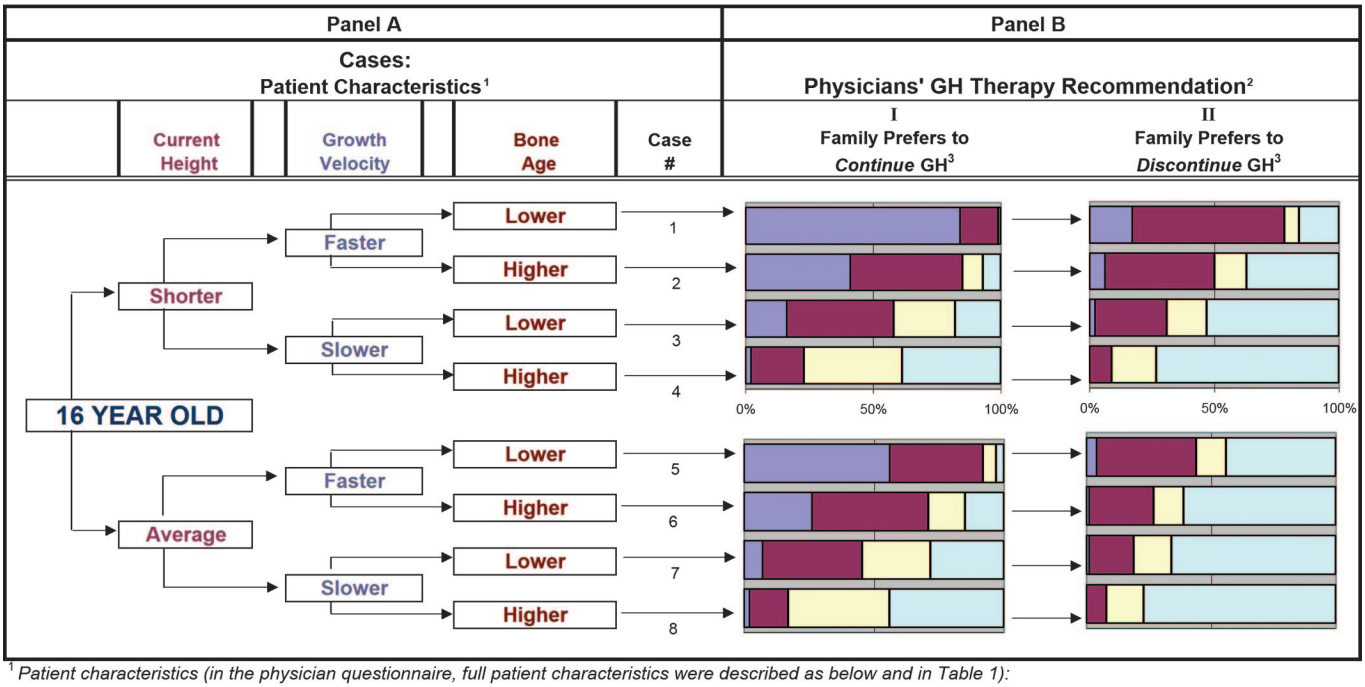
Case Description (identifies variables held constant):

A 16-year-old boy with growth hormone (GH) deficiency returns for follow up. He was diagnosed with classic GH deficiency at age 10 yr after presenting with short stature (height 3 standard deviations [SDs] below the mean) and a growth rate of 3.2 cm/yr. Investigations at that time showed peak GH <5 ng/mL, low IGF-I and IGF-binding protein 3 levels, delayed bone age, and all other tests normal. He was begun on GH therapy in standard doses[15,18,36] and followed by you since. Initially, he had a good growth response to GH but growth has tapered in the past 1 to 2 yr. His review of systems is negative and the family is adherent to therapy. The total annual cost of GH is $26,000. His mother is 5′0″ and his father 5′6″. The family is of average income with health insurance typical for your practice. The physical examination shows heights and growth velocities as specified below. The patient is pubertal. The rest of the examination is normal. The current bone ages are as described below. All other laboratory tests are normal

Decision Task Experimental Variables	Values
Patient physiological variables	
Height	Values were chosen to be the mean height for a 16-yr-old male or 2 SD below the mean (ie, average = 173.5 cm/68.3 inches and shorter = 158.8 cm/62.6 inches)
Growth velocity	Values were chosen to be 1 SD above or 1 SD below the growth rate of 2 cm/yr, which is commonly used as a reference point in defining adult height attainment (ie, faster = 3 cm/yr and slower = 1 cm/yr)[14,18,30]
Bone age	Values of bone age 18 mo (1.4 SD) apart were chosen to represent a range of remaining growth potential and to be consistent with the case and with clinical judgment as assessed in pretesting*; thus, a lower and higher bone age value 18 mo apart were used for the faster growth velocity (bone ages of 15 and 16.5 yr) and for the slower growth velocity (bone ages of 16 and 17.5 yr)†
Family preferences	Family prefers to continue or to discontinue GH
Treatment price	Price was $26,000 (base) or discounted by 85%; the price of $26,000 was calculated based on the average wholesale price ($42/mg), a dose of 0.25 mg/kg per wk consistent with standard doses of 0.2–0.3 mg/kg per wk,[15,18] and a weight of 48 kg (approximately fifth percentile for 16-yr-old boy, and consistent with published data); the alternative 85% price reduction was designed to represent a substantial price decrease, consistent with moving to a 10–15% copay, and to be comparable to previous studies of initiating GH therapy[26]

*A bone age of 15 yr suggests that 96.8% of final height has been attained, leaving 5–6 cm of growth remaining. A bone age of 17–18 yr suggests that 99% of final height has been attained, leaving under 2 cm remaining.[42,44]

†Bone ages of 16.5 and 17.5 yr were defined as "between 16 and 17 yr" and "between 17 and 18 yr," respectively.



[1] *Patient characteristics (in the physician questionnaire, full patient characteristics were described as below and in Table 1):*
Current Height: Shorter = 158.8 cm/62.6 in (-2 SD); Average = 173.5 cm/68.3 in
Growth Velocity and Bone Age: Faster = 3 cm/year (-0.3 SD), paired with bone ages of 15 years (Lower) or 16.5 years (Higher) (Δ1.4 SD)
Slower = 1 cm/yr (-2.3 SD), paired with bone ages 16 years (Lower) and 17.5 years (Higher) (Δ1.4 SD)

[2] *Physician recommendation definitions:*
No change: Continue GH unchanged (0.2-0.3 mg/kg/wk)
Discuss: Discuss discontinuing GH (i.e. discuss possibility of discontinuing GH with the family, but do not make a firm recommendation for termination of treatment)
Reduce: Reduce dose of GH to adult maintenance range (i.e. terminate growth-promoting dose and recommend adult maintenance dose of GH. This may occur after GH retesting, and may be direct or via referral to an adult endocrinologist)
Terminate: Recommend terminating GH therapy

[3] Holding the price of GH treatment constant (at $26,000 per year). Results for an 85% price reduction described in text.

FIGURE 2. Case scenarios (Panel A) and physician recommendations (Panel B) for continuation or discontinuation of ongoing growth hormone therapy.

account for dependence arising from clustering of treatment decisions within physicians.[39,40] Attitudinal variables and physician height/age were standardized (mean = 0, SD = 1) so that the estimated regression coefficients corresponding to these variables could be presented in a format consistent with those of the experimentally manipulated variables. The remaining variables were dichotomous. The independent variables were entered sequentially in blocks of similar variables, and we used a likelihood ratio test to compare nested models and an omnibus Wald test to determine whether the independent variables exerted heterogeneous effects across the 2 decision thresholds.

Thereafter, we analyzed the determinants of decisions to initiate change and take action as separate stages of the decision process. In so doing, we considered decisions to terminate GH and to reduce GH dose as distinct endpoints because 1) our interviews with the pediatric endocrinologists suggested that this was congruent with their clinical experience, and 2) our analyses of these 2 decisions showed that physicians very rarely (<5%) changed their action decisions from "reduce GH dose" to "terminate GH" or vice versa under different conditions. We fitted 3 logistic regression models to the data to identify which factors influenced physicians to choose a particular treatment decision outcome—*initiate change*, *terminate GH*, or *reduce GH dose to adult maintenance levels* (Fig. 1). Independent variables were entered sequentially in blocks of similar variables, and the likelihood ratio test was used to compare nested models. To assess model adequacy, we calculated pseudo R-squared statistics using conventional formulas[41] in addition to likelihood ratio tests.

RESULTS

In all, 222 of the 265 eligible physicians responded to the survey for a response rate of 83.8%. We excluded 25 physicians who did not use GH or were not in practice and 9 as a result of serious errors in questionnaire completion, resulting in 188 observations.

Ninety-six percent of physicians agreed that the case scenarios "included the key variables I would likely use in decisions about discontinuing GH treatment in similar cases," and 95% agreed that the decision task "accurately reflects the GH decisions I would normally make in such cases," supporting the face validity of the decision task.

Respondents were 50 ± 9 years old (mean ± SD; range, 34–70 years), 37% female, and had heights of 69.8 ±

2.9 inches (177 ± 7.4 cm) in males and 64.1 ± 3 inches (163 ± 7.4 cm) in females. Their primary practice was academic/hospital, private practice, and other in 73%, 22%, and 5%, respectively. Their practice location was large metropolitan (population over 1,000,000) in 51%, small metropolitan (50,000–1,000,000) in 46%, and rural (under 50,000) in 3%. Respondents had substantial experience; they had practiced pediatric endocrinology for 18 ± 10 years (range, 2–42 years), 80% had recommended GH within the preceding 5 years, and 63% spent over 20 hours per week in direct patient care.

Attitudes Regarding Stature and Growth Hormone Therapy

Although a strong majority (78%) believed that heights below the third percentile impair emotional well-being in children and adults (Table 2), physicians showed significant variation in evaluating the impact of GH treatment on well-being. Specifically, 43% agreed (40% disagreed) that GH can have a positive impact on emotional well-being in short children even if it does not affect adult height. Likewise, physicians were split in their evaluation that emotional well-being may be impaired by discontinuing GH after growth is complete (33% agreed; 43% disagreed) and divided regarding management of GH in GH-deficient adolescents (33% agreed that "I rarely recommend continuing GH after age 18 years"; 57% disagreed) (Table 2). Physicians' ratings of importance for factors in their discontinuation decisions were consistent with the ratings from presurvey physician interviews; on a scale from 5 (high) to 1 (low): growth velocity 4.24, bone age 4.20, child's wishes 3.43, current height 3.39, parent wishes 2.99, and treatment cost 2.58.

Descriptive Data

The first column of Figure 2, panel B shows the physicians' treatment recommendations for the base scenarios in which the family prefers to continue treatment. For cases at the extremes (eg, faster growth rate with lower bone age or slower growth rate with higher bone age, reflecting greater and lesser remaining growth potential, respectively), there was consensus in physicians' recommendations to continue growth-promoting efforts with GH (ie, case no. 1) or discontinue growth-promoting GH treatment (ie, case nos. 4 and 8). However, the other cases showed considerable variation in decisions. Beyond the base scenarios, the second column of Figure 2, panel B shows the pattern of recommendations when the family prefers discontinuation of GH. In all 8 cases, relative to base case scenarios, there was a striking shift in physician recommendations toward termination of GH, despite identical patient physiological characteristics. In addition, within the column, recommendations showed marked variation, paralleling column 1. Together, these data suggest that the scenarios used were varied enough to accommodate a broad range of physician decisions.

Analyses of Decision Thresholds

The results from the ordered logistic regression suggested clear distinction between the decisions to *initiate change* and *take action.* The full model, including all independent variables, fit well and was a substantial improvement over a naive intercept-only model (χ^2 4612.7, $df = 14$, $P < 0.001$). The estimated thresholds (intercepts of 0.750 ± 0.236 and 3.094 ± 0.222, respectively) had nonoverlapping confidence intervals, and their difference exceeded the estimated standard errors by a factor of 10. An omnibus Wald test

TABLE 2. Physician Attitudes Toward Short Stature and Growth Hormone (GH) Therapy

	Percent of Respondents Who*			Mean Score ± Standard Deviation
	Disagree†	Neutral†	Agree†	
Attitudes regarding height and GH				
In my opinion:				
… height impairs emotional well-being of				
—children with heights below the third percentile	12	11	78	5.01 ± 1.2
—adults with heights below the third percentile‡	11	12	78	4.98 ± 1.2
… compared with tall people, short people are taken less seriously in the workplace and/or have more difficulty interacting in social situations‡	20	12	68	4.65 ± 1.4
… GH can positively impact emotional well-being in short non-GH-deficient children (even if GH does not have a major impact on adult height)	40	18	43	3.85 ± 1.6
… I think emotional well-being may be impaired by discontinuing GH after linear growth is complete	43	25	33	3.65 ± 1.6
Attitudes regarding practice				
For GH-deficient children:				
… I rarely recommend continuing GH beyond 18 yr of age	57	8	33	3.62 ± 1.9
… I generally advise discontinuing growth-promoting doses of GH once an adequate adult height is reached, even if the epiphyses are not yet completely fused‡	58	5	37	3.61 ± 1.7
… I think GH should be used in adult maintenance doses after linear growth is complete	8	19	73	5.26 ± 1.3

*Totals may not equal 100% as a result of rounding.

†Summarizes results of a 7-point scale used in the questionnaire in which (1) strongly disagree, (2) disagree, and (3) somewhat disagree (1–3 combined in table); (4) neutral; (5) somewhat agree, (6) agree, and (7) strongly agree (5–7 combined in table).

‡As a result of concerns about multicollinearity, 2 attitudinal variables and 1 practice variable were not included in the multivariate analyses (shown in Table 3).

rejected the assumption of proportional odds (χ^2 194.9, $P < 0.001$), indicating that the influence of the independent variables on treatment decisions was significantly different for the 2 decision thresholds.

The fact that "discuss" discontinuation without yet making a firm recommendation to discontinue was a frequent choice (Fig. 2) provides further support for a multistage decision process. Moreover, there was clear corroborating evidence from other survey questions. Physicians reported that 7 to 12 months (median) elapsed between their first serious discussion with families about possible GH discontinuation and their final recommendation to discontinue growth-promoting efforts, suggesting that the *initiate change* and *take action* thresholds are sequential and separated by a nontrivial time interval.

Determinants of Physician Decisions

Based on this evidence regarding thresholds and our process framework, we analyzed the distinct physician decisions separately. To assess the determinants of the 3 decision outcomes (ie, *initiate change*, *reduce GH dose*, and *terminate GH*), we fit 3 separate logistic models to the data (Table 3). Likelihood ratio tests indicated that each of the full models represented a statistically significant improvement over a naive intercept-only model (χ^2 values ranging from 2311.0–4047.2; $df = 14$, all $P < 0.001$). The pseudo R^2 values for each model suggested that the physiological variables alone explained approximately one half of the variance in outcomes (46–55%). With the addition of the variables representing family preferences, price reduction, and attitudes, the pseudo R^2 values increased (60–70%).

Physiological variables, family preferences, treatment price, and physician attitudes each exerted significant effects on physician decisions. Yet, the relative contribution of these variables differed by stage of discontinuation (Table 3). In decisions to *initiate change* in ongoing therapy, growth velocity had the highest effect compared with other physiological variables (estimated coefficient, B = 4.9). The patient's height (B = 1.6) exerted approximately one third the influence of growth velocity and the bone age only about half as much influence (B = 2.6). With respect to nonphysiological variables, the effect of family preferences (B = 4.9) was similar to growth velocity and far greater than that of price (B = −0.6).

TABLE 3. Determinants of Physician Decisions

		Take Action	
	Initiate Change§ Coefficient (95% CI)	**Terminate GH¶ Coefficient (95% CI)**	**Reduce GH Dose‖ Coefficient (95% CI)**
Intercept	2.53‡ (2.04, 3.03)	7.78‡ (7.07, 8.49)	5.86‡ (5.25, 6.47)
Patient physiological variables			
Height (1 = 2 SDs taller)	1.64‡ (1.38, 1.90)	1.80‡ (1.54, 2.05)	0.82‡ (0.56, 1.07)
Growth velocity (1 = 2 SDs slower)	4.91‡ (4.51, 5.32)	4.41‡ (4.06, 4.76)	3.82‡ (3.47, 4.17)
Bone age (1 = 1.4 SDs higher)	2.55‡ (2.26, 2.84)	2.50‡ (2.23, 2.78)	1.97‡ (1.69, 2.25)
Family preference (1 = family prefers to discontinue)	4.87 (4.47, 5.27)	4.31‡ (3.96, 4.66)	0.87‡ (0.60, 1.15)
Treatment price (1 = 85% reduction)	−0.55‡ (−0.79, −0.31)	−0.34† (−0.57, −0.12)	0.03 (−0.22, 0.28)
Physician attitudinal variables*			
In my opinion, height impairs emotional well-being of children with heights below the third percentile	−0.45‡ (−0.66, −0.24)	−0.73‡ (−0.94, −0.52)	0.14 (−0.07, 0.35)
In my opinion, GH can positively impact emotional well-being in short non-GH-deficient children (even if GH does not have a major impact on adult height)	0.00 (−0.18, 0.18)	0.24† (0.07, 0.41)	−0.19† (−0.39, 0.00)
I think emotional well-being may be impaired by discontinuing GH after linear growth is complete	−0.13 (−0.41, 0.15)	−0.55† (−0.88, −0.22)	0.14 (−0.04, 0.32)
I rarely recommend continuing GH beyond 18 yr of age	0.13 (−0.09, 0.35)	0.83‡ (0.61, 1.04)	−0.03 (−0.29, 0.23)
I think GH should be used in adult maintenance doses after linear growth is complete	−0.48‡ (−0.74, −0.22)	−0.01 (−0.18, 0.16)	1.47‡ (1.18, 1.76)
Physician demographic variables			
Practice format (1 = academic center)	0.07 (−0.32, 0.46)	−0.34 (−0.78, 0.10)	−0.35 (−0.76, 0.06)
Gender (1 = male)	0.76‡ (0.36, 1.17)	0.22 (−0.17, 0.60)	0.13 (−0.22, 0.48)
Physician height* (standardized by gender)	0.22 (−0.01, 0.46)	0.00 (−0.21, 0.22)	0.15 (−0.01, 0.31)
Physician age*	−0.10 (−0.28, 0.08)	−0.36† (−0.60, −0.12)	−0.06 (−0.26, 0.14)
Pseudo R^2 for physiological variables	0.46	0.50	0.55
Pseudo R^2 for all variables	0.69	0.70	0.60

*Standardized: mean = 0, SD = 1.
†$P < 0.05$.
‡$P < 0.001$.
§Initiate change: 1 = discuss, terminate GH, reduce GH; 0 = no change.
¶Terminate GH: 1 = terminate GH; 0 = no change, discuss.
‖Reduce GH dose: 1 = reduce GH dose; 0 = no change, discuss.
GH, growth hormone; CI, confidence interval; SD, standard deviation.

For decisions to *terminate GH*, the general pattern of effects of physiological variables, family preferences, and treatment price was similar to that for decisions to *initiate change* (Table 3). Of the physiological variables, growth velocity had the dominant effect, similar in magnitude to family preferences. With a sole exception, all physician attitudes had significant influence on decisions.

Regarding decisions to *reduce GH dose* to adult maintenance levels, Table 3 shows a pattern of influence that differs considerably from decisions to *initiate change* or *terminate GH*. Height had one fifth the influence of growth velocity (B = 0.8 and 3.8, respectively). Nonphysiological variables had much less influence. Family preferences had only one fifth the influence of growth velocity (B = 0.9 and 3.8, respectively). Notably, treatment price did not affect decisions to reduce the GH dose.

There were also substantial differences in the influence of independent variables across the 3 decision outcomes. The pattern of coefficients (especially for nonphysiological factors such as family preference, treatment price, and physician attitudes) varied considerably across the 3 decision outcomes with 95% confidence intervals (CIs) that did not generally overlap. For example, family preferences had a greater effect on decisions to *initiate change* (estimated coefficient B = 4.9; 95% CI, 4.5–5.3) and *terminate* GH (95% CI, 4.0–4.7) than on decisions to *reduce* GH dose (95% CI, 0.6–1.2). Price reduction decreased the likelihood of *initiate change* (95% CI, −0.79 to −0.3) and *terminate* GH (95% CI, −0.6 to −0.1), but had no effect on decisions to *reduce* GH dose. Physicians who believed that short stature impairs emotional well-being were less likely to recommend either *initiate change* (95% CI, −0.7 to −0.2) or *terminate* GH (95% CI, −0.9 to −0.5), but this belief had no effect on decisions to *reduce* GH dose.

DISCUSSION

We found that 1) both physiological and nonphysiological variables affect physician recommendations to discontinue GH, 2) there was lack of consensus among expert physicians about when to discontinue GH, and 3) discontinuation of growth-promoting efforts is a complex decision-making process with shifting determinants at different stages. These results provide insights and raise new questions for practice and policy.

In the cases presented, the primary purpose of GH treatment is to promote growth, and GH can only exert this effect as long as the patient has physiological potential for further growth.[42] Therefore, from a strict biomedical view, one might expect indicators of remaining growth potential (bone age, growth velocity) to be the sole determinants of decisions about discontinuing GH in GH-deficient adolescents like those presented.[14,15] In fact, our data confirm that such indicators are important, but we also found that physicians' decisions were significantly affected by other factors. For example, when there is little potential for further growth, one might expect the child's current height (which does not affect further growth potential) to have little or no influence on decisions about discontinuing GH. Yet, the results indicate that, all other things being equal, physicians were less likely to discontinue growth-promoting efforts in shorter adolescents than in those of average height—even when growth potential was relatively small. This finding suggests that physicians may be motivated to continue GH to alleviate the perceived psychosocial disability of short stature, even when the prospects for significant impact are small.

Our data also show that physician decisions are strongly influenced by family preferences, particularly for decisions to *initiate change* in ongoing GH therapy and to *terminate* GH therapy. Based on the levels used, the influence of family preference was equivalent to a 2-SD decline in growth velocity. This finding is consistent with studies that emphasize the importance of family in medical decision-making.[5,6,26,43] In addition, physician recommendations were influenced by their attitudes about stature and GH. For example, physicians who believed that short stature impairs emotional well-being were less likely to initiate change in ongoing GH therapy or to terminate GH. Similarly, physicians who believed that emotional well-being may be impaired by discontinuing GH after linear growth is complete were less likely to terminate GH.

All else equal, higher prices might be expected to tip physicians' decisions toward ending growth-promoting GH therapy. However, our results offer little support for this view. Although price had a small but statistically significant effect on decisions to *initiate change* and *terminate GH*, it had no effect on decisions to *reduce GH dose*. Considering that these effects are based on an 85% decline in price, our results suggest low price elasticity. Generally, GH costs are borne by insurers and families. However, physicians are aware of GH's high cost, and prior work indicates that reducing price can influence physician decisions to begin GH for non-GH-deficient children.[26] To the extent that family preferences in practice may be influenced by GH price (thus indirectly impacting physician decisions), the effect of price on decisions may be underestimated.

The overall pattern emerging from these results is that physician recommendations regarding discontinuation of GH were influenced by a combination of physiological and nonphysiological factors, each exerting statistically significant and independent effects. There was only limited consensus on proper management based on purely physiological dimensions of the patients, allowing room for the influence of family preference and physician attitudinal factors.

There are potential limitations to this study. First, our findings are based on cross-sectional data and should be confirmed by longitudinal studies of dynamic decision processes. Because the study was designed to experimentally vary characteristics (including family preferences), it does not allow modeling of relationships among the determinants. Second, to the extent that the scenarios did not represent actual patients, they may have imposed a response structure that biased physicians' decisions, potentially not fully reflecting the reality of the prescribing process. However, over 96% of respondents judged the case scenarios to be realistic and the decision choices to be representative of those they actually made in practice. Third, because the levels of most

physiological variables were 2 SD apart, whereas others (such as physician attitudes) were standardized to one SD, we suggest caution in making direct comparisons. Fourth, although GH is an important example of chronic treatments that aim to improve quality of life, our findings for GH may not apply to other medications, particularly those addressing conditions with major impact on physiological morbidity and mortality. Fifth, despite the 83.8% response rate, caution is needed to generalize to the population of endocrinologists. Finally, we were unable to assess gender effects because the cases presented were males.

The results have several implications for practice and policy. First, our data reveal important details regarding physicians' reasoning about balancing costs and benefits of GH therapy. GH expenditures rise progressively as a child matures, because GH dosing is based on weight; however, growth slows as adolescents approach full adult height. Thus, the incremental cost increases while the incremental benefit declines. Because a 15-year-old at the third to fifth percentile for weight (42 kg) becomes a 16-year-old at the same percentile (48 kg) in our decision task, annual expenditures would rise from approximately $22,900 to $26,000 (based on the described midrange growth hormone dose). At the higher end of this range (0.3 mg/kg per week, although even higher doses have been suggested), prices would be $27,518 per year and $31,450 per year for a 42-kg and 48-kg child, respectively.[18,27,28] At this point, he would have already required aggregate expenditures of approximately $104,000 for GH (calculated based on a midrange growth hormone dose of 0.25 mg/kg per week for a child at the third to fifth weight percentile at each year of age and a conservative average wholesale price for growth hormone of $42/mg without markup[27,28]) and attained 96.8% to 99% of his adult height (based on the bone ages presented[42,44]). This leaves just 1.0% to 3.2% (1.7–5.7 cm) of height potentially to be gained by continuing GH therapy. Policymakers may question whether an increment in expenditures of approximately 25% for the next year ($26,000 ÷ $104,000) is worth the incremental 1.0% to 3.2% of benefit. The patient enjoys the potential lifetime psychosocial/societal benefits of being taller,[45,46] although costs are largely absorbed by taxpayers and the pool of insureds. The declining marginal return therefore raises questions about when to terminate growth-promoting efforts.

Our study suggests that physicians value even small remaining gains in height near the end of treatment. This may reflect the perception that there are benefits to realizing *any* remaining potential growth. Because treatment price did not contribute substantially to decisions, it may be that relatively small amounts of height gain were perceived as worth the cost. Another possible explanation is that physicians' slowness to discontinue growth-promoting efforts may reflect inertia, the tendency to resist change, a phenomenon observed in many nonmedical aspects of decision-making.[10,47]

A second implication concerns the influence of physician attitudes and family preferences on physicians' decisions about discontinuing GH. The data underscore the susceptibility of prescription drug demand and prescribing patterns to cultural, educational, and commercial forces.[18,48] These issues are likely to become even more important as GH use expands to large, new populations of short children (eg, idiopathic short stature).[22,33]

Third, the differential influence of culture on perceptions, and hence physician recommendations, may make it difficult for professional organizations to develop generally accepted practice guidelines for GH. Clarity and agreement on purely physiological criteria would likely be insufficient to reduce practice variation that stems, in part, from differences in how physicians and patients perceive the value of height.

Our findings suggest the feasibility of assessing discontinuation decisions for ongoing medications to inform practice and policy. This topic is likely to grow in importance, given the increasing impact of chronic medical conditions and the paucity of literature on decisions to change or discontinue long-term prescription medication.

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