Digital developments to improve the precision of paediatric growth disorder diagnosis and management

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Running title: eHealth in paediatric growth disorders

Article type: Mini-Review

Word count: 4386 (excluding title page, abstract, table, figure legends, figures and references)

ABSTRACT

Paediatric disorders of impaired linear growth are challenging to manage, in part because of delays in the identification of pathological short stature and subsequent referral and diagnosis, the requirement for long-term therapy, and frequent poor adherence to treatment, notably with human growth hormone (hGH). Digital health interventions hold promise for improving outcomes in paediatric growth disorders by supporting personalisation of care, from diagnosis to treatment and follow up. The value of automated systems in monitoring linear growth in children has been demonstrated in Finland, with findings that such a system is more effective than a traditional manual system for early diagnosis of abnormal growth. Artificial intelligence has potential to resolve problems of variability that may occur during analysis of growth information, and augmented reality systems have been developed that aim to educate patients and caregivers about growth disorders and their treatment (such as injection techniques for hGH administration). Adherence to hGH treatment is often suboptimal, which negatively impacts the achievement of physical and psychological benefits of the treatment. Personalisation of adherence support necessitates capturing individual patient adherence data; the use of technology to assist with this is exemplified by the easypod device. This device shares real-time recordings of the timing, date and dose of hGH delivered to the patient with the clinician, via web-based software. The use of easypod is associated with high levels of adherence to hGH treatment and improved growth outcomes. It can be anticipated that future technological advances, coupled with continued 'human interventions' from healthcare providers, will further improve management of paediatric growth disorders.

Key words: Connected device, Digital health, Digital technology, eHealth, Growth hormone, Growth disorders, Medical informatics, Paediatrics

INTRODUCTION

Paediatric growth disorders present a significant challenge to those affected, their parents/caregivers and healthcare providers (HCPs)[1] [1, 2]. Short stature can be associated with a wide range of diagnoses including Turner syndrome, growth hormone (GH) deficiency, coeliac disease, inborn errors of metabolism, chronic kidney disease and bone dysplasias [3].

There are a number of recognised practice gaps in the management of short stature. These include the early identification of and referral for abnormal height and growth; the early diagnosis of true pathological short stature; the early initiation of appropriate licensed therapy and accurate assessment of the efficacy of therapy, notably with human GH (hGH); ensuring adherence to treatment regimens; and patient support and enhancement of the patient/family-HCP relationship.

Digital technology offers the opportunity to improve the diagnosis and treatment of paediatric growth disorders. The World Health Organisation (WHO) defines digital health (eHealth) as "the use of information and communication technologies (ICT) for health" and recognises it as one of the most rapidly growing areas in healthcare [4]. eHealth has been used with some success in the management of diabetes in children [5, 6] and it has the potential to improve outcomes in other areas of paediatric medicine, including growth disorders. One of the key advantages of health digitalisation is that it enables a more individualised approach to care; by capturing additional data on the health of patients, clinicians are able to provide more

[1] *Abbreviations*: AI, artificial intelligence; AM, automated monitoring; AR, augmented reality; ECOS, easypod Connect Observational Study; GH, growth hormone; HCP, healthcare providers; hGH, human growth hormone; HVSDS, height velocity standard deviation score; ICT, information and communication technologies; IGF, insulin-like growth factor; IT, information technology; OECD, Organisation for Economic Co-operation and Development; RR, risk ratio; SDS, standard deviation score; WHO, World Health Organisation.

personalised care, and patients themselves are able to obtain more personalised health education information and support.

This review article is based on a webinar that was presented on 5 November 2020, in which the four authors presented to a large number of participating clinicians. The aim of the webinar, and thus this review, was to outline the role of digital technology in improving the management of paediatric growth disorders, with a focus on short stature and the use of hGH therapy. While appropriate data from the published literature are reviewed, the recommendations given are also based on the authors' extensive clinical experience in treating growth disorders and in developing and using digital technology in this area of paediatric care.

ROLE OF DIGITAL TECHNOLOGY IN THE IDENTIFICATION AND EARLY DIAGNOSIS OF PAEDIATRIC GROWTH DISORDERS

Growth is a well-established indicator of general health and wellbeing in children [7]. As a result, the monitoring of height and weight is a useful and widely accepted measure in identifying disorders affecting growth, particularly those associated with short stature.

Early identification of abnormal growth allows for early referral and diagnosis of growth disorders that will result in subnormal adult height if left untreated [8]. This, in turn, provides the opportunity for early intervention, which has been associated with a greater likelihood that more acceptable stature will ultimately be attained [8, 9]. Unfortunately, children with growth disorders often experience a significant diagnostic delay [10].

Currently, growth monitoring is very much based on empirical evidence and there are many unanswered questions related to such monitoring. These include:

- What is the best monitoring strategy?
- Should longitudinal or single-point measurements be used?

- At what age should monitoring be performed?
- If fewer measurements are taken, what is the optimal age for these?

In addition, perhaps the most important question is: how should normal growth be defined? It is important to consider the likely limits of normality of the child's stature, given their genetic background (i.e. the height of their parents), and growth rate at different ages.

When developing a monitoring system to screen a population, the aim is to make a distinction between the 'normal' population and the population with a condition associated with a certain trait. In this regard, two parameters are important – the specificity and sensitivity of the measures. Specificity is defined as the percentage of the normal population that is captured using a defined cut-off point for the trait. A specificity of 99% means that only 1% of the normal population is captured at this cut-off and is incorrectly included in the target population. Sensitivity is the percentage of the target condition population that is identified by the cut-off point. These two parameters are inter-related, in that the lower the specificity, the higher the sensitivity. **Figure 1** illustrates this point.

Important screening parameters that can be used to assess growth are: height-for-age [commonly expressed as height standard deviation score (SDS)], target height SDS (which takes into account parental height) and height velocity/growth rate (expressed as change in height SDS over time, which requires longitudinal height measurements). Data from these parameters can be combined, which provides the best overall separation of the normal height population from those with growth disorders, as shown in **Figure 2** using a population of girls with Turner syndrome [11]. Regarding early identification of individuals with growth disorders, the use of the combined parameters has been shown to accurately identify girls with Turner syndrome at an early age, with 85% of all affected girls detected by the age of 2 years at a 97% specificity and 68% detected by this age with a 99% specificity [11]. The method is even more accurate for girls with the 45, XO karyotype (95% detection rate at a 97% specificity and 76% detection

rate at a 99% specificity) [11].

Automated growth monitoring

Traditionally, in many countries, growth data are manually plotted onto growth charts and various cut-offs are applied by HCPs, such as primary care nurses. This is a demanding and time-consuming process in busy clinical practice settings and can easily result in cases being missed or, conversely, high numbers of referrals of normally growing children. Automated growth screening may provide more efficient growth assessment and, ultimately, the ability to increase the number of early referrals and allow more optimal timing of treatment initiation.

The Finnish experience provides an example to support the use of automated growth screening. In Finland, growth monitoring is an integral part of the regular paediatric health assessment protocol for all children, which involves as many as 25 health monitoring visits from birth to age 18 years. Primary care nurses are trained in auxology. Further, there are very good population-based growth references (which is important to allow an accurate definition of 'normality' that can then be used as a baseline for initiating therapeutic treatment) and electronic health records have been used in primary care for more than three decades. The results of growth screening at health visits are entered into the electronic health records by primary care nurses, and the three screening parameters mentioned above (height SDS, target height SDS and change in height SDS over time, usually set at a specificity of 99%) are compared with a population reference.

To overcome the problems associated with manual entry and assessment mentioned above, and to allow a more timely highlighting of potential growth problems to specialists, an automated monitoring (AM) system has been trialled in the city of Espoo, the second largest city in Finland (population 241 600). This involved the automatic/computerised flagging of any abnormal height screening results to growth specialists in secondary care, who evaluated the

growth pattern and informed the primary care nurse whether a referral was necessary. This was in addition to the usual manual growth monitoring [10].

The results of a one-year trial of the AM system (from 1 March 2008) were compared with those of the previous year (control year; 1 March 2007 – 28 February 2008), in terms of the number of referrals for abnormal growth and the diagnostic yield for growth disorders. The children involved were aged 0.01 to 12 years old and a similar number were included in each cohort (AM year = 32, 404; control year = 32, 718). In both years, 88% of children were screened. AM increased the number of growth-related referrals to secondary paediatric care versus the control year by approximately 3 times, from 0.21% to 0.64%, and halved the number of referrals of 'normal' children, from 47% of referrals to 23%. The diagnostic yield of growth disorders was also improved by AM, as evidenced by 48 new diagnoses (1 in 675) in the AM cohort versus 8 (1 in 4090) in the control cohort, a risk ratio (RR) for diagnosis of 6.06 (95% confidence interval, 2.87-12.80). In the AM cohort, there had been an average delay in diagnosis of 1.97 years, although some patients had a delay of over 5 years. A retrospective review of the growth data for some of these patients showed that they could have been diagnosed much earlier, indicating that the introduction of an AM system could reduce such delays. Based on the results of this trial, this type of automated growth monitoring is now used routinely in clinical service provision across Finland.

Despite the above outlined success, a number of issues with the use of AM remain to be fully clarified. While most of the data obtained from this trial were from children with reduced growth, monitoring for tall stature disorders should also be considered because significant pathology is seen among children who are growing at an excessive rate or who are very tall. Also, although this trial suggests that AM is effective in identifying children with growth disorders, the cost-effectiveness of the system must be assessed. It is estimated that the incremental cost of this system is only about 2% or 3% relative to manual monitoring, but is

associated with a 6-fold improvement in diagnostic accuracy (RR for diagnosis). Nevertheless, robust data are required to convince healthcare policy makers about the value of the system. Finally, the generalisability of the results to other countries is unclear. Finland has a relatively small population, a large number of well-trained primary health nurses, and, like other Scandinavian countries, a tradition of public health and prevention of illness. Therefore, the transferability of this model to other, in particular non-Scandinavian, countries needs to be assessed.

APPLICATION OF DIGITAL RESOURCES TO THE MANAGEMENT OF GROWTH DISORDERS

Digital resources used in the management of health conditions include clinical information systems (such as those that store patient information), internet-based health information (including patient-produced videos available on hosting platforms such as YouTube) and services (such as patient-accessible healthcare appointment portals), and mobile and connected devices (such as smartphones, watches and fitness trackers). Various applications (apps) on devices, whether inbuilt (camera, sensors) or downloadable, provide enormous computing power that can be harnessed for healthcare uses. These resources, in effect, represent an ecosystem of eHealth technologies.

The WHO has recognised the promise of eHealth and provides recommendations on the use of digital interventions for strengthening health systems. Three components are necessary for the effective implementation of eHealth interventions – health content, digital health interventions and digital applications - that sit on the foundation of an information/communication technology and enabling environment [12]. Effective leadership and governance, a well-defined context and strategy, and a well-trained workforce are key to enable the use of technology in clinical practice.

The most important stakeholders to consider in this context are: (i) the healthcare team, and (ii) the patient and their caregivers. Digital resources can be used to assist the healthcare team in their clinical decision making. This can include the use of digital tools to support diagnosis, monitoring of adherence to treatment and related factors (e.g. patient understanding of their disease, anxiety around the disease and its treatment, support for self-administration of treatments), integration of patient data (including patient-reported outcomes) into the treatment plan, and predictive models of response to treatment.

Artificial intelligence

Artificial intelligence (AI) has been incorporated into technologies to reduce problems of variability in manual readings of information and, thus, to assist HCPs with diagnosis. An example relevant to the management of growth disorders is BoneXpert. This is an automated system using AI to determine a child's bone age from a hand x-ray, information that can then be used to predict adult height. The technology uses machine learning that allows continuous improvement of the system. Version 2 of BoneXpert is currently used in various hospitals in Europe. Results from a recent analysis of version 3 of BoneXpert to determine bone age in children with various short stature diagnoses demonstrated that this automated system was more accurate in identifying bone age than manual ratings [13].

Another example is the FACE 2 GENE system, which is a mobile app developed to assist in identifying children with genetic disorders. It uses photographs of the patient and converts these to de-identified mathematical facial descriptors, which it compares to facial features common in children with genetic disorders and variants. A list of syndromes with similar morphology to the patient's is produced and AI suggests likely matches to the patient [14]. This system could, thus, be used to assist clinicians in diagnosing children with genetic disorders that affect growth.

Mobile technology

Mobile digital technology has been developed to allow members of the healthcare team to track patient adherence to treatment, which is a key determinant of clinical outcomes. Drug delivery devices that record adherence are available; data from these can be sent via the internet to a dashboard that allows the treating clinician to assess the patient's patterns of administration over time and identify potential issues related to adherence. Future developments in AI and machine learning may also allow the identification of patient characteristics that predispose to poor treatment adherence. This would allow the prediction of patients or cohorts that may need more assistance and the development of tailored support to prevent or reduce poor adherence.

Evidence from other endocrine disorders, such as diabetes, demonstrates that digital technology aimed at patients and caregivers can improve outcomes. A 6-month, randomised, controlled trial of the use of a Nintendo interactive video game designed to improve self-monitoring of glucose levels, insulin administration and food choice in children and adolescents found an improvement versus controls in most endpoints, particularly communication with parents about diabetes and self-care behaviours [15]. Further, an internet-based and text-delivered intervention was shown in a randomised, controlled trial to assist with the transition from paediatric to adult care in individuals with chronic diseases, including diabetes [16]. Significant improvements in the performance of disease management tasks, health-related self-efficacy and patient-initiated communications with the healthcare system were seen versus controls.

The patient/caregiver area is where digitalisation of health is moving most rapidly. Patients and caregivers frequently use their mobile phones to access or record health information, often via installed apps. A systematic review was performed to assess the mobile apps to track

growth that are available for HCPs, caregivers and patients on the Android app store, Google Play [17]. A search of Google Play, using a specified search string, identified 76 apps that were relevant to growth monitoring or GH treatment. In total, these apps have had over 3 million downloads, with two apps having more than 1 million downloads in total. Most of the apps (87%) targeted patients/relatives. HCPs were the target audience for 11% of the apps, and both groups were the target audience for the remaining apps. Non-pharmacological approaches to growth issues were mentioned in 12% of the apps, while 11% of the apps mentioned GH. The latter were all targeted to patients/caregivers and included information about GH deficiency and related diseases. The apps describing non-pharmacological approaches included information on 'natural' growth enhancers for adults and exercises, with claims of growth increases of up to 10 cm. Interestingly, more than 20% of the apps collect location information (via GPS data), most likely to personalise app-related advertisements and, thus, generate revenue.

MANAGEMENT OF GROWTH HORMONE ADHERENCE USING DIGITAL TECHNOLOGY

Optimal results of any therapy are achieved when a medication is taken as prescribed. In the 'real world' setting, adherence to medication is a major challenge. In fact, the WHO and Organisation for Economic Co-operation and Development (OECD) estimate that 1 out of every 2 patients with chronic disease does not use their medication as prescribed [18]. Various tools and devices have been developed to assist in monitoring adherence across all therapeutic areas, including video directly-observed administration; smart bottles, blister packs and pills; and electronic/add-on/connected pens and auto-injectors. These allow the recording of the number of administrations, the dose and/or the timing of administration.

The goals of hGH therapy are the normalisation of linear growth, the achievement of a normal

adult stature and the correction of metabolic abnormalities, especially in those with severe GH deficiencies. However, there are a number of factors which may influence responsiveness to hGH treatment, including baseline insulin-like growth factor (IGF)-1 concentration, dose of hGH used, duration of treatment, genetics of the individual patient, diagnosis, age at the start of treatment, bone age, height at start of treatment, parental height and adherence to treatment [19].

Few studies have reported the rate of adherence to long-term hGH treatment and the results that have been obtained are somewhat contradictory, mainly because of the variety of methods used to record adherence and the use of non-objective methods, mostly questionnaires. However, the available studies suggest that adherence is frequently suboptimal, with non-adherence rates ranging from 5% to up to 82% [20]. Non-adherence to hGH therapy may result in the patient not gaining the physical and psychological benefits of treatment. One study of 175 children and adolescents reported that height velocity SDS (HVSDS) was positively correlated with hGH treatment compliance, as assessed by an objective measure (rate of returned vials), over 6 to 8 months of treatment [21]. Patients who missed >1 to <3 doses/week and those who missed >3 doses/week had significantly lower HVSDS than those who missed <1 dose/week. Another study found that compliance with hGH treatment was associated with height velocity during a 6- to 12-month observation period, with significantly reduced velocity seen in the patients who missed more than 15 injections/month compared with those who missed 0 to 3 injections/month or 4 to 15 injections/month [22].

Adherence may be adversely affected by a number of factors related to the patient, disease, HCP or treatment, as outlined in **Table 1**. Studies report numerous reasons why patients missed their hGH injections, among the most common being forgetting to administer the injection, the device not working, short vacations/long weekends/sleeping way from home, and running out of needles [23, 24].

The administration device itself may affect adherence and this has been studied specifically in relation to hGH therapy. For example, the easypod Connect Observational Study (ECOS) was a 5-year, international (24 country) study that aimed to assess the level of adherence in children receiving hGH via an electronic device (the easypod device). Secondary objectives were to describe the impact of adherence on clinical outcomes in patients receiving hGH via the electronic device and the impact of adherence on IGF-1 levels, to identify adherence patient profiling, and to assess/describe the impact of a country-specific patient support programme [24]. The easypod device is an injection delivery system for hGH that shares real-time recordings of the timing, date and dose of hGH delivered to the patient with the HCP, via web-based software (see **Fig. 3** for an outline of the easypod 'ecosystem'). Of the 2420 patients enrolled in ECOS, 1190 patients had data for ≥3 months and were used to assess adherence. Approximately half the patients (n = 606) were hGH naïve at baseline. The most common indication for hGH treatment was GH deficiency (75%). Other indications were small size for gestational age (17%), Turner syndrome (7%) and other conditions, including chronic renal failure/kidney disease (1%). The median rate of adherence was just over 93% after 1 year of treatment in the total cohort. The rate remained high (at 87.2%) at 3 years but declined slightly through the following years to a median of 70.2% at 5 years of follow-up. A similar pattern was seen in initially hGH-naïve patients (see **Fig. 4**).

In terms of the secondary outcomes, the study demonstrated that adherence had an impact on growth outcomes, with a significant positive correlation seen between adherence rate and change in height, change of height SDS, height velocity and HVSDS after 1 year of treatment [24]. This was confirmed in a subanalysis of patients from ECOS who had GH deficiency (n = 95) and who were assessed after 2 years of treatment with hGH [25]. Suboptimal adherence was found to negatively affect the growth response, such that missing 1 injection/week over the 2-year period was associated with 0.11 SDS less height gain and missing 2 injections/week was

associated with 0.22 SDS less height gain [25]. In ECOS, adherence was not demonstrated to be affected by parent's employment status, the age or sex of the patient [24], the country of residence [26-28], the underlying disease [24] or the severity of the GH deficiency [29]. However, socioeconomic status was somewhat related to adherence, as patients with married or cohabitating parents had higher median adherence rates than those with separated or divorced parents [24].

It should be noted that new and more powerful technologies and devices are constantly emerging. One such example is augmented reality (AR). Currently, mobile devices such as phones and tablets can analyse the content of the camera and add new information on top of the images. This has been used in relation to hGH treatment, where the easypod AR app uses a gaming technique to educate children about appropriate injection technique for hGH injections using the easypod injection device, and to assist HCPs in addressing patient and caregiver questions about the use of the device, with the ultimate aim of ensuring hGH is taken as prescribed [30].

Based on the available data it can be conclude that digital, web-based technology may allow HCPs to closely and objectively monitor adherence to hGH therapy. Clinicians can then provide patients and their families with personalised data during consultations/follow-up and this can form the basis of discussions around steps to maintain or improve levels of adherence. However, it should be emphasised that technology is only one intervention that clinicians can use to increase adherence to hGH therapy. 'Human intervention' is just as important and, as such, the following remain imperative: talking to the parents and child to emphasise the value of the hGH regimen and the effect of adherence on growth outcome; eliciting the patient's feelings about his/her ability to follow the regimen; listening to the patient and customising the regimen in accordance with the patient's wishes (which is particularly important in the adolescent period); providing simple, clear instructions and simplifying the regimen as much as

possible; obtaining help from family members, friends and community services, when needed (including patient support programmes); encouraging the use of the medication-taking system; and reinforcing the desirable behaviour and results, where appropriate. When faced with a patient who is poorly adherent, the course of action will depend on the age of the patient, with the focus being on the parents for young children or the patient themselves for older (e.g. adolescent) individuals. Patients and/or family members should be questioned in a non-judgemental manner regarding the reasons for the non-adherence. HCPs need to be prepared to set aside time for such discussions. It should also be recognised that if technology (such as the easypod device) is used to monitor adherence, patients and their families should be informed prior to initiation of use that the device will provide adherence data to HCPs and their consent obtained, thus setting appropriate patient/parental expectations of the use and aims of the technology.

INCORPORATING DIGITAL TECHNOLOGY INTO THE MANAGEMENT OF PAEDIATRIC GROWTH DISORDERS: FUTURE NEEDS

The data outlined above demonstrate the promise of digital technology in improving the diagnosis and management of paediatric growth disorders; however, much is still to be accomplished before this technology is a routine component of clinical practice. When designing and implementing digital solutions for any healthcare use the focus should always be on the needs of patients/caregivers and HCPs. A number of important factors need to be considered to allow the successful establishment of a programme of automated health monitoring for the management of growth disorders, including:

- Buy-in from all stakeholders including government and healthcare policy makers and, more locally, information technology (IT) departments in academic institutions, hospitals and primary care, with a recognition that, although requiring initial investment, the technology will ultimately be cost-effective

- Understanding (by IT developers and HCPs) of the data that need to be collected and how they should be presented/visualised digitally
- Development of systems to ensure data security/patient privacy (with processes for assuring patients/parents of data confidentiality, thus encouraging the sharing of relevant lifestyle information)
- Multidisciplinary collaboration in the design, testing and updating of digital solutions, including the involvement of researchers, clinicians and patients
- Use of appropriate baseline/comparative data, e.g. growth charts for the relevant geographical region/population.

The most important factor is likely to be the availability and effectiveness of training in the use of technology for stakeholders. All HCPs involved in the care of patients need to be trained in the use of the technology to collect data. Patients and parents need training to use the technology, with the aim of obtaining accurate and meaningful data on parameters such as growth measurements, physical activity and nutrition, and behavioural and emotional issues. Initial and ongoing training of clinicians is required on how to use the technology as a complement to the clinical encounter, and how to use the data obtained from the technology in clinical decision-making. Finally, it should also be noted that patients are often leading the introduction of digital technology in the management of their own health and, therefore, HCPs need to develop the knowledge and skills to guide and support patients in this regard.

CONCLUSIONS

Digital technology has much to offer the area of paediatric growth disorders. To obtain maximum value from technology it should be used as a tool to assist stakeholders (nurses, doctors, family members, parents and patients) in working collaboratively for the benefit of the patient. Evidence discussed in this review suggests that technology can play a part in monitoring growth in children and assisting with early referrals for conditions such as GH deficiency, coeliac disease and Turner syndrome. Affected children, and their families, are

likely to benefit significantly from early diagnosis, as this allows the initiation of therapies such as hGH, where appropriate. Technologies (such as the easypod device for administration of hGH) can provide patients with feedback on injection technique and clinicians with easy access to objective data on treatment adherence. In turn, this information can be used by HCPs to offer advice to patients/families regarding the importance of adherence and its impact on treatment outcomes and quality of life.

Declaration of competing interest

LD XX. LFL is shareholder of Salumedia Labs, a digital health company which provides digital health solutions to multiple healthcare stakeholders including Merck Healthcare KGaA. SL has consulted for and received lecture fees and research support from Merck Serono, and consulted for and received lecture fees from Sandoz and Ipsen. MOS has no conflicts of interest.

Funding

This manuscript was funded by an independent educational grant from Merck Healthcare KGaA, Darmstadt, Germany.

Author contributions

MOS was the moderator of the webinar. LD, LFL, SL and MOS were presenters at the webinar. All authors read and commented on the drafts of the manuscript, and approved the final version for publication.

Acknowledgment

This review is based on the contents of a webinar titled 'Digital developments and precision medicine in paediatric growth disorder management' that was presented by the authors on 5 November 2020, which can be viewed at https://paediatric-endocrinology.medwirenews.com. The webinar was made possible by an independent educational grant from Merck Healthcare KGaA, Darmstadt, Germany. We would like to thank Kate Palmer of Springer Healthcare Communications who, under the guidance of the authors, drafted the manuscript. This medical writing assistance was funded by Merck Healthcare KGaA, Darmstadt, Germany.

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Figure legends

Figure 1. Illustrations of the relationship between specificity and sensitivity.

Figure 2. Growth screening for Turner syndrome (in all patients and those with the 45, XO karyotype) based on [A] height standard deviation score (HSDS), [B] target height standard deviations score (TH SDS), [C] HSDS deflection, and [D] a combination of these [11]. The closer that the plotted lines are to the top right-hand corner of the figure, the better the separation of the target population from the normal population [11].

Figure 3. The easypod connect system [31]. PSP, patient support programs.

Figure 4. Treatment adherence rates over time as reported in the easypod Connect Observational Study (ECOS) of growth hormone (GH) treatment in children with various indications [24]. Panel A shows adherence rates in the overall study population (n = 1190) and panel B shows rates in the GH-naïve patients (n = 606). Boxes show Q1 and Q3, with median as white line and mean as red squares.

Table

Table 1. Factors that can affect adherence to growth hormone therapy	
Patient-related factors	Confidence in the treatment Confidence in the doctor Whether the treatment regimen takes into account the patient's stage of development
Disease-related factors	Acute vs chronic disorder Understanding of the value of treatment and how it improves quality of life Severity of the disorder
Doctor-related factors	Medical competence Sufficient time and communication skills to explain benefits/adverse events
Treatment-related factors	Frequency of injections Complexity of the treatment regimen Likelihood of painful procedures Ease of use of treatment devices