

Review

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Individualised growth response optimisation (iGRO) tool: an accessible and easy-to-use growth prediction system to enable treatment optimisation for children treated with growth hormone

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Abstract

Background: Growth prediction models (GPMs) exist to support clinical management of children treated with growth hormone (GH) for growth hormone deficiency (GHD), Turner syndrome (TS) and for short children born small for gestational age (SGA). Currently, no prediction system has been widely adopted.

Content: The objective was to develop a stand-alone web-based system to enable the widespread use of an ‘individualised growth response optimisation’ (iGRO) tool across European endocrinology clinics. A modern platform was developed to ensure compatibility with IT systems and web browsers. Seventeen GPMs derived from the KIGS database were included and tested for accuracy.

Summary: The iGRO system demonstrated prediction accuracy and IT compatibility. The observed discrepancies between actual and predicted height may support clinicians in investigating the reasons for deviations around the expected growth and optimise treatment.

Conclusions: This system has the potential for wide access in endocrinology clinics to support the clinical management of children treated with GH for these three indications.

Keywords: growth hormone; prediction models.

Introduction

Recombinant human growth hormone (rhGH) was introduced in 1985 as a therapeutic option to treat children with growth hormone deficiency (GHD). Today, GH has been approved for adults with GHD and in children for the treatment of short stature associated with GHD, Turner syndrome (TS), short children born small for gestational age (SGA), chronic renal insufficiency (CRI), Prader Willi syndrome (PWS), SHOX deficiency and idiopathic short stature (ISS), although not all of these indications are currently approved in every country.

The aims of rhGH treatment in children are (i) to increase height during childhood; (ii) to attain adult height as close as possible to their target height; (iii) to minimise potential adverse events of GH therapy and (iv) to achieve cost-effective treatment [1]. The initial step when prescribing rhGH is to start on a fixed dose of GH [2] based on the weight or body surface areas (BSAs) of the child within the range approved by regulatory authorities. Subsequent dose titration is usually based on weight; adaptations guided by growth velocity or insulin-like growth factor 1 (IGF-1) as a biomarker have also been explored in clinical trials but have not been recommended in the current guidelines and have not been widely adopted [3, 4]. However, each child responds to a dose of rhGH in a unique way due to their genetic, metabolic and physical characteristics. Whilst many children with a given diagnosis respond as expected to rhGH treatment and are likely to reach the goals of intended treatment [5], some children respond less well [6] and some may respond better than expected [7].

Thus, in order to reach all aims of rhGH treatment in as many patients as possible, a more individualised approach to initiating and managing treatment would be desirable, by identifying specific patient characteristics (height, weight, dose, genetic variation, etc.) with or without biomarkers,

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which may account for some of the variability in response [8–13]. Growth prediction models (GPMs), incorporating these patient characteristics and modalities of treatment, can be used to predict the growth response to GH of an individual. As a result of the evaluation of the GPM, the ongoing clinical and/or therapeutic management of the patient may remain unchanged or is modified.

Over the past decades, a number of GPMs for short children treated with rhGH for various diagnoses have been published [11, 13–20]. Most of these models require specific information not always available to the physician at the moment of the consultation. These, and other aspects, have limited the use of GPMs in clinical practice. In addition, to date, easily accessible tools that apply the rather complicated mathematical calculations have hampered their use.

The previous growth prediction system developed by Pfizer Inc. utilised the validated, published GPMs derived from patients documented within the pharmaco-epidemiological survey KIGS (Pfizer International Growth Database), containing 83,803 children/277,264 patient years receiving rhGH therapy (mainly Genotropin™). It produced specific prediction models based on an individual's unique set of characteristics that are readily available during clinical consultations (e.g. diagnosis, age, weight, parental height and the chosen treatment modality) that could predict a child's growth over a period of time [12].

In this review, we describe the features and benefits of an easy-to-use new cloud-based tool, individualised growth response optimisation (iGRO), and demonstrate how it can support physicians in their management of children being treated with rhGH.

Materials and methods

The objective was to develop an independent (stand-alone) web-based, accessible, easy-to-use growth prediction system which incorporated clinically validated GPMs. It was important that the new tool retained the valued features of the previous system, which predicted growth before the start of treatment [15], providing pubertal and pre-pubertal growth predictions, and presented a measure of how responsive to rhGH an individual is. This tool was developed as the 'iGRO' tool. The software was designed to ensure web browser compatibility with the majority of IT platforms (desktops, laptops and tablet devices) and web browsers. Throughout its development, access to iGRO was continually tested across a number of hospitals and clinics via the use of an active iGRO web link.

The validated and published GPMs derived from KIGS [15–19] for GHD, TS and SGA indications were incorporated, as were specific disease and country reference charts for height, height velocity (HV) and weight. The tool was designed to offer flexibility to enable physicians to select and preset the appropriate reference tables for the three available indications.

Three waves of user acceptance testing (UAT), which included the involvement of external physicians, were completed to determine whether the software complies with the written system specification or user requirements. It was not intended solely to determine if respondents like or can use the system. UAT is one aspect of an extensive system/software validation process that is beyond the scope of this manuscript.

iGRO was manufactured to meet the classification of a Class 1 software medical device and complies with the criteria stated in the EU Medical Devices Directive [20] which included rigorous testing and validation prior to its release for use in clinical practice, as well as continuous monitoring of the tool's functionality post launch. A key requirement for any software medical device is the provision of a comprehensive User Guide for the physician, which was developed and embedded into iGRO.

Clinical validation of iGRO

The clinical validation assessment and analysis of clinical data pertaining to a medical device was performed to verify the clinical functionality of the device when used as intended by the manufacturer. The assessment included three steps: ensuring sufficient scientific evidence to enable use of GPMs in clinical practice through iGRO, the performance of the medical device using actual patient cases and, finally, a risk assessment to avoid any potential risks developing during its use in clinical practice.

Scientific assessment

First, the evaluation was drawn up on the basis of the most outstanding scientific literature on GPMs. Medline was searched for all studies reporting GPMs, GHD, TS or SGA. This search was then narrowed further to limit it to GPMs and GHD or TS or SGA and KIGS or the Pfizer International Growth Database from January 1990 to March 2014; the most relevant literature covering the intended use of the iGRO software was used to address both the performance and the safety of the device [21]. The various KIGS models used in iGRO illustrate the variation in responsiveness to

Table 1: Summary of patient data used to test each model in iGRO.

Tested GPM	Patient data used to test model
GHD prepubertal models	10 patients (5 boys and 5 girls; 6 with GH max peak, 4 without GH max peak)
GHD puberty models	4 patients (2 boys and 2 girls)
Turner prepubertal model	6 patients (3 girls with oxandrolone treatment, 3 girls without oxandrolone)
Turner pubertal model	2 patients
SGA prepubertal models	6 patients (3 boys and 3 girls)

GH treatment among individuals within each diagnostic group. It is also important to recognise that the degree of standardisation in diagnosis and/or in the measurement of GH levels may vary among physicians and laboratory methods. Both of these parameters vary among physicians who contributed to KIGS and also in the wider paediatric endocrine community. However, such differences clearly reflect the current clinical setting in paediatric endocrinology. Yet, it is important to note that there is high concordance between the KIGS cohorts used to develop the prediction models and cohorts from other similar pharmaco-epidemiological surveys and case-control studies [15–19, 21–23].

The identified literature was appraised and weighted as per standard criteria described in the EU guidelines [20].

Second, the actual evaluation of the performance of the medical device was done using the software to test the performance of the medical device, using real world data for the three indications included in iGRO. Each variable, output and graph were checked using data from 100 children.

For the clinical validation process of iGRO, 28 patients from KIGS, with complete data, were randomly selected to cover all prediction models and all combinations within each model (such as boys/girls, with GH max peak/without GH max peak, oxandrolone/no oxandrolone, etc.) All combinations listed in Table 1 were thoroughly tested; all calculations were accurate per the model definitions and passed the validation.

Risk assessment

The risk management process is in compliance with the EN ISO 14971:2012 standard. The analysis was carried out considering the applicable harmonised standards of the EU regulatory framework [20]. A quality management system

was applied to iGRO including a risk mitigation plan that was consistent with the ISO requirements as well as the Pfizer standard operating procedures required for software medical devices. It was established and documented that iGRO would be maintained throughout the life cycle with an ongoing process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks and monitoring the effectiveness of the controls. The process includes the following elements: risk analysis, risk evaluation and risk control at production and post-production.

The validation processes proved that the device fully meets the user requirements and the intended use when used by the intended user (i.e. paediatric endocrinologist). Therefore, after the clinical validation, iGRO demonstrated that this medical device has no intrinsic risks, as it is intended primarily to provide physicians with predictions based on the information provided and not make recommendations on any aspects of clinical management of a patient.

Data protection and privacy policy

All data entered into iGRO is considered sensitive information and is owned and accessed exclusively by the physician entering the data (users who are members of the same clinic may also view patient data pertaining to that clinic).

iGRO has been designed to ensure maximal data security; the configuration and operation complies with all relevant European data protection regulations. The responsibilities of the physician using iGRO with respect to data entry, transmission, storage and access are described in a Terms of Use document and a ‘Privacy Policy’. The physician is required to read and accept these documents before using iGRO. All patient data are encrypted during transmission between the user and iGRO and between iGRO and the data host. Encrypted data are held in a secure data storage facility located in the European Union and are accessed only by the physician who entered the data. Pfizer has no access to any individual patient data; Pfizer only receives general information for each country where iGRO has been adopted, i.e. the number of physicians using iGRO, the number of patients for whom iGRO has been applied for each of the three indications and the number of centres per country who are registered to use iGRO.

GPMs used in iGRO

Traditionally, the annualised HV is taken as a measure of the response to rhGH treatment in prepubertal children.

Table 2: Rank of predictors of first-, second-, third and fourth–eighth year height velocity in patients with GHD, SGA and TS.

Parameter	First year				Second year			Third year			Years 4–8	
	GHD+ Peak GH	GHD– Peak GH	SGA	TS	GHD	SGA	TS	GHD	SGA	TS	GHD ^a	TS
Number of patients		593	613	686	573	385	681	335	317	293	180	291
Maximum GH peak, µg/L	1 (–)											
Age at start of therapy	2 (–)	2 (–)	2 (–)	2 (–)	3 (–)	2 (–)	3 (–)	3 (–)	2 (–)	5 (–)	4 (–)	2 (–)
Height–MPH (SDS)	3 (–)	1 (–)		5 (–)								
Mid parental height			4 (+)						4 (+)			
Body weight (SDS)	4 (+)	5 (+)	3 (+)	3 (+)	2 (+)		5 (+)	2 (+)	3 (+)	3 (+)	1 (+)	5 (+)
GH dose, IU/kg/week	5 (+)	4 (+)	1 (+)	1 (+)	4 (+)	3 (+)	2 (+)	4 (+)	5 (+)	4 (+)	3 (+)	4 (+)
Birth weight (SDS)	6 (+)	3 (+)										
Height velocity, cm/year					1 (+)	1 (+)	1 (+)	1 (+)	1 (+)	1 (+)	2 (+)	1 (+)
Oxandrolone (Y/N)				4 (+)			4 (+)			2 (+)		3 (+)
Number of injections				6 (+)								
Age at puberty onset												
Bone age delay												

GH, growth hormone; GHD, idiopathic GH deficiency; SGA, children born small for gestational age; MPH, mid-parental height; SDS, standard deviation score; TS, Turner syndrome; +, variable is positively correlated with growth response; –, variable is negatively correlated with growth response. ^aAlso applicable for SGA indication; fourth through eighth years. Adapted from Ranke et al. [6], with permission of The Endocrine Society.

Mathematical analyses of large patient cohorts have shown that the magnitude of HV during GH treatment is a function of a multitude of factors such as the diagnosis, age, height, weight, the dose of GH given and other factors. Based on large cohorts of children with various growth disorders, such as GHD, TS and SGA, documented within KIGS, mathematical algorithms to predict the individual response to rhGH therapy have been derived and validated [15–19]. These algorithms (i.e. the prediction models) provide an explanation of the variability of the response (e.g. HV) of a patient during a certain period of treatment after the initiation of GH treatment (e.g. first, second and third through eighth prepubertal treatment years) based on the patients' characteristics and the treatment modalities applied with a certain likelihood and a specific margin of error of the predicted HV. In patients with GHD, the first-year HV can be predicted by an algorithm that includes the severity of GHD (most important predictor), age, the distance of height to target height, body weight, birth weight and rhGH dose. During subsequent prepubertal years, growth during the first year (most important predictor), age, weight and the rhGH dose applied have been observed to be important predictors of HV. The IGF-1 measurement is not required for any of the prediction models. The parameters and the parameter estimates in the model equations of the prediction of HV for TS and SGA during different treatment phases slightly differ from those observed in GHD [1]. In particular, in these diagnoses during the first treatment year, the rhGH dose is the most important predictor. Table 2 presents all of the

important predictors of growth for the first, second, third and fourth through eighth HV years in the three indications. After puberty onset, HV is a more complex outcome making the annualised HV a difficult, if not inadequate, outcome to evaluate the growth response to rhGH. Therefore, prediction algorithms have been developed describing the total pubertal growth phase (from start of puberty to near-adult height) for GHD, TS and SGA. For all of these diagnoses, age (most important predictor), distance to target height, bone age delay over chronological age (all at puberty onset) and the mean total GH dose have been found to be the essential predictors for total pubertal growth (Table 3).

Thus, the predicted growth responses give an accurate figure of the growth response to be expected in an individual at the beginning of each treatment phase. At

Table 3: Rank of predictors of total pubertal growth in patients with GHD, SGA and TS.

Parameter Diagnosis	Total pubertal growth		
	GHD ^a		TS
	Male	Females	
Number of patients	355	221	419
Height–MPH (SDS)	3 (–)	3 (–)	3 (–)
GH dose, IU/kg/week	4 (+)	4 (+)	4 (+)
Age at puberty onset	1 (–)	1 (–)	1 (–)
Bone age delay	2 (+)	2 (+)	2 (+)

^aAlso applicable for SGA indication.

the end of the respective treatment phase, with the comparison between observed and predicted HV, one can establish whether the particular child has achieved the height gain expected (Figure 1).

Mean/mid parental height

Mid-parental height (MPH) is calculated as the mean of paternal and maternal heights (cm or standard deviation score [SDS]), and target height (TH) is a child's predicted adult height based on the heights of their parents. In iGRO, MPH SDS was used for estimating the 'corrected height' (height SDS minus MPH SDS), where MPH SDS is calculated according to Cole's formula [24]. This method is independent of sex, where secular trends for growth charts date back one generation and are independent of ethnic origin.

Index of responsiveness

Another unique feature of iGRO is calculating an individual child's level of responsiveness to rhGH treatment, termed the Index of Responsiveness (IoR; Figure 2). The IoR is the difference between observed (obs) and predicted (pred) HV divided by the SD of the predicted HV during the first treatment year ($(\text{obsHV} - \text{predHV})/\text{SD predHV}$). In an analogy to an SDS, a positive value of the IoR indicates a better growth response; a negative value indicates a reduced growth response in comparison to the reference cohort used to develop the prediction model. This IoR has

been observed to be one of the most important predictors of the overall height achieved or gained during long-term GH treatment in GHD, TS and SGA [5, 25, 26]. These findings strongly suggest that a good initial response to GH in an individual is likely to continue and vice versa.

Hence, having both the degree of response together with the IoR ranking has the potential to support clinical decision making and treatment optimisation.

Actual vs. predicted growth responses

The iGRO GPMs explain up to 70% of variability in growth response. Hence, the growth response of most children will be close to the predicted mean response of the population. If a child's growth is as predicted and the responsiveness is as expected, GH therapy should be continued at the same dose. Kaspers et al. [7] reported that by using population modelling, a small proportion of patients may respond better than predicted and, therefore, their GH dose could be reduced, resulting in a more cost-effective therapy. On the other hand, a proportion of patients may not respond as well as expected. If their response is low but their responsiveness is normal, an increase in GH dose may improve their response. If both their response and their responsiveness are low, just increasing the GH dose is unlikely to improve their response; more importantly, this should alert the physician to investigate other factors that may impact the child's growth, e.g. poor adherence and concomitant pathologies. If a child's growth response is found to be impacted by poor adherence, the patient

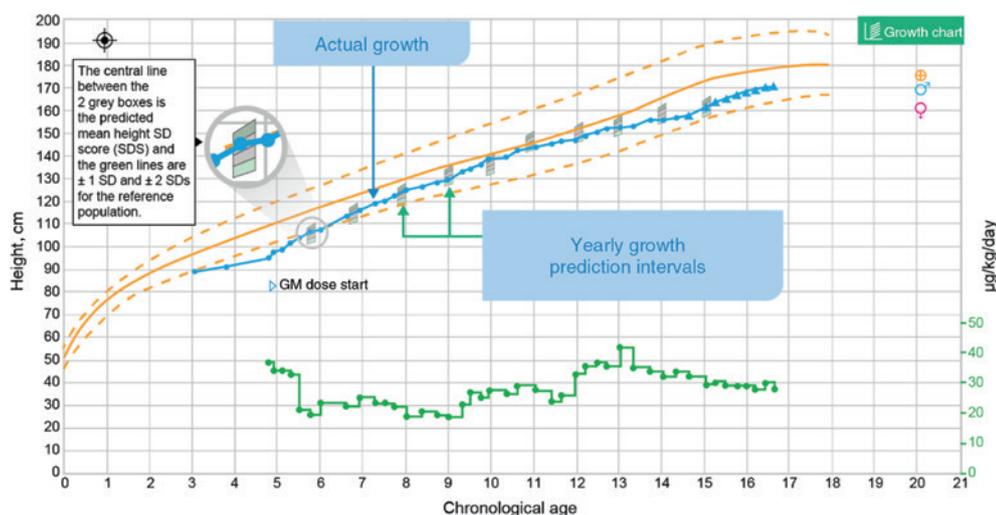


Figure 1: iGRO growth chart with predictions.

Predicted growth responses are calculated at yearly intervals and are indicated (green bars). The actual growth (blue), GH dose (green) and appropriate growth reference curve (orange) are also shown.

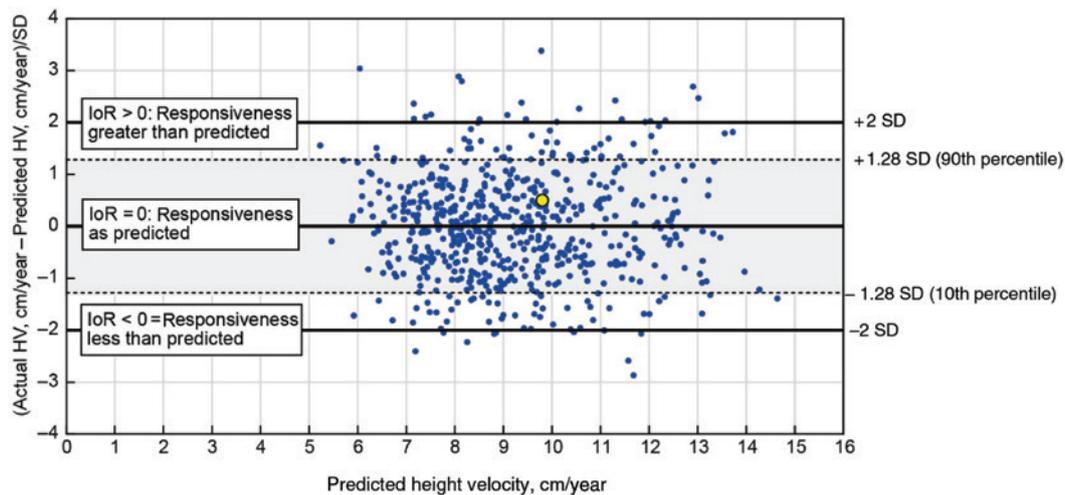


Figure 2: Index of Responsiveness (IoR).

iGRO can provide detailed information on how well a child responds to GH treatment. The enlarged dot (yellow) indicates the IoR of the individual being evaluated, whereas the small dots (blue) indicate the IoR values for the reference population from which the prediction model was derived. HV, height velocity; SD, standard deviation. Blue dots represent IoR values for the KIGS reference population on which the prediction algorithm is based. Large yellow dots represent the patients' IoR.

and their family may benefit from additional support. Research investigating adherence to GH therapy has been shown to be variable [5, 27]. The reasons for this are multifactorial: for example, patients not seeing a direct result of daily GH injections may become demotivated and comply less. Prediction models, including iGRO, have an important role in supporting an individual with adherence, as it is specific, using the patient's individual characteristics.

In children who are poor responders according to the IoR and their clinical response, after 12 months of GH treatment, questions may be raised on the original clinical diagnosis, their inconsistent adherence with treatment or the influences of other illnesses that may be present. Once the paediatric endocrinologist has completed the re-evaluation of the patient, a discussion with the family will take place, including the possibility of GH treatment discontinuation.

iGRO also has the potential to improve the cost-benefit ratio by optimising the GH dose. For example, in patients who have a better-than-expected growth response after the first year, it may be possible to continue with the same GH dose in the second year without adjusting for changes in body weight or BSA, so the dose per kg will decrease.

Results: potential clinical advantages with iGRO

As observed growth and predicted growth are visible both in numerical and in graphical terms, iGRO enables

a physician to compare the actual growth of a child with their predicted growth according to the GPMs and to monitor the child's response to rhGH throughout the years of treatment. It can, therefore, assist physicians in evaluating whether a child is responding to GH as expected, or if not, assess any potential additional medical problem or adherence issues and/or question the originally established diagnosis. Hence, iGRO has the potential to be used as a medical education and research tool.

iGRO can provide an individual growth prediction, even before treatment with rhGH has commenced. The predicted growth output can assist physicians in assessing a child's potential in responding to GH at the start of treatment and provide patients and their families with realistic expectations of short- and long-term growth outcomes. Both the actual growth and the predicted growth of an individual child are compared with an appropriate growth reference curve, selected by the physician from a list of reference curves included in the tool. Moreover, as an ongoing clinical monitoring tool (Figure 3), throughout the GH treatment period, it can be a valuable tool in following the progress of the child.

Discussion

We have presented the development of iGRO and indicated that it would have significant benefits: it is easy to use and accessible, as only requiring access to the Internet

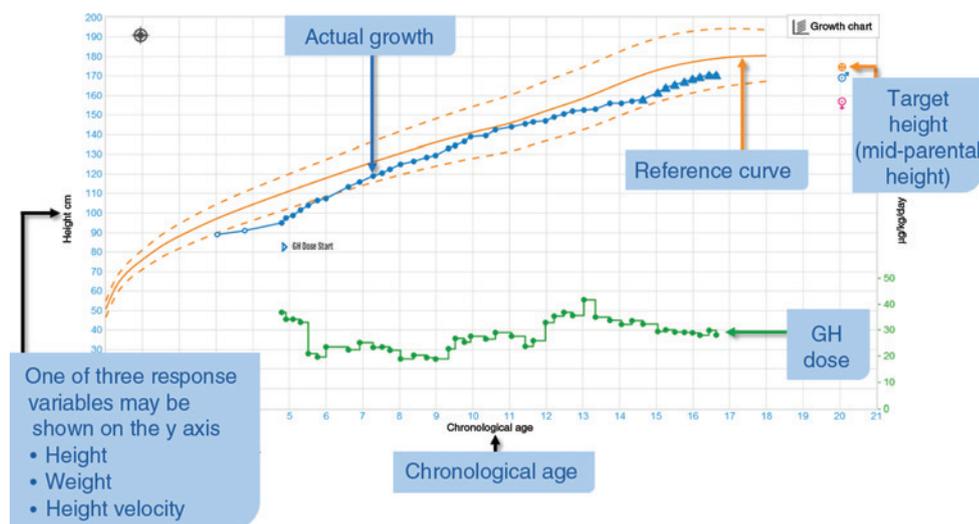


Figure 3: iGRO growth chart shows the actual growth of the patient (blue), the GH dose (green) and a reference growth curve (orange).

and the data entry of the required variables takes just a few minutes. It is compatible with most platforms and browsers. To our knowledge, these technical considerations have not been fully met in the past, preventing wider adoption.

This approved Class I software medical device in Europe provides accurate growth prediction via the application of validated and published GPMs and country- and disease-specific reference charts. The input variables for iGRO required to drive the growth prediction are readily accessible to the physician; no additional biological tests are required. iGRO enables physicians to monitor the patient's response to GH treatment and it may potentially be used to detect discrepancies early. GPMs cannot explain all of the variations in the response of a patient to rhGH treatment, and they are not a substitute for clinical expertise. Thus, it is important that physicians also utilise their knowledge and judgement when assessing the growth response of their patients and making adjustments to the treatment plan.

Currently, iGRO is the only prediction model which presents the IoR, a measure of how the actual growth response compares to the growth response that is expected based on the patient's characteristics [1]. The output from the IoR can help support individual decisions around the management of the patient, e.g. ceasing treatment if the responsiveness is very low or reducing the dose when a child over-responds. Issues with adherence to treatment may also come to light earlier and can be addressed by both physician and patient together [8]. In addition, the Patient Summary document presents all of the patient details, visit details and the graphical outputs, which can

be shared with the patient/parent or filed in the patient notes.

iGRO should be considered a live and evolving medical device whereby additional features and preferences based on user feedback will further optimise its functionality and ease of use.

Real-world use of the tool and learning from the reliability of predictions will enable further refinement of iGRO, creating the potential to advance and support management of short stature and GH treatment in children.

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References

1. Ranke MB, Lindberg A. Predicting growth in response to growth hormone treatment. *Growth Horm IGF Res* 2009;19:1–11.
2. Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Arch Dis Child* 2015;101:96–100.
3. Baron J. Growth hormone therapy in childhood: titration versus weight-based dosing? *J Clin Endocrinol Metab* 2007;92:2436–8.
4. Cohen P, Rogol AD, Weng W, Kappelgaard AM, Rosenfeld RG, et al. American norditropin study group. 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. *Clin Endocrinol (Oxf)* 2013;78:405–14.
5. Cutfield W, Lindberg A, Albertsson-Wikland K, Chatelain P, Ranke MB, et al. Final height in idiopathic growth hormone deficiency: the KIGS experience. KIGS International Board. *Acta Paediatr Suppl* 1999;88:72–5.
6. Ranke MB, Lindberg A, Mullis PE, Geffner M, Tanaka T, et al. Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. *Horm Res Paediatr* 2013;79:51–67.
7. Kaspers S, Ranke MB, Han D, Loftus J, Wollmann H, et al. Implications of a data-driven approach to treatment with growth hormone in children with growth hormone deficiency and Turner syndrome. *Appl Health Econ Health Policy* 2013;11:237–49.
8. Hindmarsh PC, Cole TJ. Evidence-based growth hormone therapy prediction models. *J Paed Endocrinol Metab* 2000;13:1359–64.
9. Land C, Blum W, Shavrikova E, Kloeckner K, Stabrey A, et al. Predicting the growth response to growth hormone (GH) treatment in prepubertal and pubertal children with isolated GH deficiency – model validation in an observational setting (GeNeSIS). *J Paed Endocrinol Metab* 2007;20:685–93.
10. Lechuga-Sancho A, Lechuga-Campoy JL, del Valle Núñez J, Rivez-Crespo F. Predicting the growth response of children with idiopathic growth hormone deficiency to one year of recombinant growth hormone treatment: derivation and validation of a useful method. *J Paed Endocrinol Metab* 2009;22:501–9.
11. Ranke MB. New paradigms for growth hormone treatment in the 21st century: prediction models. *J Paed Endocrinol Metab* 2000;13(Suppl 6):1365–9.
12. Wit JM, Ranke MB, Albertsson-Wikland K, Carrascosa A, Rosenfeld RG, et al. Personalized approach to growth hormone treatment: clinical use of growth prediction models. *Horm Res Paediatr* 2013;79:257–70.
13. Schönau E, Westermann F, Rauch F, Blum WF. A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. *Eur J Endocrinol* 2001;144:13–20.
14. Wikland KA, Kristrom B, Svensson BR, Nierop AF. Validated multivariate models predicting the growth response to GH treatment in individual short children with a broad range in GH secretion capacities. *Paediatr Res* 2000;48:475–84.
15. Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, et al. Derivation and validation of a mathematical model for predicting the response to exogenous recombinant human growth hormone (GH) in prepubertal children with idiopathic GH deficiency. KIGS international board kabi pharmacia international growth study. *J Clin Endocrinol Metab* 1999;84:1174–83.
16. Ranke MB, Lindberg A, Cowell CT, Wikland KA, Reiter EO, et al. Prediction of response to growth hormone treatment in short children born small for gestational age: analysis of data from KIGS (Pharmacia International Growth Database). *J Clin Endocrinol Metab* 2003;88:125–31.
17. Ranke MB, Lindberg AJ, Martin DD, Bakker B, Wilton P, et al. The mathematical model for total pubertal growth in idiopathic growth hormone (GH) deficiency suggests a moderate role of GH dose. *J Clin Endocrinol Metab* 2003;88:4748–53.
18. Ranke MB, Lindberg AJ. Observed and predicted total pubertal growth during treatment with growth hormone in adolescents with idiopathic growth hormone deficiency, Turner syndrome, short stature born small for gestational age and idiopathic short stature: KIGS analysis and review. *Horm Res Paediatr* 2011;75:423–32.
19. Ranke MB, Lindberg AJ. Prediction models for short children born small for gestational age (SGA) covering the total growth phase. Analyses based on data from KIGS (Pharmacia International Growth Database). *BMC Med Inform Decis Mak* 2011;11:38.
20. EU medical devices directive Guidelines on Medical Devices, Clinical Evaluation A guide for Manufacturers and Notified Bodies. European Commission. Enterprise and Industry Directorate General MEDDEV 2009; 2.7.1. Rev 3.
21. Straetmans S, Roelants M, Thomas M, Rooman R, De Schepper J. Reference curve for the first-year growth response to growth hormone treatment in prepubertal children with idiopathic growth hormone deficiency: validation of the KIGS first-year growth response curve using the Belgian register for the study of growth and puberty problems. *Horm Res Paediatr* 2014;81:343–9.
22. Cowell CT, Diestch S, Greenacre P. Growth hormone therapy for 3 years: the OZGROW experience. *J Paed Child Health* 1996;32:86–93.
23. Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W. Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. KIGS International Board, Kabi International Growth Study. *J Clin Endocrinol Metab* 2000;85:4212–8.
24. Cole TJ. [Some questions about how growth standards are used.](#) *Horm Res* 1996;45(Suppl 2):18–23.
25. Ranke MB, Lindberg A, Longas AF, Darendeliler F, Wikland KA, et al. on behalf of the KIGS international board. Major determinants of height development in Turner syndrome (TS) patients treated with GH: analysis of 987 patients from KIGS. *Paediatr Res* 2007;61:105–10.
26. Ranke MB, Lindberg A. On behalf of the KIGS International Board. 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 Med Inform Decis Mak* 2011;11:38.
27. Cutfield WT, Derraik JG, Gunn AJ, Reid K, Delany T, et al. Non-adherence with growth hormone treatment in children is common and impairs linear growth. *PLoS One* 2011;6:e16233.