Growth hormone treatment for growth hormone deficiency and idiopathic short stature: new guidelines shaped by the presence and absence of evidence

Adda Grimberg[a,b,c] *and David B. Allen*[d,e]

Purpose of review
The Pediatric Endocrine Society recently published new guidelines for the use of human growth hormone (hGH) and human insulin-like growth factor-I (hIGF-I) treatment for growth hormone deficiency, idiopathic short stature, and primary IGF-I deficiency in children and adolescents. This review places the new guidelines in historical contexts of the life cycle of hGH and the evolution of US health care, and highlights their future implications.

Recent findings
The new hGH guidelines, the first to be created by the Grading of Recommendations Assessment, Development and Evaluation approach, are more conservative than their predecessors. They follow an extended period of hGH therapeutic expansion at a time when US health care is pivoting toward value-based practice. There are strong supporting evidence and general agreement regarding the restoration of hormonal normalcy in children with severe deficiency of growth hormone or insulin-like growth factor-I. More complex are issues related to hGH treatment to increase growth rates and heights of otherwise healthy short children with either idiopathic short stature or 'partial' isolated idiopathic growth hormone deficiency.

Summary
The guidelines-developing process revealed fundamental questions about hGH treatment that still need evidence-based answers. Unless and until such research is performed, a more restrained hGH-prescribing approach is appropriate.

Keywords
growth hormone, growth hormone deficiency, guidelines, idiopathic short stature, insulin-like growth factor-1, value

INTRODUCTION

The advent of recombinant human growth hormone (hGH) marked a paradigm shift in pediatric endocrinology, expanding its scope beyond replacement of deficient and suppression of excess hormones to include pharmacological hormonal augmentation therapy. A remarkable era of hGH therapeutic expansion ensued, spearheaded by industry and facilitated by pediatric endocrinologists. Enthusiasm for increasing height in children who are short for reasons other than GH deficiency (GHD) arose from prior assumptions that severe short stature in children is a disabling condition requiring and deserving of treatment; hGH is well tolerated for short children without GHD, even at escalating and supraphysiologic dosages; and hGH-induced height augmentation would measurably enhance quality of life. Today, however, the validity and value of each of these assumptions are being challenged because of paucity of evidence, weakening hGH therapeutic expansion, and favoring

[a]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, [b]Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, [c]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania, [d]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health and [e]Division of Endocrinology and Diabetes, American Family Children's Hospital, Madison, Wisconsin, USA

Correspondence to Adda Grimberg, Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, 3401 Civic Center Blvd. Suite 11NW30, Philadelphia, PA 19104, USA. Tel: +1 215 590 3618; fax: +1 215 590 3053; e-mail: Grimberg@E-Mail.chop.edu

Curr Opin Pediatr 2017, 29:000–000
DOI:10.1097/MOP.0000000000000505

KEY POINTS

- Endorsed by decades of evidence worldwide, hGH treatment for children and adolescents with GHD was strongly recommended and is not controversial.
- hGH treatment of 'partial' IGHD and ISS continue to inspire debate because of philosophical disagreements and weaker supporting evidence for therapeutic benefit.
- Important evidence gaps persist related to diagnostic limitations, appropriate outcome measures, and long-term posttreatment safety of hGH therapy.
- These gaps, combined with current healthcare constraints, support a transition in the hGH life cycle from expansion to restraint.

restraint [1▪▪]. Further, defining and delivering 'high-value healthcare' [2] requires an increasingly evidence-based and honest appraisal of the benefits, risks, costs, and value of hGH treatment.

Like most biological systems, GH secretion and response spans a continuum, encompassing profound GHD to laboratory-defined 'partial' GHD to idiopathic short stature (ISS) and primary insulin-like growth factor (IGF)-I deficiency (PIGFD). Controversy is minimal and guidelines consistent regarding children with severe and permanent GHD, often associated with hypoglycemia, central nervous system malformations, or multiple pituitary hormone deficiencies; such children need to be treated, many into adulthood. More complex is the analysis of hGH treatment to increase growth rates and heights of children with 'partial' isolated idiopathic GHD (IGHD; short but otherwise healthy children with stimulated GH levels below the traditional diagnostic threshold of 10 ng/ml but not markedly low, normal MRI scans, no other pituitary hormone deficiencies, and no identifiable reason for GHD) or ISS (short, healthy children distinguished from IGHD only by higher GH testing results). These two groups comprise the majority of and most controversial hGH-treated patients, in part because the threshold test result that distinguishes normal variation from partial GHD requiring treatment has not been well established. Prior guidelines and consensus statements on the treatment of short stature not related to GHD [3,4] address interpretation of GH stimulation tests and IGF-I levels, hGH dosage, risks [5▪▪], height increasing benefits, and aspects of treatment follow-up. These guidelines do not, however, address how evidence regarding hoped-for quality-of-life improvement and other factors apart from the surrogate marker of height gain should impact clinical decision-making. This paper places the new hGH treatment guidelines from the Pediatric Endocrine Society (PES) [6▪▪] in historical contexts of the life cycle of hGH and the evolution of US health care, and highlights their future implications.

Life cycle of human growth hormone

Thirty years ago, news of Creutzfeldt–Jakob disease transmission by treatment with pituitary-derived GH stunned the pediatric endocrinology community. Serendipitously, hGH became available within months. In an environment fertile with concerns about unexpected adverse effects, the US Food and Drug Administration mandated manufacturers of hGH to establish, manage, and support postmarketing studies to monitor safety of hGH. This systemic industry physician collaboration also facilitated expansion of hGH use by spawning clinical trials – usually observational, noncontrolled, and relatively short term – and by fostering queries of the postmarketing hGH databases for escalating doses or off-label causes of inadequate growth. When favorable results from these industry sponsored studies were presented and published by key opinion leaders, education, promotion, and persuasion became intertwined to reinforce off-label prescribing and undermine prospects for long-term randomized, controlled trials. Subsequent Food and Drug Administration approval of hGH treatment for children with ISS and other non-GHD indications (Table 1) validated the notion that if hGH treatment is effective at increasing height in children without GHD, then the etiology of short stature is not relevant in deciding who is entitled to treatment [1▪▪]. Within this permissive environment, hGH treatment became a paradigm of 'expansive biotechnology' wherein a biomedical technology, originally designed for treatment of disease, expanded, with the encouragement of well intended physicians and support of industry, into treatment of conditions that blur the conceptual boundary between disease and variation. Expansive biotechnology vis-à-vis hGH also benefits from the assertion that short stature is a maladaptive condition rooted in biology, whether in genes or in faulty signaling, either hormonal or autocrine/paracrine within the growth plate, as physiological defects rather than variations or alterations [7]; this implies that use of costly hGH to overcome them is a medically necessary endeavor.

Evolving US health care

America outpaces most developed countries in healthcare spending relative to gross domestic product, yet falls short on many outcome metrics. In

Table 1. Indications for recombinant human growth hormone treatment approved by the US Food and Drug Administration

Year of FDA approval	Indication	Therapeutic goal	
		Restoration of normal growth/ Height augmentation	Metabolic, body composition, and health benefits
Pediatrics			
1985	GH deficiency	√	√[a]
1993	Chronic renal insufficiency	√	
1996	Turner syndrome	√	
2000	Prader–Willi syndrome	√	√[a]
2001	Small-for-gestational age without catch-up growth	√	
2003	Idiopathic short stature	√	
2007	*SHOX* gene haploinsufficiency	√	
2008	Noonan syndrome	√	
Adults			
1996	HIV/AIDS-associated wasting		√
1997	GH deficiency		√
2003	Short bowel syndrome and dependent on parenteral nutrition (4-week course of hGH)		√

FDA, Food and Drug Administration; GH, growth hormone; hGH, human growth hormone; SHOX, short stature homeobox.
[a]All pediatric FDA approvals were specifically for height and growth considerations, but afterwards health benefits were recognized as well for patients with GH deficiency or Prader–Willi syndrome, which is associated with a high prevalence of GH deficiency.

2001, the Institute of Medicine defined six priorities for improving quality and hence value (value = quality/cost) in redesigning the US healthcare system, namely, making health care more: safe, effective, patient-centered, timely, efficient, and equitable [8]. It further listed evidence-based decision-making as a rule to guide innovations necessary to achieve those six attributes of higher quality. Value-based reimbursement, rather than traditional fee-for-services model, was codified into law by the Medicare Access and Children's Health Insurance Program Reauthorization Act of 2015 [9].

Aligned with the growing emphasis on evidence-based decision-making, new strategies for developing clinical practice guidelines have incorporated systematic analysis and transparent reporting of the quantity and quality of the supporting evidence as intrinsic to guidelines. One such strategy, developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [10,11▪], has been adopted by over 100 organizations worldwide. The new PES hGH guidelines [6▪▪] were the first to apply the GRADE approach to hGH therapy. Key questions related to the clinical management of pediatric patients with GHD, ISS or PIGFD were drafted, along with guiding principles to be followed in judging the evidence supporting the practices in question. Quality of the evidence was then rated (very low, low, moderate, or high), with recommendations proposed accordingly as either strong (we recommend) or conditional (we suggest). 'Ungraded good practice statements' were also included that lack direct supporting evidence but are generally uncontestable, often describing related counseling for patients.

Synopsis of the new Pediatric Endocrine Society guidelines

For children and adolescents with GHD, the new PES guidelines cover: efficacy of hGH treatment, consideration, and diagnosis of GHD, dosing of hGH, safety issues, and transitional care after childhood hGH treatment. The strongest recommendations reflect high quality of supporting evidence for four points. First, the guidelines recommend 'the use of hGH to normalize adult height and avoid extreme shortness in children and adolescents with GHD.' Inclusion of this point serves as an important reminder that there is a group of patients for whom hGH treatment is not controversial, endorsed by decades of evidence worldwide, in contrast to other aspects of hGH treatment that continue to inspire debate because of weaker supporting evidence and philosophical disagreements. The next two strongest recommendations acknowledge that tests for diagnosing GHD are flawed. The guidelines recommend 'against reliance on GH provocative test

results as the sole diagnostic criterion of GHD,' in recognition of the limited sensitivity and specificity of these tests, and call for harmonization of GH assays [12]. A major diagnostic challenge in the GH field has been the use of different methods and assays to measure circulating GH concentrations. Because different assays can lead to different results from the same sample, misclassification of patients as having GHD, or not can occur, confounding clinical practice and cross-study comparisons. The final strongest recommendation for GHD stresses regular monitoring of hGH recipients for potential development of intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression, well documented potential side-effects associated with hGH treatment.

Other points related to hGH treatment of GHD, as well as all the points related to hGH treatment of ISS, merited weaker recommendations. The ISS section makes three points: treatment for ISS should be pursued through a shared decision-making approach that assesses each patient's physical and psychological burdens and treatment risks and benefits; effects on height and psychosocial impact should be reassessed after 12 months of hGH treatment; and clinicians should use a restrained dosing strategy. These recommendations reflect the profound heterogeneity of ISS patients as a group and the marked variability in individual responses to hGH treatment, including nonresponse.

For patients with PIGFD, treatment with hIGF-I (included in these guidelines for the first time) merited the strongest level of supporting evidence for treatment efficacy in increasing height and for safety monitoring during treatment. However, in contrast to hGH treatment, which corrects insulin hypersensitivity in patients with GHD and increases insulin resistance in GH-replete patients, the main safety concern with hIGF-I treatment involves increased risk for hypoglycemia. The other points in the hIGF-I section dealt with diagnostic and dosing issues, as well as which patients should receive hIGF-I treatment directly or first pursue a trial of hGH.

Following the recommendations and evidence reviews per GRADE approach, the new PES guidelines include discussions of the balance of benefit, risk, and cost of hGH treatment; the expansion of use of growth-promoting treatment; and conclusions and future directions.

Evidence gaps in assessing benefits of human growth hormone treatment

Adult height was selected as the primary outcome for assessing efficacy because surrogate short-term outcomes, such as growth velocity, change in height Z-score or change in predicted height, are dynamic and do not reliably predict adult height for many patients [13]. However, much of today's clinical practice is based on studies with short-term outcomes, which were downgraded in reliability by the GRADE approach. Although adult height and other long-term outcomes remain the gold standards to be sought, logistical and cost requirements make such long-term studies challenging to conduct prospectively, and difficulties in cleanly defining study participant groups and treatment parameters make such long-term studies tricky to design and interpret retrospectively.

Those limitations notwithstanding, is height the most appropriate outcome measure of the therapeutic goal (and if it is, what is the appropriate height target as 'normal' is arbitrarily defined when considering a continuous variable like height)? Parents rate concerns about the impact of short stature on psychosocial function, both current in childhood and projected into adulthood, as strongly influencing their decision to seek medical care for a child's short stature [14▪▪]. Similarly, 18% of study participants in all four US hGH registries combined were treated for ISS [15▪], that is, for psychosocial, not health, reasons. This is likely an underestimate which does not include study participants who sought hGH treatment for psychosocial concerns and were found to have an underlying condition like IGHD as part of their evaluations. However, as height is a poor predictor of psychosocial adaptation [16], direct measures of psychosocial adaptation may indicate better the effectiveness of hGH treatment.

In addition to gaps regarding outcome measures, significant limitations persist in the ability to clearly identify which patients have GHD or PIGFD. The new PES guidelines highlight the hazards of relying on discrepant, nonharmonized GH assays, and GH provocative tests and IGF-I generation tests for distinguishing patients with GHD or PIGFD, respectively. These limitations continue to hamper advancement in evidence-based practice for hGH treatment.

Evidence gaps in assessing safety of human growth hormone treatment

Assessment of on-treatment safety of hGH therapy for children with GHD or ISS, derived mainly from postmarketing surveillance studies, indicates a low frequency (i.e., <3% of treated children) of adverse effects, reinforcing a favorable on-treatment safety profile [5▪▪,6▪▪]. Although it is unlikely that catastrophic side-effects have been missed, the full spectrum of potential hGH adverse effects is not comprehensively elucidated by postmarketing surveillance studies because of incomplete ascertainment, changes in hGH dosage and/or recipient

characteristics, failure to capture adverse events that become manifest only after treatment, and lack of a valid control population for comparisons.

The guidelines recommend that prospective recipients of hGH treatment receive counseling and monitoring for potential intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression. Owing to physiological effects of GH on glucocorticoid metabolism and peripheral deiodination of levothyroxine, adrenal and thyroid axes should be reassessed after initiation of hGH therapy in patients whose cause of GHD is associated with possible multiple pituitary hormone deficiencies. Because GH decreases insulin sensitivity, monitoring for development of diabetes in hGH recipients with increased risk for insulin resistance, or increased medication requirement in those who already have diabetes, is recommended.

Growth hormone and IGF-I appear to have a permissive/facilitative rather than causative role in oncogenesis. The new guidelines concur with other recommendations [5▪▪,17▪] in stratifying risk of neoplasia with hGH treatment according to patients' baseline risks. hGH treatment of GHD or ISS does not increase incidence of malignancy in children without cancer-associated risk factors, nor does it increase recurrence in those successfully treated for a primary tumor. However, hGH treatment of children with a history of malignancy (particularly when treated with irradiation) appears to be associated with an early risk of subsequent neoplasms that diminishes with time. For patients with an increased cancer risk at baseline (e.g., from genetic syndromes), data are insufficient to determine whether hGH treatment further increases that risk.

Data conflict regarding long-term posttreatment safety of hGH. A French study of adults who had been treated for IGHD, ISS, or small for gestational age revealed a 30% increase in all-cause mortality [18] and an increased risk of stroke [19] compared to the general population. However, no effect of hGH exposure and/or dosage on mortality or incidence of cardiovascular events was found in following similar patients from other European countries [20,21▪▪]. The French data could be confounded by lack of an untreated control population, appropriateness of the reference population chosen, a large number of 'idiopathic deaths,' and missing data about hGH treatment details and concomitant conditions and medications. The new PES guidelines recommend that prospective recipients of hGH treatment be informed about the uncertainty regarding potential posttreatment adverse effects and the need for ongoing study of long-term safety.

Although data overall are reassuring, caution is warranted when extrapolating findings from earlier studies to safety of hGH as currently prescribed. Higher doses of hGH could increase risk for remote metabolic or malignancy issues not detected in current analyses. Changes in recipient characteristics because of ethnic demographics and rising childhood obesity rates could increase risk for hGH-precipitated type 2 diabetes. Finally, safety is a relative concept, affected by illness severity and availability of alternative treatments (including no treatment). For a child with growth failure because of GHD following central nervous system malignancy, a small increase in earlier development of a second malignancy may be an acceptable trade-off for normalization of growth and metabolic consequences of GHD. In contrast, for a healthy child with ISS, even the smallest risk for a long-term adverse effect may not be outweighed by an unpredictable and poorly defined benefit [22]. Alleviating these concerns requires global collaborative follow-up of children long after completion of hGH treatment [23,24].

CONCLUSION

Application of current practice guideline methodologies yielded PES guidelines for hGH treatment that are more conservative than previous guidelines, and also reflect progression of the hGH drug life cycle and evolving constraints of the US healthcare system. The guidelines-developing process revealed fundamental questions about hGH treatment that still need evidence-based answers. Willing and capable investigators and private, government, and commercial support for research funding are both needed to advance hGH therapy in a value-driven way. Unless and until such research is performed, a more restrained hGH-prescribing approach is appropriate.

Acknowledgements

We would like to thank our coauthors of the new PES hGH and hIGF-I guidelines – Sara A. DiVall, Constantin Polychronakos, Laurie E. Cohen, Jose Bernardo Quintos, Wilma Rossi, Chris Feudtner, and M. Hassan Murad – for contributing their time, talent, and effort to this complex endeavor. We would like to also thank the Drug and Therapeutics Committee, Ethics Committee, and Board of Directors of the Pediatric Endocrine Society for their support of the project.

A.G. serves on the Steering Committee of the Pfizer International Growth (KIGS) database, and was supported by grant 1R01 HD57037 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). D.B.A. has nothing to disclose.

Financial support and sponsorship

The Pediatric Endocrine Society provided funding for a 1-day meeting attended by all taskforce members in preparation of the Guidelines. A.G. was supported by grant 1R01 HD57037 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Allen DB. Growth promotion ethics and the challenge to resist cosmetic ■■ endocrinology. Horm Res Paediatr 2017; 87:145–152.

A critical analysis of clinical and ethical issues arising from the hGH era.

2. Gabow P, Halvorson G, Kaplan G. Marshaling leadership for high-value healthcare: an Institute of medicine discussion paper. JAMA 2012; 308:239–240.
3. 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; 93:4210–4217.
4. Wilson TA, Rose SR, Cohen P, *et al.* Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr 2003; 143:415–421.
5. Allen DB, Backeljauw P, Bidlingmaier M, *et al.* GH safety workshop position ■■ paper: a critical appraisal of recombinant human GH therapy in children and adults. Eur J Endocrinol 2016; 174:1–9.

Important consensus conference assessment of current knowledge of hGH safety and need for long-term surveillance.

6. Grimberg A, DiVall SA, Polychronakos C, *et al.,* Drug and Therapeutics ■■ Committee and Ethics Committee of the Pediatric Endocrine Society. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: Growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 2016; 86:361–397.

The new hGH and hIGF-I treatment guidelines from the Pediatric Endocrine Society, created by the GRADE approach, that is the focus of the current study.

7. Savage MO, Burren CP, Rosenfeld RG. The continuum of growth hormone-IGF-I axis defects causing short stature: diagnostic and therapeutic challenges. Clin Endocrinol 2010; 72:721–728.
8. Institute of Medicine (US) Committee on Quality of Healthcare in America. Crossing the quality chasm: A new health system for the 21st century. Washington (DC): National Academies Press (US); 2001.
9. Public Law No: 114-10 (04/16/2015 at https://www.congress.gov/bill/114th-congress/house-bill/2/text.
10. Alonso-Coello P, Schünemann HJ, Moberg J, *et al.,* GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. BMJ 2016; 353:i2016.
11. Alonso-Coello P, Oxman AD, Moberg J, *et al.,* GRADE Working Group. ■ GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ 2016; 353:i2089.

Description of GRADE evidence to decision frameworks to assist panels in the creation of, and clinicians in the utilization of, clinical practice guidelines.

12. Clemmons DR. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. Clin Chem 2011; 57:555–559.
13. Topor LS, Feldman HA, Bauchner H, Cohen LE. Variation in methods of predicting adult height for children with idiopathic short stature. Pediatr 2010; 126:938–944.
14. Grimberg A, Cousounis P, Cucchiara AJ, *et al.* Parental concerns influencing ■■ decisions to seek medical care for a child's short stature. Horm Res Paediatr 2015; 84:338–348.

Mixed qualitative–quantitative study that provides insights to aid clinicians in enhancing the patient centeredness, and hence quality, of care given to children and their families who are concerned about short stature.

15. Grimberg A, Huerta-Saenz L, Grundmeier R, *et al.* Gender bias in U.S. ■ pediatric growth hormone treatment. Sci Rep 2015; 5:11099.

The largest study to date providing evidence of gender bias in U.S. pediatric hGH treatment, particularly for ISS, thereby supporting the notion that psychosocial considerations greatly influence hGH treatment.

16. Sandberg DE, Gardner M. Short stature: is it a psychosocial problem and does changing height matter? Pediatr Clin North Am 2015; 62:963–982.
17. Raman S, Grimberg A, Waguespack SG, *et al.* Risk of neoplasia in pediatric ■ patients receiving growth hormone therapy: a report from the Pediatric Endocrine Society Drug and Therapeutics Committee. J Clin Endocrinol Metab 2015; 100:2192–2203.

A more detailed review of the evidence regarding neoplasia risk associated with pediatric hGH treatment than the other statements on general hGH safety.

18. Carel J-C, Ecosse E, Landier F, *et al.* Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab 2012; 97:416–425.
19. Poidvin A, Touze E, Ecosse E, *et al.* Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. Neurology 2014; 83:780–786.
20. Sävendahl L, Maes M, Albertsson-Wikland K, *et al.* Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: Preliminary report of 3 countries participating in the EU SAGhE study. J Clin Endocrinol Metab 2012; 97:E213–E217.
21. Albertsson-Wikland K, Martensson A, Savendahl L, *et al.* Mortality Is not ■■ increased in recombinant human growth hormone-treated patients when adjusting for birth characteristics. J Clin Endocrinol Metab 2016; 101:2149–2159.

Most recent and well designed analysis of posttreatment mortality in recipients of hGH.

22. Allen DB, Cuttler L. Clinical practice. Short stature in childhood: challenges and choices. New Engl J Med 2013; 368:1220–1228.
23. Allen DB. Growth hormone postmarketing surveillance: safety, sales, and the unfinished task ahead. J Clin Endocrinol Metab 2010; 95:52–55.
24. Rosenfeld RG, Cohen P, Robison LL, *et al.* Long-term surveillance of growth hormone therapy. J Clin Endocrinol Metab 2012; 97:68–72.