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ORIGINAL ARTICLE

Dose-sparing and safety-enhancing effects of an IGF-I-based dosing regimen in short children treated with growth hormone in a 2-year randomized controlled trial: therapeutic and pharmacoeconomic considerations

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Summary

Context and objective Titrating the dosage of growth hormone (GH) to serum levels of insulin-like growth factor-I (IGF-I) is a feasible treatment strategy in children with GH deficiency (GHD) and idiopathic short stature (ISS). The objective was to assess the dose-sparing effect and theoretical safety of IGF-I-based GH therapy.

Design, setting and patients This was a *post hoc* analysis of a previously described 2-year, multicenter, open-label, randomized, outpatient, controlled clinical trial in 172 prepubertal short children [age 7·5 ± 2·4 years; height standard deviation score (HSDS) −2·64 ± 0·61] classified by baseline peak GH levels as GHD (<7 ng/ml) or ISS (≥7 ng/ml).

Intervention Conventional weight-based dosing of GH (0·04 mg/kg/day) (n = 34) or GH dosing titrated to an IGF-I target of 0 SDS (IGF0T; n = 70) or an IGF-I target of +2 SDS (IGF2T; n = 68).

Main Outcome Measures Change in HSDS per GH mg/kg/day dose (ΔHSDS/GH dose ratio) and proportion of IGF-I levels above +2 SDS at the end of 2 years.

Results GH dosing titrated to an IGF-I target of 0 SDS was the most dose-sparing treatment regimen for GHD or ISS children (mean±SE ΔHSDS/GH dose ratios 48·1 ± 4·4 and 32·5 ± 2·8, respectively) compared with conventional dosing (30·3 ± 6·6 and 21·3 ± 3·5, respectively; P = 0·02, P = 0·005) and IGF2T (32·7 ± 4·8 and 16·3 ± 2·8, respectively; P = 0·02, P < 0·0001). IGF0T also resulted in the fewest IGF-I excursions above +2 SDS (6·8% *vs* 30·0% for conventional dosing; P < 0·01).

Conclusions IGF-I-based GH dosing, targeted to age- and gender-adjusted means, may offer a more dose-sparing and potentially safer mode of therapy than traditional weight-based dosing.

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Introduction

The dosage of GH for the treatment of children with short stature or growth failure has been based historically on body weight, usually in the range of 25–100 mcg/kg/day in pediatric patients with growth disorders, depending on age and pubertal status. Although effective and widely used, the high cost of GH therapy and variability in treatment response has led to ongoing efforts to optimize dosing strategies to improve not only the efficacy and cost-effectiveness of treatment, but also its long-term safety.[1–4] GH continues to have a favourable overall safety profile;[5] however, concerns over long-term safety have been revisited[5–9] and elevated serum concentrations of insulin-like growth factor-I (IGF-I), the presumed mediator of GH-induced somatic growth, are associated with certain cancers.[10,11]

Variability in response to a given dose of GH likely reflects differences in the severity of GH deficiency (GHD) and the patient's sensitivity to treatment. Several approaches have been explored to optimize the safety and efficacy of GH therapy in children with short stature. For example, prediction-based models have been developed to optimize GH therapy;[12–15] however, the exact contribution of prediction-derived indices to adult height remains unclear.

Titrating the dosage of GH to serum levels of IGF-I is a feasible treatment strategy in children with GHD or idiopathic short stature (ISS).[1,2,16] Nevertheless, the potential benefits pertaining to safety and the advantages of dose-sparing on cost for this method have yet to be determined. Therefore, we undertook a *post hoc* analysis of a previously conducted study[1,2] in which GH dose was

titrated based on serum IGF-I levels to determine the potential dose-sparing effect of this method compared with conventional weight-based dosing, as well as the theoretical effects on safety.

Methods

Study design and participants

The original study was a 2-year, multicenter, open-label, randomized, controlled clinical trial.[1,2] Briefly, 172 prepubertal short children [age 7·5 ± 2·4 years, height standard deviation score (HSDS) −2·64 ± 0·61] with low IGF-I levels were randomized in a 1:2:2 manner to 1 of 3 groups: conventional weight-based dosing of GH (0·04 mg/kg/day) (n = 34); GH dosing titrated to an IGF-I target of 0 SDS (IGF0T group; n = 70); and GH dosing titrated to an IGF-I target of +2 SDS (IGF2T group; n = 68). The dose of GH was adjusted every 3 months based on weight (conventional group) or, in the IGF0T and IGF2T groups, by 20% per SDS unit difference between the target and current IGF-I SDS. Children were classified as GHD (peak GH <7 ng/ml, n = 63) or ISS (≥7 ng/ml, n = 102) based on GH stimulation testing at baseline. The original study was conducted after approval by the institutional review board in all centers and in accordance with the Declaration of Helsinki. Written informed consent was obtained by the parent/legal guardian before any study procedure.

Statistical analysis

For this *post hoc* analysis, the 2-year change in HSDS (ΔHSDS) per mg/kg/day dose of GH used at the end of 2 years (ΔHSDS/GH dose ratio) was calculated and expressed in arbitrary units. Theoretical safety was assessed by the proportion of IGF-I measurements above +2 SDS at the end of 2-year treatment period. For the ΔHSDS/GH dose ratio, between-group (i.e., IGF0T, IGF2T, conventional dosing) comparisons were performed using analysis of covariance with treatment effect, sex and baseline HSDS values included in the model. For comparison of the proportion of IGF-I SDS levels above +2 at the end of 2 years, Fisher's exact test was used.

Results

Study population

The study population has previously been described.[1,2] Briefly, mean ± SD bone age for the study population (5·51 ± 1·93 years) was approximately 2 years behind their chronological age (7·53 ± 2·40 years).[1] More males (n = 132; 77%) than females (n = 40; 23%) were enrolled in the study.[1] At baseline, the mean HSDS for all patients was −2·64 ± 0·61 and the mean IGF-I SDS was −3·56 ± 1·74.[1] By design, the peak stimulated GH values were significantly lower in children classified as GHD compared to those classified as ISS (3·96 ± 1·94 *vs* 12·87 ± 4·77 ng/ml; $P < 0·001$) and children classified as GHD had significantly lower mean IGF-I SDS values (−4·10 ± 1·95 *vs* −3·27 ± 1·53; $P < 0·05$).[2] Otherwise, the demographics and baseline information for the patient population were similar between treatment groups and between GHD and ISS subgroups within each treatment group.[2]

Change in HSDS after 2 years

The change in HSDS (ΔHSDS) after 2 years of treatment was previously reported.[2] Briefly, the mean±SE values for ΔHSDS in GHD children for the IGF0T, IGF2T and conventional dosing groups were 1·41 (0·13), 2·04 (0·17) and 1·23 (0·12), respectively. The mean±SE values for ΔHSDS in ISS children for the IGF0T, IGF2T and conventional dosing groups were 0·84 (0·07), 1·33 (0·09) and 0·87 (0·09), respectively. The respective mean ± SE values for ΔHSDS in GHD and ISS children were significantly greater for the IGF2T group than for the IGF0T ($P < 0·001$) and conventional dosing groups ($P = 0·001$ and $P < 0·001$, respectively). There were no significant differences between the IGF0T and conventional dosing groups for ΔHSDS. The ΔHSDS was significantly greater among GHD than ISS children in all treatment groups ($P < 0·05$).[2]

Mean daily dose of GH

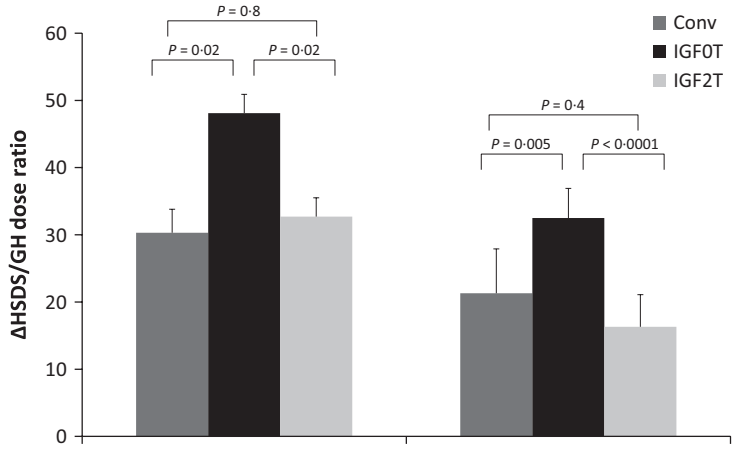
Mean daily doses of GH, calculated as the dose in mg/kg/day at the end of 2 years of treatment, were also previously reported.[2] The respective mean ± SE daily dose of GH in GHD and ISS children at the end of 2 years was significantly higher for the IGF2T group (0·091 ± 0·017 and 0·114 ± 0·009 mg/kg/day, respectively) than for the IGF0T (0·037 ± 0·004 and 0·032 ± 0·003 mg/kg per day, respectively; $P < 0·001$) and conventional dosing groups (0·041 ± 0 mg/kg/day for both GHD and ISS; $P = 0·002$, $P < 0·001$, respectively). There were no significant differences between the IGF0T and conventional dosing groups for GH daily dose.

Post hoc analysis of ΔHSDS/GH dose ratios

Among the three different treatment groups, the respective mean ± SE values for the ΔHSDS/GH dose ratios in GHD and ISS children were highest in the IGF0T group (48·1 ± 4·4 and 32·5 ± 2·8, respectively), with significant differences compared to both the conventional dosing group (30·3 ± 6·6 and 21·3 ± 3·5, respectively; $P = 0·02$ and $P = 0·005$, respectively) and the IGF2T group (32·7 ± 4·8 and 16·3 ± 2·8, respectively; $P = 0·02$ and $P < 0·0001$, respectively) (Fig. 1). Thus, while ΔHSDS was greater in the IGF2T group than in either of the other groups, the GH dose was also significantly higher. The resultant ΔHSDS/GH dose ratios were not only significantly lower than those for the IGF0T group, but were also not significantly different from those for the conventional dosing group (Fig. 1).

Theoretical safety based on IGF-I excursions above +2 SDS

Target IGF-I levels were attained at 6 months in the IGF0T group and at 9 months in the IGF2T group and remained stable



	GHD	ISS
	ΔHDS/GH dose ratio Mean (SE)	ΔHDS/GH dose ratio Mean (SE)
Conv	30·3 (6·6)	21·3 (3·5)
IGF0T	48·1 (4·4)	32·5 (2·8)
IGF2T	32·7 (4·8)	16·3 (2·8)

Fig. 1 ΔHSDS/GH Dose Ratio After 2 Years of GH Treatment in Children with GHD and ISS. Conv, conventional weight-based dosing (GH 0·04 mg/kg/day); ΔHSDS/GH dose ratio, change in height standard deviation score per mg/kg/day GH dose; GHD, growth hormone deficiency; ISS, idiopathic short stature; IGF0T, dose titration to IGF-I target of 0 standard deviation score; IGF2T, dose titration to IGF-I target of +2 standard deviation score; SE, standard error.

thereafter. Mean±SE IGF-I SDS values for GHD children in each treatment group at the end of 2 years were 0·46 ± 0·24 for IGF0T, 2·83 ± 0·39 for IGF2T and 0·66 ± 0·87 for the conventional dosing group. For ISS children, the mean ± SE IGF-I SDS values were 0·05 ± 0·24 for IGF0T, 1·93 ± 0·38 for IGF2T and 0·97 ± 0·52 for the conventional dosing group. At the end of 2 years, IGF-I SDS was significantly higher for the IGF2T group than the IGF0T group (GHD, $P < 0·001$; ISS, $P = 0·001$). Nevertheless, for the combined population of GHD and ISS children, while the mean IGF-I SDS was comparable between the IGF0T and conventional dosing groups, the percentage of IGF-I levels above +2 SDS at the end of 2 years was significantly lower in the IGF0T group than in the conventional dosing group (7% for IGF0T, 30% for conventional dosing; $P = 0·0083$) (Fig. 2).

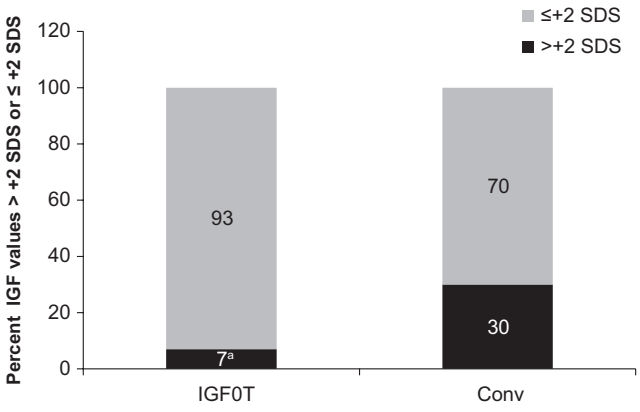


Fig. 2 Proportion of IGF-I Measurements Above +2 SDS by Dosing Strategy in Children with GHD and ISS. Conv, conventional weight-based dosing; IGF0T, dose titration to IGF-I target of 0 standard deviation score, SDS, standard deviation score. [a]$P<0·01$ compared with conventional dosing for proportion of IGF-I levels above +2 SDS, Fischer's exact test.

Discussion

Previous analyses demonstrated the feasibility of two IGF-I-based treatment regimens.[1,2] Increases in growth (ΔHSDS) at 2 years were comparable between the IGF-I target of the mean (0 SDS) and conventional weight-based dosing groups for both GHD and ISS patients; the IGF-I target of upper normal (+2 SDS) resulted in significantly greater ΔHSDS compared to the other two treatment groups in these patients.[1,2] As the dose required to achieve an IGF-I level of +2 SDS was also significantly higher than the other treatment groups, the current analysis was undertaken to compare the three treatment regimens in terms of increment in height SDS per dose as it may relate to dose- sparing potential. Furthermore, as both weight-based dosing and GH dosing targeted to the mean IGF-I SDS resulted in comparable IGF-I levels on average, a comparison between these dosing regimens was made to assess the proportion of IGF-I SDS values that exceeded the upper range of normal (+2 SDS) as a theoretical measure of safety.

An effective dose-sparing strategy can save substantial healthcare costs for managed care organizations and patients receiving GH therapy.[17] Previous pharmacoeconomic studies with GH relying on the use of decision-modelling have produced variable findings[17–19] and the applicability of such methodology to real-world situations may be limited.[20,21] Results from this analysis found that the most dose-sparing treatment regimen, based on analyses of ΔHSDS/GH dose ratios, for children with GHD or ISS was a GH dose titrated to an IGF-I target of 0 SDS. To our

knowledge, this is the first demonstration that a feasible dosing strategy based on IGF-I target can potentially be more cost beneficial (based on ΔHSDS/GH dose ratio) than conventional weight-based dosing while having comparable efficacy (as measured by ΔHSDS). Not only was targeting the IGF-I SDS to the mean the most dose-sparing treatment regimen, it also resulted in a significantly lower proportion of IGF-I levels above +2 SDS than did conventional dosing, which could have important implications for long-term safety.

IGF-I can produce alterations in cell proliferation and apoptosis, and elevated levels of IGF-I have been linked to some cancers in adult populations including colon, prostate and certain types of breast cancer.[10,22–24] Long-term observational studies have reported on safety outcomes for children receiving GH treatment, including malignancies.[5,8,25] For the most part, recent results have been reassuring. Findings from the National Cooperative Growth Study reported no appreciable increase in *de novo* cancer [standardized incidence ratios (SIR) 1·12, 95% CI 0·75–1·61] and a lower than expected incidence of new-onset leukaemia (SIR 0·54; 95% CI 0·11–1·58).[5] However, a risk for second neoplasms among children treated with GH has been reported. A large retrospective cohort of childhood cancer survivors treated with GH reported an approximate threefold higher rate of second neoplasms than expected (SIR 3·2, 95% CI 1·9–5·5) at 15 years of follow-up.[25] This rate decreased somewhat after 32 years of follow-up, but still remained elevated (SIR 2·1, 95% CI 1·3–3·5).[8]

Although a definitive link between elevated IGF-I levels associated with GH treatment and biological end-points has not been shown, it has been recommended that IGF-I levels in individual patients should be maintained within age- and gender-based reference ranges.[26–28] We found that in patients dosed conventionally with 0·04 mg/kg/day, the proportion of IGF-I levels above +2 SDS was 30%. Others have reported similar excursions. For example, 28% of pubertal patients treated with 0·7 mg/kg/week had high IGF-I concentrations,[29] as did 45% of SGA patients treated with 0·057 mg/kg/day for 2 years.[30] In another report, 17% of GHD patients had IGF-I excursions above +2 SDS after 2 years even when the GH dose was based on body surface area at an average dose of 1 mg/m^2/day (equivalent to 0·035/mg/day).[31] A GH dose-sparing effect of IGF-I-based dosing was also noted in a study of adult Japanese patients with GHD who were switched from a conventional weight-based dose regimen, with a concomitant increase in the number of patients who were maintained within the reference range for IGF-I SDS.[32] The present analysis demonstrated that targeting IGF-I to the mean (i.e., 0 SDS) significantly decreased the proportion of IGF-I measurements >+2 SDS at the end of year 2 compared to conventional weight-based dosing. Decreasing the risk of exposure to high IGF-I levels potentially reduces the theoretical risk of cancer and other adverse events related to high IGF-I levels.

There are limitations to the present analysis. It was not prospectively designed for the purpose of dose-sparing and was not intended to provide any specific dosing target or recommendations. With that said, based on our analysis, an IGF-I level around the mean for the population rather than at the upper limit of normal would seem to be a reasonable approach in terms of cost-effectiveness and more prudent in terms of safety, without incurring any compromise of efficacy, especially for patients with GHD. Although IGF-I targets were met equally in patients with GHD and ISS, gains in height were significantly less for ISS patients.[2] This may indicate a degree of IGF-I insensitivity, as well as GH insensitivity, in the ISS patients, who may require a more aggressive IGF-I target.[2] Also, the 2-year duration of the study may not have been long enough for all patients to achieve optimal catch-up growth.[3] As other IGF-I targets have yet to be fully examined, the optimal IGF-I target, particularly for non-GHD conditions, remains to be identified, and long-term clinical benefits of dosing based on IGF-I targets still need to be demonstrated. One proposed model suggests using higher IGF-I targets (+2 to +3 SDS) to maximize height during the catch-up phase followed by lower targets for maintenance.[33] Furthermore, a general IGF-based dosing strategy would not preclude also individualizing treatment based upon responsiveness in growth.

The lack of IGF-I assay standardization and accepted normative reference ranges are additional factors that may impact the generalizability of the reported results. A consensus statement put forth by the Growth Hormone Research Society has outlined the obstacles and steps needed to move towards a standardized process.[34] Until an accepted standardized assay is available, clinicians should utilize an assay with demonstrated reliability, collect and process samples appropriately and adjust to appropriate age and gender-matched reference norms,[28] which should be requested from each laboratory whenever possible. When feasible, clinicians should attempt to utilize the same assay and technique for a patient over time, although patient factors, such as health insurance, may be a barrier.[28] In addition to interassay variability, clinicians should also be aware of intrapatient variability when interpreting IGF-I assay results, especially with regard to borderline values.[34]

In conclusion, IGF-based GH dosing targeted to the age- and gender-adjusted mean (0 SDS) in GHD and ISS children resulted in a higher ΔHSDS/GH dose ratio than conventional weight-based dosing, despite comparable levels of IGF-I and ΔHSDS achieved, and may offer a more dose-sparing mode of GH therapy than traditional weight-based GH dosing. IGF-I-based dosing targeted to the mean SDS also decreased exposure to IGF-I levels above +2 SDS and may therefore address some of the theoretical safety concerns related to GH treatment.

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Disclosures

PC and RGR are consultants to Novo Nordisk; ADR is consultant to AbbVie, Novo Nordisk, SOV Therapeutics, LG Biopharmaceuticals and Sanofi; WW and JG are employees of Novo Nordisk, AMK is an employee and shareholder of Novo Nordisk.

References

1 Cohen, P., Rogol, A.D., Howard, C.P. *et al.* (2007) Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. *Journal of Clinical Endocrinology & Metabolism*, **92**, 2480–2486.

2 Cohen, P., Germak, J., Rogol, A.D. *et al.* (2010) Variable degree of growth hormone (GH) and insulin-like growth factor (IGF) sensitivity in children with idiopathic short stature compared with GH-deficient patients: evidence from an IGF-based dosing study of short children. *Journal of Clinical Endocrinology & Metabolism*, **95**, 2089–2098.

3 Kristrom, B., Aronson, A.S., Dahlgren, J. *et al.* (2009) Growth hormone (GH) dosing during catch-up growth guided by individual responsiveness decreases growth response variability in prepubertal children with GH deficiency or idiopathic short stature. *Journal of Clinical Endocrinology & Metabolism*, **94**, 483–490.

4 Lee, J.M., Davis, M.M., Clark, S.J. *et al.* (2006) Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *Archives of Pediatrics and Adolescent Medicine*, **160**, 263–269.

5 Bell, J., Parker, K.L., Swinford, R.D. *et al.* (2010) Long-term safety of recombinant human growth hormone in children. *Journal of Clinical Endocrinology & Metabolism*, **95**, 167–177.

6 Savendahl, L., Maes, M., Albertsson-Wikland, K. *et al.* (2012) 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. *Journal of Clinical Endocrinology & Metabolism*, **97**, E213–E217.

7 Carel, J.C., Ecosse, E., Landier, F. *et al.* (2012) Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE Study. *Journal of Clinical Endocrinology & Metabolism*, **97**, 416–425.

8 Ergun-Longmire, B., Mertens, A.C., Mitby, P. *et al.* (2006) Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *Journal of Clinical Endocrinology & Metabolism*, **91**, 3494–3498.

9 Sperling, M.A. (2012) Long-term therapy with growth hormone: bringing sagacity to SAGHE. *Journal of Clinical Endocrinology & Metabolism*, **97**, 81–83.

10 Renehan, A.G., Zwahlen, M., Minder, C. *et al.* (2004) Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet*, **363**, 1346–1353.

11 Gallagher, E.J. & LeRoith, D. (2011) Minireview: IGF, insulin, and cancer. *Endocrinology*, **152**, 2546–2551.

12 Ranke, M.B. & Lindberg, A. (2010) Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. *Journal of Clinical Endocrinology & Metabolism*, **95**, 1229–1237.

13 Bakker, B., Frane, J., Anhalt, H. *et al.* (2008) Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. *Journal of Clinical Endocrinology & Metabolism*, **93**, 352–357.

14 Ranke, M.B. & Lindberg, A., International Board. (2011) Prediction models for short children born small for gestational age (SGA) covering the total growth phase. Analyses based on data from KIGS (Pfizer International Growth Database). *BMC Medical Informatics and Decision Making*, **11**, 38.

15 Schonau, E., Westermann, F., Rauch, F. *et al.* (2001) A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. *European Journal of Endocrinology*, **144**, 13–20.

16 Cohen, P., Rogol, A.D., Weng, W. *et al.* (2013) Efficacy of IGF-based growth hormone (GH) dosing in non GH-deficient (non-GHD) short stature children with low IGF-I is not related to basal IGF-I levels. *Clinical Endocrinology*, **78**, 405–414.

17 Joshi, A.V., Munro, V. & Russell, M.W. (2006) Cost-utility of somatropin (rDNA origin) in the treatment of growth hormone deficiency in children. *Current Medical Research and Opinion*, **22**, 351–357.

18 Christensen, T., Fidler, C., Bentley, A. *et al.* (2010) The cost-effectiveness of somatropin treatment for short children born small for gestational age (SGA) and children with growth hormone deficiency (GHD) in Sweden. *Journal of Medical Economics*, **13**, 168–178.

19 Takeda, A., Cooper, K., Bird, A. *et al.* (2010) Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation. *Health Technology Assessment*, **14**, 1–209, iii–iv.

20 Hill, S.R., Mitchell, A.S. & Henry, D.A. (2000) Problems with the interpretation of pharmacoeconomic analyses: a review of submissions to the Australian Pharmaceutical Benefits Scheme. *The Journal of the American Medical Association*, **283**, 2116–2121.

21 Rennie, D. & Luft, H.S. (2000) Pharmacoeconomic analyses: making them transparent, making them credible. *The Journal of the American Medical Association*, **283**, 2158–2160.

22 Rowlands, M.A., Gunnell, D., Harris, R. *et al.* (2009) Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. *International Journal of Cancer*, **124**, 2416–2429.

23 Morgillo, F., De Vita, F., Antoniol, G. *et al.* (2013) Serum insulin-like growth factor 1 correlates with the risk of nodal metastasis in endocrine-positive breast cancer. *Current Oncology*, **20**, e283–e288.

24 Clayton, P.E., Banerjee, I., Murray, P.G. *et al.* (2011) Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. *Nature Reviews Endocrinology*, **7**, 11–24.

25 Sklar, C.A., Mertens, A.C., Mitby, P. *et al.* (2002) Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Endocrinology & Metabolism*, **87**, 3136–3141.

26 Cohen, P., Rogol, A.D., Deal, C.L. *et al.* (2008) 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. *Journal of Clinical Endocrinology & Metabolism*, **93**, 4210–4217.

27 Higham, C.E., Jostel, A. & Trainer, P.J. (2007) IGF-I measurements in the monitoring of GH therapy. *Pituitary*, **10**, 159–163.
28 Pawlikowska-Haddal, A., Cohen, P. & Cook, D.M. (2011) How useful are serum IGF-I measurements for managing GH replacement therapy in adults and children? *Pituitary*, **15**, 126–134.
29 Mauras, N., Attie, K.M., Reiter, E.O. *et al.* (2000) High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. *Journal of Clinical Endocrinology & Metabolism*, **85**, 3653–3660.
30 Cabrol, S., Perin, L., Colle, M. *et al.* (2011) Evolution of IGF-1 in children born small for gestational age and with growth retardation, treated by growth hormone adapted to IGF-1 levels after 1 year. *Hormone Research in Paediatrics*, **76**, 419–427.
31 Feigerlova, E., Diene, G., Oliver, I.*et al.* (2010) Elevated insulin-like growth factor-I values in children with Prader-Willi syndrome compared with growth hormone (GH) deficiency children over two years of GH treatment. *Journal of Clinical Endocrinology & Metabolism*, **95**, 4600–4608.
32 Chihara, K., Kato, Y., Kohno, H.*et al.* (2008) Safety and efficacy of growth hormone (GH) during extended treatment of adult Japanese patients with GH deficiency (GHD). *Growth Hormone & IGF Research*, **18**, 307–317.
33 Park, P. & Cohen, P. (2004) The role of insulin-like growth factor I monitoring in growth hormone-treated children. *Hormone Research*, **62**(Suppl 1), 59–65.
34 Clemmons, D.R. (2011) Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. *Clinical Chemistry*, **57**, 555–559.