Child growth evaluation and charting – congress and newsupdate

Congress presentations on childhood growth during 2022 highlighted the value that accurate digital growth charts for children, importantly those with rare conditions can provide in the diagnosis and management of growth failure. PC PAL has worked with specialists to provide a large number of specialised charts in a convenient digital format.

Overgrowth syndromes

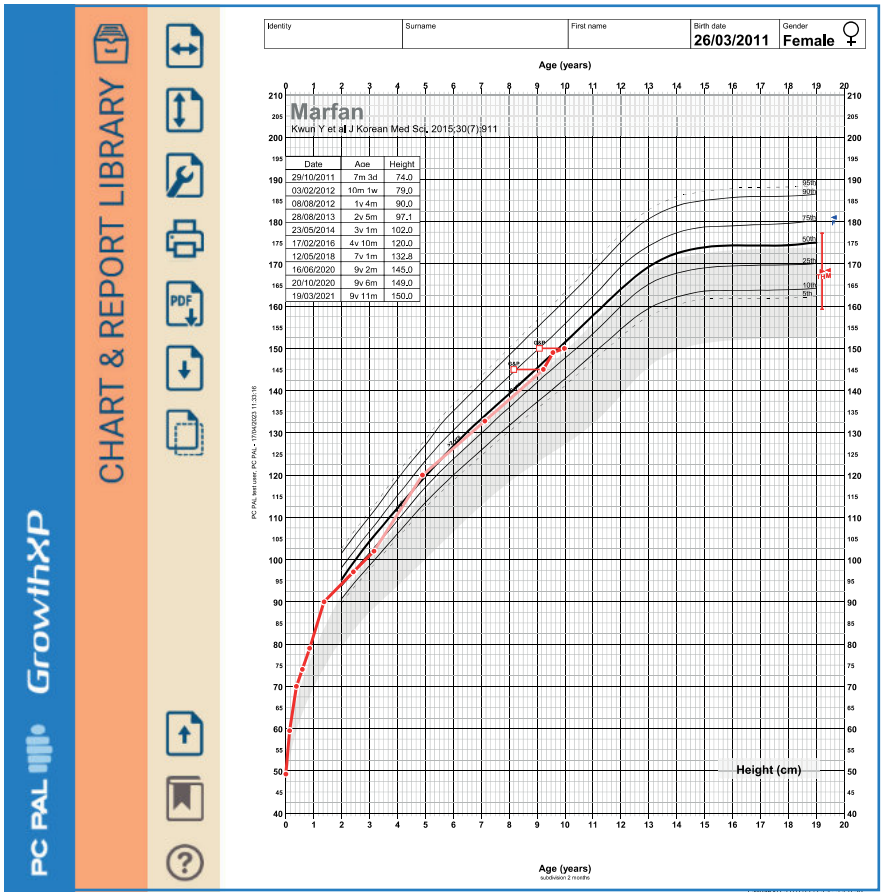
Although so much of the clinical case load of growth specialists comprises children with short stature, conditions of overgrowth have also become a focus of study. Presenting the wide spectrum of overgrowth syndromes, Professor Katrina Tatton-Brown (London, UK) shared the findings of a study of children with height and/or head circumference >2.0 SD above the mean. The conditions identified in more than 2000 families enrolled in the study are associated with intellectual disability, the so-called OGID (Overgrowth and Intellectual Disability) syndromes. Examples, include Sotos syndrome (OMIM: 117550), Tatton-Brown-Rahman syndrome, DNMT3A (OMIM: 615879), Cohen Gibson syndrome, Smith Kingsmore syndrome (OMIM: 616638), Weaver syndrome (OMIM: 277590).

For some overgrowth syndromes, specific growth references are available and these can be provided in digital form to aid patient management.

Genetic determinants of overgrowth conditions fall into one of two categories:

- epigenetic regulatory genes
- P13K/AKT pathway genes

Professor Tatton-Brown recommends expanding the bench to bedside model of patient care, stressing the need to allow clinical findings to feedback to bench research by making use of longitudinal data, registries and natural history studies.



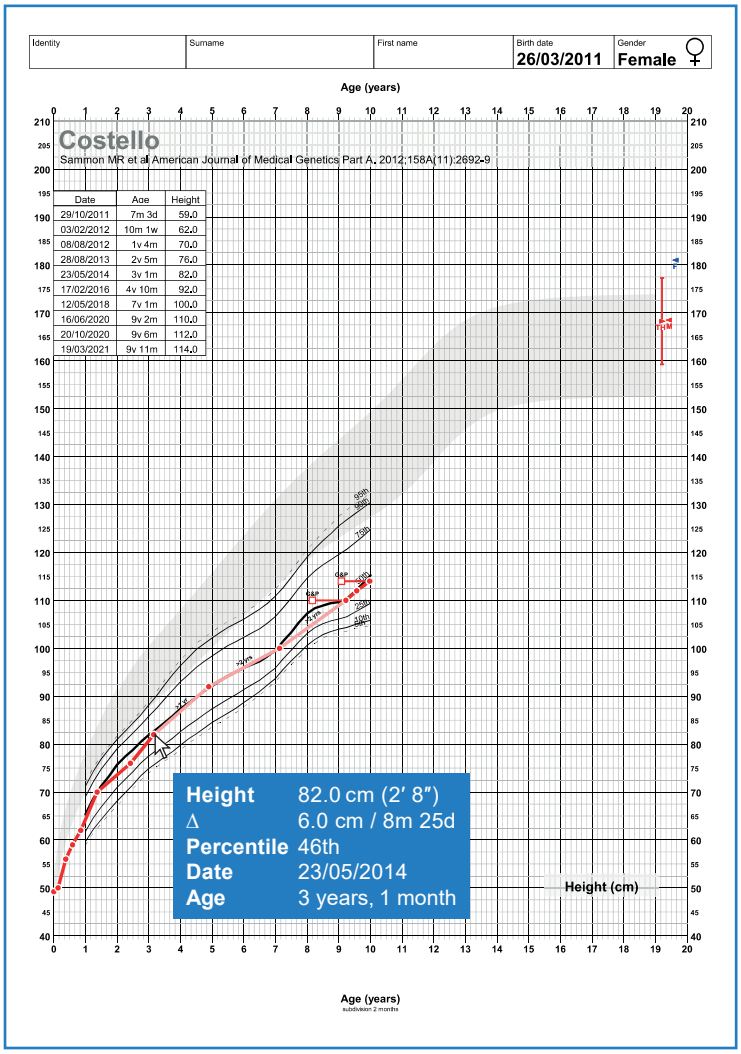
Marfan-specific growth chart. The shadow range is the reference population. Also shown are bone ages, target height range and tabulated values. (Kwan Y *et al*, 2015).

Syndromes of laterilized overgrowth (LO)

Professor Alessandro Mussa (Turin, Italy) defines laterilized overgrowth as asymmetric regional body overgrowth due to abnormal cell proliferation. Although there is a distinction between isolated and syndromic LO, in practice it can be difficult in isolated cases to distinguish between overgrowth and contralateral undergrowth.

The phenotype of LO is extremely wide and individual cases result from somatic (epi) genetic events, mosaicism. Taking Beckwith-Wiedemann syndrome (BWS) as one of the most common examples of LO syndromes, cases range from isolated through to atypical BWS to 'classical' BWS and results from deregulation of the genetic imprinting mechanism.

LO syndromes are caused by genetic changes affecting key cellular pathways. One of these, RAS-MAPK pathway, is familiar to paediatric endocrinologists. Germline mutations in RAS-MAPK are responsible for RAS-o-pathies including classic Noonan syndrome and Costello syndrome. However, the same mutation occurring in the somatic cell line, gives rise to a very different condition, Klippel-Trenaunay syndrome.



Costello-specific growth chart showing curves based on Sammon MR *et al*, 2012. This chart is included in GrowthXP; the tooltip shows visit data and change in height since the previous visit. The shadow range is the reference population.

Disproportionate short stature (DSS)

Dr Štěpánka Průhová (Prague, Czech Republic) has divided the spectrum of proportional/ disproportional stature into three categories based on sitting height to height ratio.

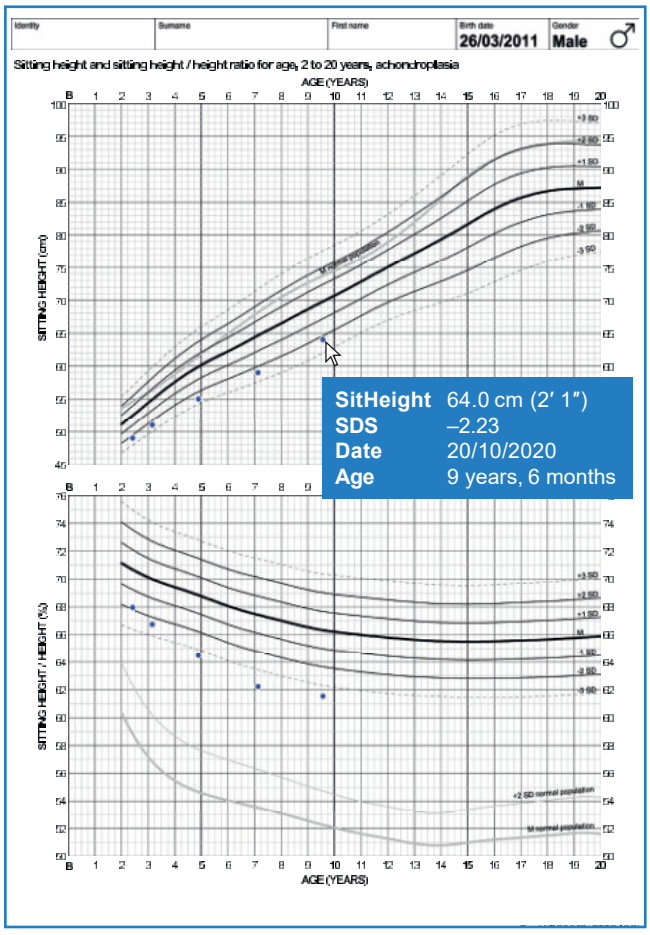
Proportional: -1.0 to +1.0 SD

Mild disproportionality: -1 to -2 SD (short trunk) or +1 to +2 SD (short limb)

Severe disproportionality: <2.0 SD (short trunk) or short trunk and >2.0 SD (short limb)

The short limb form is more frequent with the familiar example of achondroplasia. Like other forms of DSS, changes in genes controlling the growth plate have been implicated. Before puberty, the severe forms of DSS are easier to identify compared to milder forms (for example, Leri-Weill dyschondrosteosis). Affected children are frequently found in families with one short parent, as dominantly inherited familial short stature.

The disproportion likely to affect the child can be visible in the parent (and the child is often born SGA). Dr Průhová recommends seeing both parents and presented one family in which the mother had normal proportion but the father showed mildly disproportionate SS (short lower limbs). Their daughter, treated with growth hormone reached a final height (FH) within the parental target range



but showed the same disproportion as her father not apparent when she was aged 10 years. Bone age before puberty is appropriate or mildly delayed or mildly advanced to calendar age. Genetic investigation identified an NPR2 variant in three generations.

Genetic characterisation of mild forms of DSS can help understand the growth failure, notably outlook for FH and disproportionality, and complications such as scoliosis.

Achondroplasia growth chart obtained from GrowthXP, showing sitting height and sitting height / height ratio. (Reference: Neumeyer *et al*, 2018 and Fredriks *et al*, 2005 [median of normal population]).

Referencegrowth charts in Congenital Adrenal Hyperplasia (CAH)

Dr Kyriakie Sarafoglou (Minneapolis, US) argues that CAH-specific growth charts can help guide treatment better than charts for the general population. The pattern of growth in CAH differs from the general population and adult height is reduced. Furthermore, potentially the obesity status in affected children who are tall for their age can be misclassified when using CDC charts.

In order to construct CAH-specific charts, data (age, height, weight) was obtained from medical records for patients attending the two major hospitals in Minnesota between 1961 – 2022. Longitudinal visit data was used to generate curves for height, weight and BMI and then compared to CDC 2000 reference charts. Relative to CDC charts, height-for-age and BMI-for-age percentiles of CAH patients vary dramatically over the entire growth period.

Body Mass Index (BMI) – NewCDC extendedcharts for children and adolescents

BMI as a measure of obesity is well established for children and adolescents. BMI growth charts from the CDC have been available since 1977. Although these charts were revised in 2000, for the most obese individuals they suffered from data weakness above 97th percentile, relying on data extrapolation rather than real data. As a result, above this level the charts cannot reliably differentiate significant differences in BMI.

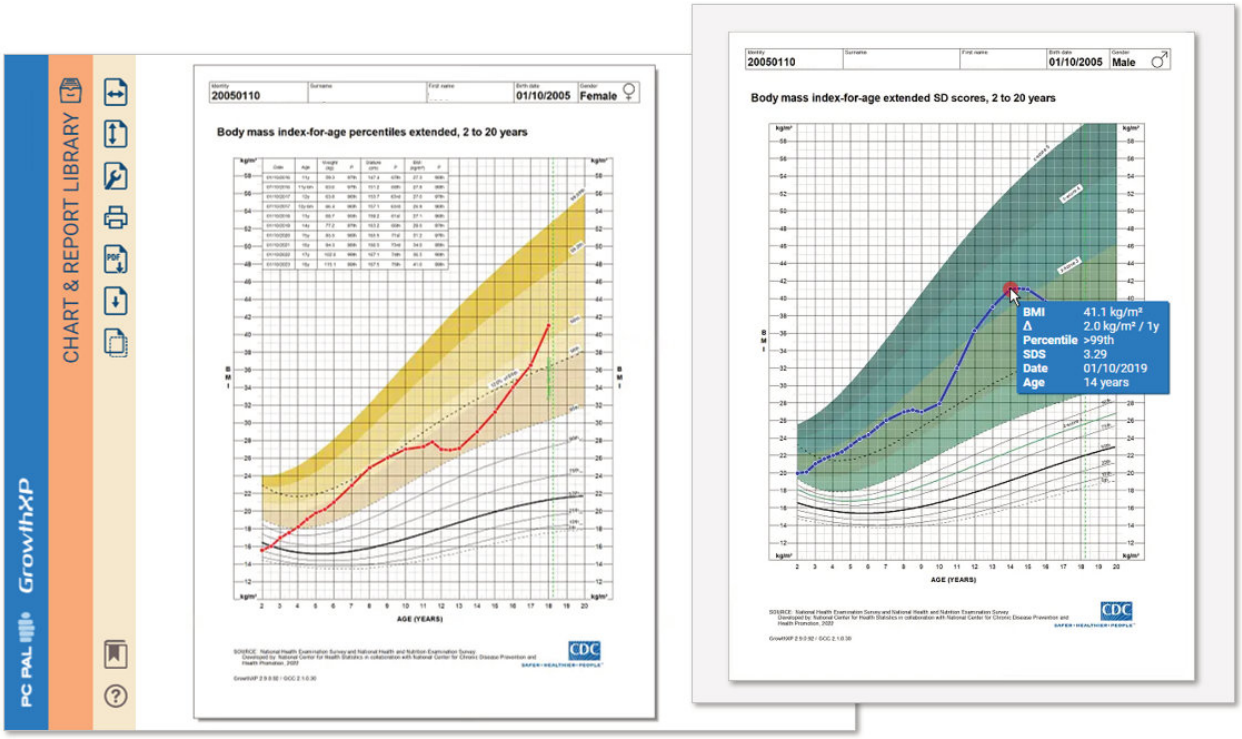
As a response to the need, in 2022 the CDC released new BMI charts for 2–18-year-olds, which provide curves above the 97th percentile (98th, 99th, 99.9th and 99.99th) based on real measurements rather than extrapolation. The data source for the new curves is derived from an updated reference population including obese children (data from the period 1999 – 2016). The new curves accurately cover individuals up to a

BMI of 60 and BMI z-score of 5, greatly improving on the previous limit of values beyond the 97th percentile.

The CDC emphasizes that the threshold for severe obesity has not changed and that the 2000 BMI-for-age growth charts are applicable to growth monitoring of children without obesity. The advice for clinical practice is to use the new 2022 charts to replace the growth charts for severely obese children found in the Electronic Health Chart. Clinicians have access to the CDC's new BMI charts in the digital growth chart application, GrowthXP.

Despite the CDC's extended charts, using BMI percentiles to visualise results of weight loss might not reveal the significance of the outcome on weight, compared to the appearance on a standard body weight chart. This is because percentiles are non-linearly correlated with the numeric BMI changes; the percentiles change little despite a huge drop in BMI in very obese patients. For this reason, BMI SDS values, which do correlate linearly with the change in BMI, offer an advantage.

The development of new treatments and spread of existing approaches, notably bariatric surgery and new obesity drugs, will focus attention on the accuracy and utility of BMI charting especially in the higher range.



Illustrative BMI charts in GrowthXP based on the new, 2022 CDC reference. (Left: female percentile chart; Right: male percentile z-score chart). New bands are shaded to facilitate discussion with patients. The tooltip function within GrowthXP shows visit data. Based on Hales *et al*, 2022.

Provided as a service to medicine by PC PAL

PC PAL

www.pcpal.eu www.GrowthXP.com

USA: 1-877-469-7272 (toll free)
SWEDEN: Harpsundsv. 78 BV, 124 58 Bandhagen, Sweden
FRANCE: BP 2, 91570 Bièvres CDX, France