Predicting Response to Growth Hormone Treatment

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Abstract Despite extensive experience over the past 25 y in managing growth failure with growth hormone (rhGH), predicting treatment efficacy in individual children remains a challenge. In this paper, the authors present the methods that are currently available to clinicians for predicting the growth response, and other more sophisticated techniques which have the potential to pave the way for individualised therapy in the future.

Keywords Growth hormone · Growth failure · Growth prediction · Growth hormone response · Molecular biomarkers

Introduction

Recombinant human growth hormone (rhGH) is approved as replacement treatment for growth hormone deficiency (GHD) and for the management of growth failure in children with Turner syndrome (TS), short stature homeobox (SHOX) gene haploinsufficiency, Prader-Willi syndrome (PWS), chronic renal insufficiency (CRI) and those born small for gestational age (SGA). It is also approved for idiopathic short stature (ISS) and Noonan syndrome in some countries such as USA [1]. These approvals by regulatory bodies are based on the wide safety margin in conjunction with compelling evidence of significant gain in growth over both short and long term as well as in improved final height in various cohorts.

When a child is diagnosed with one of the approved indications, current practice is to discuss the potential benefits of rhGH treatment with the patient and family based on results from published studies for the specific etiology. This has a major influence on the decision to embark on treatment even though a beneficial response cannot be guaranteed for a particular child. For individual children, the response to rhGH treatment varies considerably across all indications and also within each indication. Thus, drug response is heterogeneous, and influenced by an interplay of both auxological, environmental and genetic factors. As treatment entails daily subcutaneous injections for many years and at mounting costs, it poses a major burden for families and health services. Reliable methods of predicting the clinical outcome for individual children can enable targeting treatment to those children most likely to benefit, thus optimising growth whilst minimising cost. Such practice can obviate inadvertent profligacy and unnecessary burden for those in whom treatment might not have a clinically significant effect. In this paper, the authors present the methods that are currently available to clinicians for prediction, and other more sophisticated techniques which have the potential to pave the way for individualised therapy in the future.

Methods Currently Available to Predict Response

Differentiating a Good Response from a Poor Response

Treatment of children with growth failure with rhGH is aimed at normalising stature during childhood and improving final adult height. In clinical practice, all children are regularly
reviewed throughout the period of treatment until final height is attained and beyond. A change in the height trajectory on a growth chart and in calculated height velocity are most commonly used to evaluate the response: the observed growth response is compared with the child’s previous growth and the response expected for the diagnosis [Table 1].

A number of definitions of poor response have been proposed in clinical trials and consensus statements [Table 2]. The first year growth response is especially informative as it predicts growth in the subsequent years and also correlates with the final height attained [10–13]. From Genentech’s large post-marketing surveillance database, the National Cooperative Growth Study (NCGS), curves of first year growth responses to standard daily GH doses in prepubertal children (aged 2–14 y at start of treatment) have recently been generated for four major indications: idiopathic GHD, organic GHD, TS and ISS [8]. Height velocity (HV, cm/year) in the first year of GH treatment was less influenced by age than change in Ht standard deviation score (SDS) and HV SDS in the first year of rhGH treatment. Bakker and co-workers, therefore, recommend evaluating HV in the first year and comparing it with the HV charts provided to identify treatment efficacy, an HV above −1 SDS being considered acceptable [8]. Bang et al. have compared the various growth parameters used to define a poor response to rhGH treatment in prepubertal children with idiopathic and organic GHD, TS, SGA, ISS and other conditions [14]. The lowest and greatest number of poor responders was identified using the definitions of 1st year change in height SDS <=0.3 and change in height velocity <3 cm, respectively. Although no definition was found to be superior, the authors recommend 1st year height velocity SDS <0.5 as clinically relevant.

Biochemical Assessment of Growth Hormone Secretary Status

In children with growth failure, evaluating endogenous GH secretary status with provocation tests offers a crude prediction of response to treatment. Those with genuine GHD and peak GH levels to stimulation tests of <3 μg/L as a group have a better growth response to rhGH treatment than those who have borderline (GH insufficiency or ‘partial’ GHD) or normal GH levels (non-GHD or GH sufficiency [14]. However, even within the GHD category, there is considerable variation in response to rhGH [15]. Some, but not all, of this variation can be explained by a number of factors: the difficulty in being confident about the diagnosis of GHD owing to the lack of an ideal diagnostic test, inadequate replacement doses of rhGH, failure to titrate doses according to IGF-I levels and poor adherence to the daily injection routine.

The arbitrary cut-off levels in GH provocation tests to differentiate GHD from non-GHD are convenient in clinical practice. However, their limitations include poor specificity when peak GH levels are low as well as lack of information about GH secretary pattern in those with ‘normal’ GH levels to provocation. As might be expected, a reduced capacity for GH secretion has been observed in children with GHD from serial overnight GH profiles with 20-min sampling, and this is effective in predicting a response to rhGH treatment [16]. Children with ISS demonstrate a disorderly GH secretary pattern which is more disorganised and associated with lower IGF-I levels in those with severe short stature (height SDS <−3.33) compared to those who are modestly short (height SDS ~2.33–1.64). In contrast to GHD, serial sampling was not found to be a useful predictor of the response to treatment in children with ISS [16].

IGF-I and IGFBP-3 Levels, and the IGF-I Generation Test to Evaluate GH Responsiveness

Assays for IGF-I and IGFBP-3 levels are now routinely available and contribute to the evaluation of endogenous GH secretion as well as GH insensitivity. Among the non-GHD states, children born SGA and those with ISS can be further categorised by their IGF-I levels: a large group with an apparently intact GH-IGF-I axis (normal GH levels to provocation tests, and normal IGF-I and IGFBP-3 levels) and a smaller group with tests consistent with GH

<table>
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<tr>
<th>Table 1 Recommended dose of growth hormone (rhGH) and expected growth response for the approved indications [2, 3]</th>
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<tr>
<td><strong>μg/kg daily</strong></td>
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<td>----------------</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>Turner Syndrome</td>
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<tr>
<td>Prader Willi Syndrome</td>
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<tr>
<td>Chronic renal insufficiency</td>
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<tr>
<td>Small for gestational age and poor postnatal growth</td>
</tr>
<tr>
<td>SHOX haploinsufficiency</td>
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<td>Idiopathic short stature</td>
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insensitivity (normal or high GH levels but low circulating IGF-I). GH insensitivity is thus a description of a hormonal pattern and is not necessarily a primary diagnosis. It extends over a spectrum from partial to no responsiveness to rhGH treatment. The latter does include severe primary IGF-I deficiency due to recognised clinical conditions such as molecular defects in the GH receptor, GH signalling pathway and the IGF-I gene [17]. For these rare defects, a trial of rhGH is not recommended and recombinant human IGF-I is the treatment of choice. Short children born SGA and who have specific syndromes also do not respond well to rhGH treatment [18].

The IGF-I generation test provides information about the IGF-I and IGFBP-3 response to a short 4- or 7-d course of rhGH. Although this contributes to assessing the extent of GH sensitivity, the acute biochemical response does not necessarily correlate with long term gain in linear growth [19, 20].

### Mathematical Growth Prediction Models

With the ample availability but high cost of rhGH, considerable effort has been devoted over the past two decades to developing and evaluating mathematical growth prediction models that can provide a realistic expectation of response to rhGH treatment for individual patients with specific diagnoses [21]. Using multiple regression analysis, models have been derived from both prospective and retrospective studies, and based on data from clinical trials as well as large clinical databases, such as the Pfizer International Growth Database (KIGS).

The variables evaluated in the models tend to be those that are readily available to clinicians such as etiology, patient characteristics (age, bone age, gender, pubertal status), growth measurements (height, height velocity, weight, mid-parental height, birth weight), biochemical parameters (peak GH to provocation test, IGF-I, IGFBP-3) and treatment related factors (dose, injections per wk, age at start of treatment). Some models have also tested parameters that are not routinely monitored in children on rhGH treatment, such as biochemical growth markers (urine deoxypyridinoline) [9]. Details of models and variables used to predict first year height velocity, height velocity at a given point during rhGH treatment and adult height are described in the comprehensive review and critique by Ranke and Lindberg [21].

An algorithm can be derived from the extent to which the best combination of variables in a model correlate with the linear growth of a cohort and validated with other known cohorts [21]. Thereafter it can be used to predict the long term response for an individual child. The variables that are included contribute to defining the practical utility of the model in two ways. Firstly, a prediction can be made before actually initiating treatment to evaluate the likely benefit and inform decisions about whether to start. Significant variables tested in these models include chronological age, height SDS compared to mid-parental height, height velocity in the preceding year, peak GH to provocation test (for GHD), IGF-I level and dose of rhGH. Secondly, initial linear growth over the first 3–12 mo after rhGH treatment is commenced can be included in the model and compared with the predicted response to decide whether to continue, modify or stop treatment. Models are available for first year responses, in some conditions for subsequent years as well as for total pubertal growth [21–23].

The predictive power of the models reported to date remains suboptimal, at best accounting for 50–90% of the variation in linear growth with the models with the greatest $r^2$ being those that include responses on treatment such as changes in bone markers [9, 24]. While this illustrates very well the complexity of linear growth and the variable impact of rhGH treatment, it also reinforces the role of unknown factors in reliably predicting treatment efficacy. The best prediction model is expected to fully explain linear growth, should be accurate with minimum error (the difference between the predicted calculation and actual height velocity) and should have high specificity to identify non-responders. Including variables identified through genomics, proteomics and novel methodologies may contribute to refining models so that they can be successfully used to individualise treatment in the future.

### Pharmacogenomic and Pharmacoproteomic Approaches

Genomics and proteomics have potential applications both in the diagnosis as well as management of children with growth disorders. Pharmacogenomics is the determination of the impact of an individual’s genetic variation across the whole genome on their response to a drug. Transcriptomics relates to the study of gene expression profiles using array technologies and correlating this to treatment outcomes stratified by variables such as diagnosis or GH secretory status. Pharmacogenetics is the relationship between variations

#### Table 2: Definition of poor response to growth hormone treatment

- 1st year change in height SDS <0.3 [4]
- 1st year change in height SDS <0.5
- 1st year height velocity SDS <0.5 [5]
- Height velocity SDS <±1 for age and sex [6]
- Change in height velocity <3 cm [7]
- Height velocity <-1 SDS of expected 1st year treatment response (according to age at baseline) [8]
- Height velocity on treatment < double pre-treatment height velocity [9]
in individual genes and the response to drug treatment and includes both single nucleotide and larger polymorphisms.

Ultimately, it is the proteins translated from mRNA that are critical in regulating and mediating cellular processes. Pharmacoproteomics is the study of both qualitative and quantitative changes in proteins within a cell or tissue in response to a treatment such as rhGH [25]. Expression Proteomics involves the analysis and comparison of protein expression profiles, called the proteomes. Modern proteomic techniques have been used to discover GH regulated protein biomarkers from serum and peripheral blood leukocytes in healthy adults [26–28], prepubertal children with GHD [29] and ISS [30]. In the children with GHD and ISS treated with rhGH, a number of novel biomarkers related to the lipoprotein profile (transferrtin, apolipoproteins and serum amyloid A 4) were identified that differentiated good responders from poor responders [29, 30].

Functional proteomics entails examining protein interactions and their effect on biological processes. Such novel approaches with their rapidly developing technologies have already provided insights into the inherited nature of growth disorders and identified a number of important associations between genetic variation in single genes/proteins and response to rhGH treatment (see below). As their cost continues to fall, the technology will be used to investigate the effects of the whole genome and proteome on drug response. In the future, they will allow individualised rhGH treatment by providing information about the likely treatment response for that child based on their genomic and proteomic profile.

### Polymorphisms in Genes Associated with GH Action

GH circulates bound to GH-binding protein (GHBP), which is the extracellular domain of the GH receptor (GHR). Levels of GHBP serve as a marker of GHR expression and GH responsiveness in target tissues [31] GH binds to the GHR in a two-to-one configuration. This activates the intracellular signal cascade, principally via the Janus tyrosine kinase 2 (JAK2) - signal transducers and activators of transcription (STAT) pathway [32], and induces IGF-I gene transcription. In the circulation, IGF-I is principally bound to IGFBP-3 and together they form a ternary complex along with the acid labile subunit (ALS). Common polymorphic variants in the genes in this GH – IGF pathway, such as in GH1, GHR, JAK2, STAT5, IGF-I, IGFBP-3 and ALS, may thus contribute to the inter-individual differences in treatment efficacy seen in children with growth failure across the spectrum from severe GHD to partial GH insensitivity [Table 3].

### Exon 3 Polymorphisms in the Growth Hormone Receptor

The GH receptor (GHR) is encoded by a gene on chromosome 5 and contains 10 exons. It consists of an extracellular domain (encoded by exons 2–7), a single transmembrane domain (encoded by exon 8) and an intracellular domain (encoded by exons 9 and 10). The presence or absence of exon 3 results in the full length receptor protein (fl/fl) or a shorter form (d3/d3 or fl/d3) [39]. *In vitro* studies suggest that the

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**Table 3** Common polymorphic variants in the genes in the GH – IGF pathway reported to contribute to inter-individual differences in response to growth hormone treatment

<table>
<thead>
<tr>
<th>Gene variant</th>
<th>Reported effect on linear growth in children treated with growth hormone</th>
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<tbody>
<tr>
<td>GH1 gene: Variants in the promoter and locus control region (LCR)(super promoter)</td>
<td>LCR single nucleotide polymorphisms (SNPs) 1 and 2, and promoter SNP 6 associated with first year growth in children with isolated GHD [33]</td>
</tr>
<tr>
<td>GH receptor (GHR) gene: Presence or absence of exon 3 results in full length receptor (fl/fl) or a shorter form (d3/d3 or fl/d3)</td>
<td>d3-GHR is associated with a better first year response regardless of underlying diagnosis [34]</td>
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<tr>
<td>GHR gene: c.1319 G&gt;T polymorphism</td>
<td>T allele associated with a better first year response in children with GHD [35]</td>
</tr>
<tr>
<td>IGFBP-3-3 gene: –202 A/C polymorphism</td>
<td>A allele associated with higher IGFBP-3 levels during treatment and a better first year response in children with severe GHD [36]</td>
</tr>
<tr>
<td>IGFBP-3-3 gene: –202A/C and –185 C/T polymorphisms</td>
<td>C-202/C-185 haplotype associated with lower IGFBP-3 and shorter stature at baseline but greater increase in IGFBP-3 and height in the first year in children born SGA [37]</td>
</tr>
<tr>
<td>IGF-I gene: Microsatellite with variable CA repeats in the promoter</td>
<td>Allele with 19 CA repeats associated with lower first year growth in GHD [38]</td>
</tr>
<tr>
<td>Interactions between genes at different loci: GHR, IGF-I and IGFBP-3</td>
<td>IGF-I non-19 CA/* with IGFBP-3 A/A found to be a favourable genotype for first year growth, and IGF-I non-19 CA/* with d3-GHR/* positively determined adult height in GHD [38]</td>
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absence of exon 3 alters transactivation, production, structure, stability, glycosylation or transport of the receptor [39, 40].

In 2004, Dos Santos et al. observed that the first year growth response to rhGH was significantly better in children carrying the d3-GHR allele than in those homozygous for the full length allele [39]. This study was restricted to children with unexplained short stature and short children born SGA. It stimulated further investigations into the influence of the d3-GHR allele on the growth response to rhGH in a range of disorders. Findings both concordant as well as conflicting with those reported by Dos Santos have been published in growth hormone deficiency (GHD) [41, 42], Turner Syndrome (TS) [43], in short children born SGA [44, 45] and ISS [46].

A recent systematic review and meta-analysis based on 15 studies assumed a dominant inheritance pattern and concluded that the d3-GHR genotype is associated with an increased height velocity (approximately 0.5 cm in the first year of treatment) [34]. Interestingly, this effect was observed regardless of the underlying diagnosis, and was more pronounced at lower doses of rhGH and older age at start of rhGH treatment [34].

The lack of consensus from different study cohorts is intriguing and suggests that the effect of this GHR polymorphism is either not significant, very small, or overpowered by other influences, genomic or environmental, and thus not observed consistently. Alternatively, differences in genotyping techniques [44, 46], the units chosen to assess growth response, or the doses used to treat the short stature may all influence the observed effect of this allele.

c.1319 G>T Polymorphism in the Growth Hormone Receptor

Single nucleotide polymorphism (SNP) analysis can be used to identify polymorphisms in potential candidate genes associated with GH and IGF-1 signalling. Wan and coworkers examined the frequencies of 13 known SNPs of genes in this axis among 154 prepubertal children with GHD, 208 with familial short stature and 100 healthy children of normal stature [35]. SNPs of the following genes were evaluated: GHR, JAK2, STAT5a, STAT5b, IGF-I, IGFBP-3, ALS and SOCS-2. The genotype frequencies of these SNPs were not different among the three subject groups and did not influence height. Of the 13 polymorphisms examined, c.1319 G>T of the GHR gene was associated with the first year response to rhGH in the children with GHD. Although the T allele was less frequent and found in a third of the population (TT 2%, GT 27%, GG 71%), it was associated with a better first year height velocity (mean 11.8 cm/y in TT and 8.6 cm/y in GT) compared to the GG genotype (mean 7.8 cm/y) in the GHD group treated with rhGH. These findings have not been replicated in other cohorts. However, the observations were supported by in vitro studies which showed greater bioactivity of GHR c.1319 T in conjunction with increased STAT5 activation.

−202 A/C IGFBP-3 Polymorphism

A number of SNPs have been identified in the promoter region of the IGFBP-3 gene, which is located on chromosome 7 [47]. Of these, the −202 A/C polymorphism comprises an A to C nucleotide change. The functional relevance of this SNP was indicated by an association with IGFBP-3 levels in healthy adults, levels being highest in those with the AA genotype, and in vitro studies showing significantly greater promoter activity for the A allele than the C allele. The influence of this SNP on the biochemical and growth response to rhGH in short children with severe GHD and those born SGA has subsequently been assessed by separate groups [36, 37].

During rhGH treatment, IGFBP-3 levels (highest with AA genotype) as well as first year height velocity (AA 13.1 cm, AC 11.4 cm, and CC 10.8 cm) were related to the −202 A/C IGFBP-3 genotype in 71 children with severe GHD [36].

In a multicentre study of 292 short prepubertal children born SGA, van der Kaay and coworkers investigated the interaction of two SNPs, the −202 A/C and −185 C/T, in the IGFBP-3 promoter and compared the biochemical and growth response by haplotypes [37]. Compared to SGA children with the A-202/C-185 haplotype, those with the C-202/C-185 haplotype had lower IGFBP-3 levels and were shorter at baseline but had a greater increase in IGFBP-3 as well as height SDS after 12 mo of rhGH treatment. Such an inverse relationship between the first year response to rhGH and pretreatment IGFBP-3 levels as well as stature is well recognised, and reflects endogenous GH secretion and sensitivity [48, 49].

Consistent with observations in GH sufficient adults [47], the SGA children with the −202 AA genotype had the highest IGFBP-3 levels at baseline while those with the C allele had lower levels [37]. However, IGFBP-3 levels did not differ by −202 A/C IGFBP-3 genotype in the GHD children pre-treatment [36]. These findings highlight the contribution of endogenous and exogenous GH to the functional effect of the −202 A/C polymorphism on circulating IGFBP-3 [36] and are in keeping with the known stimulating effect of GH on IGFBP-3 levels [50, 51].

IGF-I Promoter CA Repeat Polymorphism

The IGF-I gene is located on the long arm of chromosome 12. A polymorphism involving a microsatellite with variable number of cytosine-adenosine repeats (CA)n in the IGF-I promoter region has been found to be associated with circulating IGF-I levels and stature in adults [52]. The
most common allele among Caucasians comprises 19 CA repeats but the sequence can range from 10 to 24 repeats. The effect of this variant as well as the previously reported d3-GHR and −202 A/C IGFBP-3 genotypes have recently been evaluated by Costalonga et al. in 84 prepubertal children with GHD [38]. Subjects homozygous for the 19 CA repeat allele had lower height velocity in the first year of rhGH treatment and attained lower adult height compared to those with at least one variant allele. From the combined analysis of the three GH-IGF axis genes, IGF-I non-19 CA/* and IGFBP-3 A/A emerged as the favourable genotype for first year height velocity, while the combination of IGF-I non-19 CA/* and d3-GHR/* positively determined adult height. This study lends support for the effects of multiple genes at different loci in determining the response to rhGH treatment.

GH1 Gene Defects

The human GH gene, GH1, is located on the long arm of chromosome 17 within a cluster of five related genes and its structure comprises 5 exons. A number of defects in this gene are known to cause isolated GHD [53]. They are inherited as autosomal dominant (type II) or recessive (types IA and IB), and the phenotype varies from modest to severe short stature. While GH-antibody formation is associated with rhGH treatment in those with the autosomal recessive form, the development of antibodies, the growth inhibiting potency of the antibody and the response to treatment GH are also variable [54, 55].

The expression of GH1 is regulated by the GH1 promoter and a locus control region (LCR) or “super promoter”. SNPs in the GH1 promoter region are common and a number have been studied in patients with ‘idiopathic’ isolated GHD in whom no mutations have been identified [33, 56]. The genotype of SNPs in intron 4 (A/T 1664) and the promoter (T/G 218; G/T 439) were found to be associated with peak GH to provocation tests, IGF-I levels and height in 43 Japanese children with GH insufficiency, 46 short children with GH sufficiency and 294 normal adults [56]. As these biochemical parameters are indicative of GH secretory status, GH1 variants studied are thought to account for some of the variation in clinical outcome from rhGH treatment in patients with isolated GHD.

In 62 Dutch children with isolated GHD, De Graaff et al. did not find an association between intron 4 SNP and growth related parameters [33]. They analysed additional variants in the promoter/LCR and found that LCR SNPs 1 and 2, and promoter SNP 6 were associated with IGF-I levels, baseline height and linear growth during the first year of rhGH in their patients with isolated GHD [33]. They proposed that the promoter and LCR SNPs had a dominant effect which also accounted for intron 4 effects.

Microarray Based Gene Analysis from Peripheral Blood

Changes in mRNA expression in peripheral blood mononuclear cells (PBMC) in response to rhGH can be evaluated using array technology. The authors explored the validity and practicality of this approach in three children with GHD and three children with Turner Syndrome [57]. Gene expression profiles were compared by diagnosis and by initial response to rhGH treatment. Inter-individual differences in gene expression both within and between the two diagnostic

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**Fig. 1** Algorithm for the management of the first year of growth hormone (rhGH) treatment and for deciding when to stop treatment based on the information that is readily available to clinicians at the present time [61] in patients who also have deficiencies of cortisol and thyroxine, replacement for these should be started before initiating rhGH treatment.
groups overshadowed the changes associated with rhGH. In response to rhGH however, there was a distinct pattern of gene expression by diagnostic group and major changes were observed in GHD but not Turner syndrome. The rhGH-induced genes identified in GHD were novel targets and included CREM (a transcription factor that binds to the cAMP response element (CRE)), RGS1 (the gene encoding a regulator of G-protein signalling, which acts as a GTPase activating protein), SOCS1 (Suppressor of cytokine signalling 1) and amphiregulin (AREG, a member of the epidermal growth factor family). Their role in GH-dependent growth remains to be elucidated. Further attempts to identify potential biomarkers of rhGH response from changes in gene expression profiling in PBMC have been reported from a study of 10 adult female patients with severe adult-onset GHD [58]. Twenty four genes were found to be differentially expressed from PBMCs taken before and after rhGH treatment. However, these did not overlap with the genes the authors found to be affected by rhGH treatment in children [57].

**Noonan Syndrome and Known Molecular Defects**

rhGH was approved for the treatment of short stature in children with Noonan syndrome in USA in 2007. Traditionally the diagnosis was based on clinical assessment but causative mutations have now been identified. Missense mutations in the PTPN11 gene are found in nearly 50% of cases. Defects in SOS1 and KRAS genes are found in 10% and 1% cases respectively [59]. Patients with PTPN11 mutations have relative GH insensitivity and demonstrate a reduced growth response to rhGH treatment when compared with cases who do not have this defect [60].

**Summary and Conclusions**

Despite extensive experience over the past 25 y in managing growth failure with rhGH, predicting treatment efficacy in individual children remains a challenge. In current clinical practice, the outcome is deemed to be more favourable with a diagnosis of GHD as opposed to GH sufficiency, younger age and prepubertal status at start of treatment when there is still a considerable potential for linear growth, optimal dosing guided by IGF-1 and IGFBP-3 levels, and good compliance. However, a beneficial response cannot be guaranteed. Based on the information that is readily available to clinicians at the present time, the authors have provided an algorithm for the management of the first year of rhGH treatment and for deciding when to stop treatment [Fig. 1] [61].

In pursuit of a reliable method to predict the short and long term treatment response for individual patients, the predictive power, accuracy, and specificity of numerous mathematical models have been investigated. As yet, none fulfil the ideal requirements. The formulae are complicated, no applications are available to simplify calculations and the models are therefore not routinely used in clinical practice. As genetic factors can contribute to variations in therapeutic response, inclusion of molecular biomarkers in the growth prediction armamentarium offers potential for an individual approach to rhGH treatment in the future. Selecting patients and population subgroups by their unique genetic profiles will make treatment safer and more effective.

**Conflict of Interest** None.

**Role of Funding Source** None.

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