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review

Important Tools for Use by Pediatric Endocrinologists in the Assessment of Short Stature

Labarta et al. Tools for Short Stature Assessment

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Abstract
Assessment and management of children with growth failure has improved greatly over recent years. However, there remains a strong potential for further improvements by use of novel digital techniques. A panel of experts discussed developments in digitalization of a number of important tools used by pediatric endocrinologists at the third 360° European Meeting on Growth and Endocrine Disorders, funded by Merck KGaA, Germany, and this review is based on those discussions. It was reported that electronic monitoring and new algorithms have been devised that are providing more sensitive referral for short stature, and computer programs have improved ways in which diagnoses are coded for use by various groups such as healthcare providers and government health systems. Innovative cranial imaging techniques have been devised that are considered safer than using gadolinium contrast agents and are also more sensitive and accurate. Deep-learning neural networks are changing the way that bone age and bone health are assessed, which are more objective than standard methodologies. Models for prediction of growth response to GH treatment are being improved by applying novel artificial intelligence methods that can identify non-linear and linear factors that relate to response, providing more accurate predictions. Determination and interpretation of IGF-I levels are becoming more standardized and consistent, for evaluation across different patient groups, and computer-learning models indicate that baseline IGF-I SDS is among the most important indicators of GH therapy response. While physicians involved in child growth and treatment of disorders resulting in growth failure need to be aware of and keep abreast of these latest developments, treatment decisions and management should continue to be based on clinical decisions. New digital technologies and advancements in the field should be aimed at making clinical decisions more efficient and consider patient-centered approaches.
Keywords: Short stature, height monitoring, bone age, cranial imaging, growth hormone treatment, prediction models

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Introduction

One of the most important tools in monitoring the health of children is an assessment of how an individual child is growing relative to his/her peers. Linear growth monitoring of apparently healthy children can provide early indications of serious conditions (1), which may be identified through growth algorithms and the expertise of clinicians (2,3). If a child is noted to be particularly short, the cause should be determined and referral to a pediatric endocrinologist is likely, where a diagnosis can often be assigned from factors such as body proportions and clinical and family history (1,4). Although genetic abnormalities associated with short stature are continually being identified (5), a high percentage of cases remain idiopathic with no specified cause (6). While identified causes are often associated with defects in the growth hormone (GH)–insulin-like growth factor (IGF)-I axis, a large proportion of cases do not involve GH or IGF abnormalities, but may involve factors such as growth plate abnormalities (3,5,7).
GH therapy to improve linear growth is approved for a number of conditions associated with growth failure in children, although this varies to some extent by GH formulation and country (2,8,9,10,11). It is important for

clinicians to identify ways of optimizing treatment; while starting GH treatment at a young age generally improves outcomes, for many indications, referral, diagnosis and GH initiation occur later than optimal (2,8). Artificial intelligence and machine-learning are revolutionizing diagnostic tools in all areas of medicine, including child growth and development. It remains important for pediatric endocrinologists to continually assess the innovative techniques that are becoming available with regard to identifying the nature of growth failure in children and how to tailor the management of the condition.

The present report is based on a meeting held in Rome, Italy, funded by Merck KGaA, Darmstadt, Germany, which discussed important new tools being developed and used by pediatric endocrinologists. Accurately identifying which children should be defined as short, what is the cause of the short stature, problems relating to bone maturation and how a child with growth failure will respond to treatment can all be aided by digital technologies, leading to improved clinical decisions and patient-centered approaches.

Growth monitoring and algorithms

Among children referred for evaluation of short stature, the prevalence of pathological conditions is only approximately 5%, with reported variation from 1.3% to 19.8% depending on the criteria considered (12,13,14). Thus, the majority of referrals show no pathology and diagnostic work-up may be carried out unnecessarily (3,15). Additionally, use of growth charts that are not population-specific can result in a large proportion of incorrect referrals for diagnostic work-up (14,16,17). Using appropriate growth references is of paramount importance when assessing a child's height because of the impact on eligibility for therapy (17). Wide variations are reported in population height measurements and the choice of auxological criteria for referral for short stature (12,13,14,18). Current protocols for growth monitoring frequently result in delayed diagnosis, and a consequent delay in the treatment of growth failure (19,20,21). Appropriate referrals will avoid unnecessary procedures and enable earlier diagnosis of cause of growth failure and prompt initiation of therapy, thus improving outcomes and diminishing complications. Therefore, it is important that clinical practice should be optimized by standardization of growth monitoring, with validated evidence-based protocols (2,12,13).

There is currently a lack of consensus on criteria for definition of abnormal growth. Seven different algorithms have been published in the last 20 years, involving around eight auxological parameters to be evaluated (22). However, the level of validation is low for each of the algorithms, with widely varying sensitivities and specificities. While height standard deviation score (SDS) is used in all algorithms, there is no consensus concerning the cut-off. A study across 23 European countries found height SDS cut-off ranged from –1.64 to –2.67 SDS and growth deflection or height velocity cut-off ranged from –0.50 to –2.32 SDS (18). Distance to target height SDS is the second most frequently used parameter, but different formulae may be used for calculation and there may be inaccuracies in measurements of parental heights. Other parameters were based on dynamic growth indicators, such as height deflection and height velocity SDS.

Comparison of children using the Dutch, Finnish and UK guidelines showed variations in sensitivity and specificity (14). Distance to target height provided the best specificity, particularly using the Dutch guidelines, and combination with height SDS provided effective growth monitoring. However, sensitivity was much lower and, even using combinations of up to four criteria, at least 20% of children with pathological growth failure may not be identified by these auxology measurements. Adding growth deflection may improve sensitivity and in the pre-pubertal period recent growth deflection should be considered a red flag leading to referral to a specialist clinic (14). Strict application of guidelines and cut-offs may lead to excessive numbers of referrals and other parameters may need to be added (15). In children younger than 3 years height/length measurements are often inaccurate; referral at this age should be based on extreme short stature or repeated measurements (23).

In children over 3 years of age, it was shown that electronic monitoring of growth, together with algorithms for assessment of auxology, could identify patients for referral for specialist care, and resulted in increased detection of pathological conditions associated with growth failure (24). In order for electronic health records to be clinically advantageous, good infrastructure and databases are required. With increasingly widespread collection, monitoring of height of individual children in relation to their peers should become automatic and improve accuracy of referrals. Despite this availability, few countries have currently adopted such use of electronic records and automated growth algorithms. Electronic monitoring of height and weight has been used to assess obesity in children in Canada (25,26), but not linear growth and it was noted that better documentation by physicians was required. Currently, only the Scandinavian countries of Norway, Sweden and Finland have fully developed centralized systems for electronic recording and only Finland has implemented automated height growth analysis. However, it should be noted that factors such as being born small for gestational age, dysmorphic features or disproportionate short stature should also be assessed and appropriate algorithms be applied, emphasizing the importance at present of clinical judgment in making a diagnosis of the cause of growth failure.

Categorization of diagnoses

When growth monitoring has indicated that a child has growth failure, the cause is determined from auxology, clinical history and biochemical assessments, and a diagnosis is ascribed. In order to analyze data on diagnoses from large populations it is necessary to transform the reported medical conditions into code numbers. These codes can then be used by health researchers, healthcare providers, government health programs, health insurance companies and others, for a variety of applications. A number of different systems have been designed to classify the diagnoses. The classification should allow inclusion of all patients, enable new etiologies and pathogenetic aspects to be accommodated, define diagnoses accurately to prevent misclassification, follow one general principle, be easy to use and optimally serve the designed purpose (27). The International Classification of Diseases (ICD) was started in 1948 by the World Health Organization, and is now in version ten (http://apps.who.int/classifications/icd10/browse/2010/en). Its aim is to delineate all major disease groups, but diagnoses are not well defined, with too many conditions included together. For example, the term 'endocrine,

nutritional and metabolic disease' includes thyroid disorders, diabetes and disorders that are not really related to endocrinology, such as malnutrition and obesity; thus, the system does not prevent misclassification. Online Mendelian Inheritance in Man (OMIM; https://www.omim.org/) can only be used for genetic disorders. Also, unless phenotypic features or clinical history indicate what genes to examine, in most children with short stature there is no specific "candidate gene" for targeted analysis.

The European Society of Pediatric Endocrinology (ESPE) Classification of Pediatric Endocrine Diagnoses aimed to define all pediatric endocrine disorders and included multiple specific sections, such as the one for all conditions involving short stature (27). This has now been superceded by the online International Classification of Pediatric Endocrine Disorders (ICPED), which is a comprehensive system of pediatric conditions developed by an international group of experts and endorsed by all pediatric endocrinology societies (28,29). The system incorporates the most recent versions of ICD-10 codes and OMIM numbering in order to be easily assimilated into hospital registries, and continues to be developed and added to. The online version is freely available (www.icped.org); while it is used to a reasonable extent in the USA and Netherlands, its use in most other countries is limited. Worldwide standardization within pediatric endocrinology requires the use of ICPED for healthcare, economic and scientific purposes in order that electronic health records can be linked to diagnostic classification and coding systems.

Cranial imaging

As part of the work-up for assigning a diagnosis for the cause of growth failure, cranial imaging is frequently included. However, the only consensus specifying which patients require cranial imaging were published in 2000 and have not been updated (30). They stated that patients with known or suspected intracranial tumors, optic nerve hypoplasia, septo-optic dysplasia or other structural or developmental anomalies should be assessed by magnetic resonance imaging (MRI) or computed tomography of the central nervous system. In patients with confirmed GH deficiency, pituitary height and/or volume, anatomy of the stalk and position of the posterior pituitary should be determined. The guidelines noted though that further normative data were required to improve the quality of assessment.

Standard MRI protocols include sagittal and/or coronal sections of 2-3 mm, with or without contrast medium, and pituitary height and/or volume, stalk anatomy and posterior pituitary position should be determined. Knowledge of the normal shape and volume of the pituitary is required to interpret the images and identify abnormalities (31,32). It is also advised that a survey of the entire brain should be carried out, such as use of fluid attenuation inversion recovery (FLAIR) or diffusion-weighted imaging (32,33). MRI signals for the anterior pituitary and posterior pituitary are similar in the first few months of life, becoming different thereafter. The size/height of the anterior pituitary is 2.6-5 mm in the first post-natal 6 weeks, decreasing to 3 mm by 2 years and then increasing over time until puberty at 6-8 mm; however, it should be noted that pituitary height at puberty is greater in females than in males. The position of the pituitary gland and connection with surrounding tissue are also important because abnormal development or migration of the pituitary is part of the congenital hypopituitary features, confirming the requirement for assessing the surrounding brain from the imaging, along with the pituitary features.

Different imaging studies of patients with a diagnosis of hypopituitarism have shown normal pituitary in 0 to 86% of patients, hypoplastic anterior pituitary in 0 to 84%, and ectopic posterior pituitary in 4% to 100% (34). However, ectopic posterior pituitary was observed more frequently when patients had multiple pituitary hormone deficiencies (>50% in 15 of 18 studies) rather than isolated GH deficiency (<50% in 13 of 18 studies) (34). Abnormal pituitary features may help to predict the development of pituitary hormone deficiencies and the most likely genes involved (34,35). Thus, genetic studies can be better targeted by using MRI data together with associated phenotypic features such as abnormalities of the brain, eyes and palate and additional central nervous system anomalies. Pituitary abnormalities also help in determining long-term status of GH deficiency; ectopic posterior pituitary or stalk abnormalities are associated with permanent GH deficiency whereas patients with isolated GH deficiency and a normal or small pituitary may have sufficient GH secretion at near-adult height and require re-testing (36,37).

In order for such predictions of genetics and endocrine status to be accurate, the MRI techniques must be as sensitive as possible. To enhance the contrast of MRI scans, intravenous gadolinium-based agents have routinely been administered to patients for more than 20 years and were generally considered safe (38,39,40). However, studies have indicated that gadolinium may be retained in the body, particularly in the brain when administered for pituitary imaging; after multiple administrations the contrast agents remained and deposits could be identified (40,41). This raised questions as to whether such deposits have harmful effects and indicated that further research was needed. The studies prompted new evaluations by regulatory bodies and warnings have been added to the labels for gadolinium formulations (42,43). This has led to new computer-aided techniques being developed, such as T2-DRIVE (driven equilibrium), whereby enhanced contrast can be attained without gadolinium administration (44). T2-DRIVE actually appears to be more accurate than gadolinium contrast and enables extremely reliable evaluation of pituitary size and identification of abnormalities. Thus, the technique can greatly improve the diagnosis and knowledge of the pathogenesis of non-tumoral hypothalamic-pituitary disorders.

Determination of bone age

Another part of the work-up for evaluation of growth failure is an accurate assessment of bone age, which is important because bone age delay or advancement is a useful diagnostic clue, and is used to predict adult height (45,46). Conventional assessments are known to be fraught with difficulties due to the many short-comings of the methods. There is no universally accepted method for manual assessment and great variability between individuals making the assessments. Healthcare personnel making the rating may differ in training, experience, motivation and alertness, and bias may be introduced if the rater knows the chronological age and clinical background of the patient. Variability can also occur due to ethnic differences, use of old/inappropriate reference data and lack of

validation of methods; the original atlases were developed using data from particular ethnic and socio-economic groups (47).

It was recognized many years ago that computerized ratings could be better than conventional manual methods and a computer-assisted version of the Tanner-Whitehouse method was designed (48,49). However, it was not fully automatic, cumbersome and only ever used by a small number of research centers. Advances in computer technology allowed better methods to be developed and the first reports of the fully-automated BoneXpert method were published just over 10 years ago (50,51). The method uses x-radiographs of 15 bones in the wrist, hand and fingers, and originally did not use the carpals, which are considered to be less useful, although a new version does include carpals (52). The process interprets the shape, intensity and texture by principal component analysis and BoneXpert is currently the only medical device that has been certified for bone age determination.

Other systems have also recently been developed that use computer learning with deep convolutional neural networks, which do not require prior identification of features and calculations because these are part of the machine-learning process (53,54,55). While not fully automated or validated, such techniques are improving the accuracy, shortening the time required and increasing the cost efficiency of bone age assessments (56,57). A recent report provided evidence that an artificial intelligence, deep-learning neural network method could estimate bone age with at least similar accuracy to expert radiologists and other existing automated models (58). These data for 12,611 hand radiographs, plus a further 1,425 validation data set, were used as part of a challenge issued by the Radiological Society of North America (RSNA) to create new machine-learning techniques in medical imaging to accurately determine bone age (59). The 10 best entries were considered to out-perform the model used originally in the data-set study, and the Toronto-based 16Bit system (www.16bit.ai) achieved first place (59,60). At present, there is only very limited understanding or control of deep-learning algorithms, making such techniques difficult to validate. However, eHealth technology is incorporating pediatric endocrinology into novel processes, enabling communication between technology experts and clinicians and ensuring assessments become more efficient and precise.

The BoneXpert system, which does not require deep-learning techniques, came fourth in the RSNA challenge, with less than 0.5% difference in performance from the 16Bit system. Because BoneXpert is based on more traditional machine-learning techniques it has some advantages over the novel deep-learning methods and is currently being used in over 150 clinics. It is validated for boys aged from 2.5 to 19 years and girls 2 to 18 years, although a new version extends the range to new-borns; it can be used across multiple ethnicities and is consistent with all prevailing bone age scales (52,61,62,63). Precision is ≤0.18 years when comparing two concurrent x-radiographs, and accuracy is ≤0.72 years relative to experienced manual raters. It provides visual feedback on delineation of each bone and automatically rejects an image if the rating is at risk of being incorrect, giving the potential to replace manual rating, although radiologists may still check the image to look for findings such as skeletal dysplasias. It has been validated with an adult height prediction model, with root mean square deviation of predicted from observed of 2.8 cm for boys and 3.1 cm for girls (63). The technique can also be used to provide an index of bone health from the relationship of the cortical thickness to the length and width of the bones (64,65).

These developments that have occurred in recent years in bone age measurements using artificial intelligence systems now allow much more objective evaluation. The models continue to be refined and validated and are providing much greater accuracy that provides increased precision in assessment of adult height prediction.

Prediction models

One of the still not completely resolved problems of GH treatment of a short child is how much height growth should be expected, in the short-term and long-term. Growth response has commonly been expressed as either observed height velocity (cm/year) or change in height SDS, based on normal reference data. The characteristics of height and height velocity show specific average patterns and changing degree of variance around the mean with age (66). Therefore, specifying a set figure, e.g. height SDS gain >0.5 during the first GH-treatment year (67), as a "normal" growth response is inadequate for children of different sex or age.

After it was recognized that the growth response to GH was correlated with several factors related to the treated children and the mode of treatment, the problem of a more complex response evaluation was approached by several groups in the early 1990s by means of growth prediction models (68,69). In principle, prediction models are mathematical algorithms based on empirical observations from large cohorts of GH-treated children with specific diagnoses (70). Prediction models aim to explain as much as possible of the growth response within a set period of time, with the least possible error. This requires taking into consideration a child's characteristics, such as diagnosis, age and sex, and the chosen treatment modality (dose, injection frequency, time on treatment). The incorporation of laboratory parameters such as IGF-I concentration, and factors such as genetic and proteomic markers (70), may also be considered, but this requires their standardization before implementation in models suitable for wider clinical use.

Data from the large KIGS (Pfizer International Growth Study) surveillance database provided the basis for development of various growth prediction models, in children at differing pubertal stages and diagnoses (71,72). These models have been independently validated and are accessible through freely available software (https://igro-gh.com). GH dose is a prediction variable of relevance for the utility of these models in clinical practice, since dose is the only parameter that can be modified. Incorporating multiple pre-pubertal factors in the prediction models identified GH dose as the most important factor for patients with Turner syndrome or born small for gestational age. However, prediction analyses showed that in children with GH deficiency, disease severity is the most important predictor of growth during the first pre-pubertal year of treatment (73). The extent of responsiveness to GH observed during the first year of therapy is an indicator of the overall response.

Thus, early prediction of response to GH treatment of a child with growth failure potentially enables optimization and individualization of treatment in terms of efficacy and costs (70). Height velocity targets provide a simpler

model to evaluate the appropriate response in children treated for the first two pre-pubertal years, by considering age, sex and diagnosis, but not the individual dose and other factors found relevant in prediction models (66,74). The Gothenburg prediction model focused on children with idiopathic short stature or partial GH deficiency and assumed nothing about diagnosis (75). They compared a standard GH dose (43 µg/kg/day) with a dose adapted for predicted sensitivity (17-100 µg/kg/day); as expected, the variation in response was reduced by 32% with the individualized dose (76,77). The Cologne model uses both baseline and 3-month data for prediction of subsequent response to GH, and includes baseline factors of insulin-like growth factor (IGF)-I level, deoxypyridinoline (as a marker of bone resorption) and bone age retardation, and height velocity in the first 3 months of treatment (78). Because the bone resorption marker is rarely measured, the model has only been used to a limited extent. However, the Cologne model was recently shown to effectively predict first year response to GH treatment in patients with short stature homeobox-containing gene (*SHOX*) deficiency (79).

Baseline IGF-I SDS is used in the Cologne model, whereas values both at baseline and during treatment have been used in other prediction studies in children with growth failure due to GH deficiency and other conditions (70,80,81,82). These models use multivariate linear regression to identify factors associated with response for inclusion in the models. However, artificial intelligence techniques of machine-learning and neural networks have been suggested to detect both linear and non-linear variables with no pre-conceived assumptions, and may prove more flexible and useful in clinical practice (83). Initial studies suggest that early growth response and IGF-I concentration changes were among the most important predictors of long-term response (84). Accurate prediction of growth outcomes could help in educating patients and their families and managing their expectations. While apps that incorporate prediction models are being developed (85), accuracy and validation are so far unknown. Very few apps currently include education and links between patients, caregivers and healthcare professionals. A better understanding of how patients can use such apps is required and there remains an unmet need for assessment of quality and physician endorsement of such tools for use in clinical practice.

Interpretation of IGF-I data

Determination of IGF-I level has many uses in children with growth failure because it has a long half-life in blood and a stable circadian concentration. Therefore, single daily measurements can be taken and a consensus guideline for measurement was developed (86). Current methods for measuring total IGF-I concentration require separation from its binding proteins using two-step acidification and neutralization, with blocking of re-aggregation by adding an excess of IGF-II (87). Nevertheless, different commercial assays are available and their reference intervals vary, so it is important to note which assay is used when comparing data (88,89). Because IGF-I concentrations change with age and gender, normative data have been determined from large numbers of healthy children and adolescents (87). This enables appropriate correction to provide SDS values, although the correct normative data should be used because diverse cohorts may give different reference measurements (90,91). Such differences may give clinically relevant variation when used to establish a diagnosis of GH deficiency (92). Clinical background of the patient should be considered when determining whether an IGF-I assay is necessary and how the result should be interpreted; also the test may require repeating if clinical features and laboratory results are discrepant [(93). Nutritional history should also be considered in evaluation of IGF-I when assessing GH status; both short-term and chronic under-nutrition or over-nutrition can affect circulating concentration and body mass index should be considered when interpreting IGF-I level (94).

IGF-I SDS is used not only to aid in identifying the cause of growth failure, but also to assess whether, and how well, a short child will benefit from GH treatment (95). In patients with GH deficiency, normalization of IGF-I SDS is not always required for a good response, particularly in patients with severe deficiency. A greater response is generally seen in those with the lowest baseline values. Using artificial intelligence neural networks on data for patients with non-acquired isolated GH deficiency, more severely reduced IGF-I SDS at baseline was shown to be a significant indicator of GH response, both in the first year and for adult height (84). In evaluating IGF-I level, the cause of GH deficiency should be considered, because children with acquired deficiency have higher IGF-I SDS than those with non-acquired deficiency (96). In patients without obvious GH deficiency and who are classified as idiopathic short stature, IGF-I SDS may be below normal for approximately 40% (87). During GH treatment, a low IGF-I SDS may be due to low sensitivity, concomitant illness or malnutrition/malabsorption, or poor adherence with the therapy (96,97). A normalized IGF-I SDS with low response may also suggest poor adherence, with GH correctly administered only for a few days before evaluation; better evaluation of continuous adherence may then be necessary, and addressing issues of adherence could improve response (98,99). Maintaining a normalized IGF-I SDS, without excessive values, is also required from a safety point of view (95,100). While guidelines recommend a decrease in GH dose when IGF-I SDS is >+2 (101), this may not always occur in practice, particularly if response is only assessed from height velocity (102). Maintaining a set IGF-I SDS has also been used to adjust GH dose in studies of children with GH deficiency or idiopathic short stature and was shown to enable a better growth response (103). However, non-approved high doses of GH were used in some children when IGF-I was titrated to +2 SDS in that study, and titrating to 0 SDS was subsequently shown to achieve a better long-term height gain per dose and was potentially safer (104).

Conclusions

Digital health and computer-based technologies are rapidly altering healthcare services to make medicine much more patient-centered and personalized. While there have been great advances in use of digital tools and use of artificial intelligence, the importance of this research is only just beginning to be recognized in the field of pediatric endocrinology and growth failure. Algorithms for height monitoring can now be integrated into electronic health records, which can increase the diagnostic yield and identify individual children who may have growth failure. However, the lack of accurate centralized health records in many countries is slowing this referral and diagnosis progress. At a more individual level, various digital health tools are being developed that can

provide better identification of disorders and promote effective engagement between clinicians and patients. Growth monitoring applications for phones and tablet computers are being developed, based on longitudinal growth studies. Such technologies should form part of the overall clinical management of children with growth failure.

When short stature is identified, standardizing the diagnoses associated with pediatric endocrinology requires a comprehensive classification system, in which the organization of diagnoses are well defined in order to prevent misclassification. Computerization of health records enables transformation of identified medical conditions into code numbers, which can then be used by multiple organizations to analyze population data on health and healthcare. Most systems currently in use are either complicated or diagnoses are insufficiently defined and, therefore, do not fit the needs of the scientific, governmental and healthcare communities. ICPED is an online classification system that is simple, comprehensive and fulfills the needs of such users, can be standardized worldwide and incorporated into hospital registries. This would allow wider access and better use of electronic health records.

Assessment of the cause of growth failure in a child frequently includes cranial imaging and new techniques are being devised. A recent development is the routine inclusion of T2-DRIVE into sellar MRI protocols. In light of recent safety concerns regarding gadolinium contrast agents, the computer-aided technique is considered a valid alternative for pituitary imaging without gadolinium in patients with pituitary hormone deficiencies. T2-DRIVE is advocated for more accurate diagnosis of pituitary gland abnormalities since it has been shown to provide better contrast than gadolinium agents. However, it should always be noted that knowledge of the normal pituitary dimensions is required for interpretation of any technique and good clinical expertise remains vital for accurate diagnosis.

New computerized techniques for measurement of bone age are using machine-learning to become much more accurate and precise. Because they are objective, rather than previous subjective manual ratings, they are much less variable, can be used for both short and tall children, and are adaptable to various ethnicities. The BoneXpert system, which uses machine-learning though not deep-learning, is the only medically certified and systematically validated technique. As well as providing rapid and accurate bone age measurements and adult height predictions, it also provides a bone health index that can be used for multiple medical conditions. However, automated techniques such as BoneXpert, should continually be compared with manual ratings in order that clinicians do not become totally dependent on them. The techniques are still developing, with mistakes occasionally occurring, and at present syndromes and anomalies cannot be automatically detected; therefore, clinical judgment is still required.

A variety of models to predict the response to GH treatment in individual children with growth failure have been developed and validated over time. However, they are still largely underused in assessment of growth potential. Various factors are included in different models, such as patient characteristics and treatment modalities, but incorporating further laboratory, proteomic and genetic predictors could potentially improve accuracy. Until recently, the models relied on multivariate regression analysis. However, newer methods are beginning to be developed that use deep-neural networks and machine-learning techniques, which can analyze non-linear as well as linear relationships and do not require *a priori* assumptions about importance of various factors. Prediction models are now also being incorporated into apps, to educate and help patients understand their condition; however, these require clarity on models being used, expert validation and assessment by endocrinologists.

Some prediction models use IGF-I SDS as a factor and IGF-I SDS may also be used to evaluate response to GH treatment for short stature. Machine-learning techniques indicated that baseline IGF-I SDS is among the most important indicators of response to GH treatment. However, IGF-I measurements should be considered with care because results can vary widely between different assays. Laboratories should ensure that appropriate normative data are used to determine SDS values, and pubertal stage of the child should be taken into consideration in addition to age, gender and nutritional history, when interpreting results. Because of imprecision in assays, borderline values for use in clinical diagnosis of short stature should be repeated using a second blood sample and clinical history assessed when evaluating IGF-I level. Titrating GH dose to IGF-I helps to take into account the sensitivity of treatment due to diagnostic factors and has been reported to provide better clinical outcomes.

Thus, rapid advances in computing and artificial intelligence technologies are providing many new tools for pediatric endocrinologists. Such tools are improving identification of short stature and enabling better diagnosis of causes of growth failure. Cranial imaging is becoming more accurate and sensitive, bone age and bone health can be evaluated more objectively, prediction of response to GH treatment is improving and use of IGF-I measurement is becoming more consistent. However, this research has only really scratched the surface and development of new computer-learning techniques could be further explored in terms of digitalization and development of patients-centric solutions. New eHealth tools can help pediatric endocrinologists by making their clinical assessment and patient management more efficient. The majority of tools are currently designed to be used by clinicians, although future directions may need to explore new ways in which patients can access the technologies more directly. While clinicians need to keep abreast of all these new techniques, clinical decisions should always be based on their experience; however, these new digital technologies should provide better communications between clinicians and patients. Treatment decisions based on these new techniques should always be patient-centered, in order to personalize and optimize assessment of child growth and management of growth failure.

Conflicts of Interest

JIL, MR, DM, and LG report no conflicts of interest.

MM has received speaker's fees from Merck, Sandoz, Pfizer and Novo Nordisk, and served on advisory boards of Merck, Sandoz, Pfizer, Novo Nordisk and Ascendis.

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JMW has served as consultant to Merck KGaA, Agios, Aeterna Zentaris and Ammonett, and received speaker's fees from Pfizer, Versartis, Sandoz, Lilly, Merck, JCR, Ipsen and Novo Nordisk.
EK is an employee of Merck KGaA, Darmstadt, Germany.

Author Contributions

All authors were involved in the critical revision of the current work for important intellectual content, and gave final approval of the version of the manuscript to be published. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of it are appropriately investigated and resolved.

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