SUPPLEMENTARY INFORMATION

Towards a rational and efficient diagnostic approach in children referred for growth failure to the general paediatrician

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1. Procedures

The guideline was constructed according to national guidelines based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II) [1]. In the preparatory phase an inventory of the bottlenecks was made by the chair and secretary of the working group in collaboration with representatives of various patient support groups. Based on this inventory, draft starting questions were formulated by chair and secretary of the working group in collaboration with the advisor from the Netherlandish Knowledge Institute of Medical Specialists, which were discussed within the working group and confirmed. Per starting question outcome measures were chosen which were considered relevant for the patients. The starting questions were then transformed into sub-modules, which were transformed to so-called PICOs (Patient-Intervention-Comparison-Outcome).

This guideline refers to children who either present with short stature (SS), growth faltering (GF), or a combination of both (SS/GF). For efficiency reasons, in the main document as well as in this Supplementary Information, we have chosen to use the abbreviation GF for growth failure, which should be read as short stature and/or growth faltering.

The general starting question read as follows: "What should be discussed and done during the first consultation by the paediatrician seeing a child referred for GF, and which investigations should be performed?" This general question was further subdivided into three questions: 1) what are the elements that should be met when taking a medical history from a child and its parents?; 2) what are the necessary elements of the physical examination and assessment of the growth curve?; and3) which additional investigations are indicated?

Submodules and corresponding search questions and PICOs included the following:

1. In which children and adolescents (0-18 years) referred for GF are additional examinations and investigations indicated? Search question: Should in children referred for GF, in whom the medical history and physical examination by the paediatrician did not show any clue for a pathological cause, still additional investigations be performed?
P: patients referred to a paediatrician because of GF, in whom no abnormalities were found at medical history and physical examination
I: screening panel of hand radiograph and laboratory investigations aimed at detecting subclinical pathological causes that may be associated with apparent isolated short stature
C: no or alternative screening
O: relevant outcome for patients, e.g. timely diagnosis and treatment with gluten-free diet (if coeliac disease is detected), levothyroxine treatment (if hypothyroidism is detected), growth hormone treatment (if growth hormone deficiency, Turner syndrome, *SHOX* haploinsufficiency or small for gestational age without catch-up (SGA) is detected), diet and medication (if inflammatory bowel disease is detected), operation (if a brain tumour is detected), etc.

2. What is the value of chromosomal investigation to diagnose or exclude Turner syndrome in girls with short stature?
P: girls with GF referred to the paediatrician in whom no abnormalities are found at medical history and physical examination
I: chromosomal investigation
C: no chromosomal investigation, possibly clinical follow-up, e.g. progression of puberty

O: diagnostic yield, sensitivity, specificity, positive and negative predictive value.

3. What is the value of investigation of *SHOX* haploinsufficiency in children referred for GF?
P: children with GF referred to the paediatrician in whom no clinical features are observed that suggest a pathological cause
I: genetic analysis of the SHOX gene and enhancer regions through MLPA and Sanger sequencing
C: no genetic analysis, possible clinical follow-up, e.g. by checking for the appearance of disproportion and/or Madelung deformity
O: diagnostic yield, sensitivity, specificity, positive and negative predictive value.

4. What is the value of investigations aimed at detecting anaemia, renal failure, serum electrolyte disturbances, calcium-phosphate disorders, hypothyroidism, growth hormone deficiency and inflammatory disorders as screening in children referred for GF?
P: children with GF referred to the paediatrician in whom no clinical features are observed that suggest a pathological cause
I: screening tests for anaemia, renal failure, serum electrolyte disturbances, calcium-phosphate disorders, hypothyroidism, growth hormone deficiency and inflammatory disorders
C: no testing, possibly clinical follow-up
O: diagnostic yield, sensitivity, specificity, positive and negative predictive value.

Literature search and selection

For each of these PICOs a literature search was carried out in the databases Medline, Embase and the Cochrane Library with relevant search terms (details can be provided on request). Selection criteria were the following: Period: dependent on PICO; Study design: systematic review, RCT or other similar studies. Language of full text: English or Dutch. A preselection was made based on title and abstract by two members of the working group. After reading the full texts, a definitive selection was made.
Results:
PICO 1: published between January 2017 and July 2017. Preselection 70 abstracts. If all components of the PICO were retained, all were excluded. After leaving out the C component of the PICO, 16 papers were retained, showing results of laboratory screening in children referred for GF. An additional 23 papers were used for information on height SDS and clinical features of various pathological causes of GF.
PICO 2: published between January 1987 and July 2017. Preselection of 24 abstracts; 22 were excluded after reading the full text.
PICO 3: published between January 1987 and January 2018. Preselection of 18 abstracts; 16 were excluded after reading the full text.
PICO 4: published between January 1946 and July 2017. Preselection of 34 abstracts; all were excluded after reading the full text.
Additional papers published between July 2017 and December 2018 were collected through similar search terms.
After consultation of various other specialist societies (Clinical Genetics, Primary Youth Health Care, Internal Medicine, Clinical Chemistry/Laboratory Medicine) a revised version of the guideline was authorized in November 2018. In the coming years, implementation of the guideline will take place. Further information (in Dutch language) via the following link:
https://www.nvk.nl/Kwaliteit/Richtlijnen-overzicht/Details/articleType/ArticleView/articleId/741

2. Definitions

While there is no strict dividing line between normal and abnormal linear growth, it is still helpful to define the limits of what the clinician should consider statistically "normal" or "abnormal" for each of the three parameters of growth: height compared to the population, height compared to parental heights (a proxy for genetic variants affecting height) and the longitudinal pattern of growth.

Growth diagrams

Regarding the interpretation of the child's height in comparison to the background population, the first step is to decide which growth diagram should be used. For countries with a homogeneous population in which nation-wide growth studies are performed regularly, the clinician does not have to think hard. However, many countries are far from homogeneous in terms of ethnicity, and in many countries no recent nation-wide growth studies are available. Under these circumstances, the clinician has to make a choice which growth reference is most suitable for the individual child presenting at the clinic. For example, in the Netherlands there is a relatively large percentage of children of Moroccan or Turkish origin, who are considerably shorter than children from families of "originally Dutch" origin [2-4] (disregarding the fact that the Dutch population is a mix of immigrants when one considers a longer time span). Like for other immigrant groups in the world [5], secular change has been rapid (2-3 cm per 13 years) for Moroccan and Turkish children [4], while the secular change in children and adults of Dutch origin has stopped [6], illustrating that information on ethnicity as well as secular change is needed for a rational choice of the most appropriate growth diagram for a certain child. If no specific growth chart is suitable for a child, the "global" growth chart developed by WHO [7, 8] can be used, which is approximately halfway the national growth charts of the tallest and shortest nations [9].

After choosing the most suitable reference population, the next step is to convert the height measurement in cm to an indicator independent of age and gender, which is usually done by expressing height as SDS (HSDS). Its conventional limits of normality are -2 and +2, so that a HSDS<-2 is considered as "short stature" (SS). This implies that 2.3% of a group of (assumed) normal children is labelled "short".

Target height

Comparing a child's height with parental heights is an important next step, but there is no agreement on how this should be assessed best [10]. Tanner developed the concept of target height (TH) [11], which was defined as the gender corrected average of parental heights. It is considered an indicator of the parental genetic information regarding linear growth, under the assumption of equal contribution of genetic variants from both parents. In the original equation, a mean difference of 12 cm was used between male and female height, so that TH was defined as [paternal height + maternal height + or -12]/2 for a boy and girl, respectively. In most population growth studies in western countries the average difference between male and female adult height is 13 cm, so that in the equation 12 cm is usually replaced by 13 cm. Tanner rightly advocated that an additional correction should be made for secular change, but in practice this has rarely been done.

In 1986 Hermanussen and Cole argued that adjustment is needed for the association between a child's height and parental height, and for the association between paternal and maternal height

(assortative mating). They proposed the use of the conditional TH (cTH) SDS, which is defined by 0.72 times the average of parental height SDS [12], and calculated that the height of 95% of children should be in the range of cTH ± 1.6 SD. This formula was consistent with observational data of the Fifth Dutch Growth Study (though a factor 0.75 fitted the data better) [13]. The use of the cTH was advocated in the consensus document on idiopathic short stature (ISS) [14] and is routinely calculated in the electronic patient record system in Dutch hospitals. However, various alternative formulas have been reported, for example by investigators in the United Kingdom [10] and Finland [15]. In this mini-review we use the term target height (TH) and THSDS for any equations used. Since the discovery of many autosomal dominant growth disorders in the last decades, it is not only useful to assess TH, but also to assess separate HSDS of both parents.

Longitudinal growth

Decisions about (ab)normality of longitudinal growth are even more difficult than the two other parameters. Traditionally, as a legacy of the work by Tanner, height velocity (HV) in cm/year has been used as primary indicator for normal or abnormal growth [16]. However, its dependency of age and HSDS position (and slightly of sex) would imply that one single cut-off over the whole paediatric age period would be of little use. In theory, this problem could be partially obviated by calculating HV SDS for age and gender [17], but the disadvantage of such approach is that longitudinal growth studies were performed many decades ago on relatively small cohorts [18-21]. Furthermore, HV SDS is still dependent on HSDS and has shown to be age dependent in response to GH treatment as well [17].

We favour the use of the change of HSDS over time (delta HSDS, ΔHSDS) as parameter of longitudinal growth. This indicator is based on the observation that in healthy children HSDS remains relatively stable between 2 and 10 years of age, a phenomenon called “canalization” of growth [22]. Since the individual “channel” can show fluctuations [20, 23] and deviations associated with tempo of maturation, the challenge is to define the normal range for these fluctuations or deviations, adjusted for age and time interval. In the absence of computerized referral algorithms as used in Finland [15], the Dutch guideline for referrals of children with GF proposed a cut-off of a ΔHSDS<-1 over an undetermined time interval in combination with short stature for the population. This guideline showed acceptable specificity [24, 25], though at the expense of a sensitivity of approximately 50% in GHD and Turner syndrome [25]. Based on the Swedish growth study s [20] a cut-off of a ΔHSDS of -0.5 over a 1-2 year interval and of -0.6 to -0.9 over 3-4 years would be statistically abnormal, but the specificity in a field study has not been studied.

Before the age of 2 years, HSDS can shift up- or downwards, depending on the mutual relationship between birth length SDS and THSDS (length SDS is expected to move into the direction of THSDS). After the age of 10 years height SDS can either increase or decrease depending on onset and tempo of puberty, so that ΔHSDS should be interpreted in the context of pubertal development and THSDS.

Idiopathic short stature

Besides clarity about definitions of growth parameters, it would also be helpful if there would be consensus about the terminology of unusually short stature or slow growth for which no pathological cause can be found in spite of a detailed clinical assessment including radiologic and laboratory investigations. Conventionally, two “variants of normal growth” have been described [familial short stature and constitutional delay of growth and puberty (CDGP)], that are assumed to be diagnosed

without further investigations [16]. In contrast, already in 1996 [26] the conclusion of a “consensus” meeting was to replace these terms by a single term that would not imply “normality” but rather “unknown cause”: “idiopathic short stature” (ISS). ISS is further subcategorised into familial and non-familial (within or below TH range), each further subdivided into normal or delayed puberty [14, 26-29]. Children with non-familial ISS and delayed pubertal onset, traditionally labelled “constitutional delay of growth and puberty” (CDGP), should thus be considered a subcategory of ISS rather than a separate entity.

It is assumed that in most children with familial ISS their short stature is of polygenic origin, i.e. associated with inherited multiple relatively frequent genetic variants (polymorphisms) [30] and/or somewhat less frequent variants with stronger negative effects on growth [31]. However, the relatively high prevalence of autosomal dominant growth disorders and the fact that short individuals tend to marry short spouses, suggests that short children with apparent familial ISS may well carry dominant monogenic defects. Consequently, the diagnostic yield of monogenic gene defects may be higher in children with familial ISS than in other short children, especially if one of the parents is dysmorphic or disproportionate [32].

Supplementary Table 1. Selected primary growth disorders, which can present with (apparent) isolated short stature

Diagnosis, ICPED code (MIM code)	Incidence/yr (I) Prevalence (P) Prevalence in referred short children (Pr)	Clinical features
Turner syndrome~ 1A.1a.21	I: 10-50/100,000 P: 50/100,000 [33, 34] Pr: 2.3-2.7% (girls) [35, 36]	For full list, see [37] **General:** hypertension **Skin:** pigmented naevi **Head/neck:** strabismus, epicanthus, ptosis, narrow mandibula, dysmorphic or rotated ears, low posterior hairline, webbed neck **Thorax:** broad chest, inverted/hypoplastic or wide-spaced nipples, pectus excavatum, cardiac murmur (aortic coarctation) **Skeleton/muscles:** scoliosis, hip dislocation, knee disorder, cubitus valgus or ulnar dislocation **Hand/foot:** lymphoedema of hands and feet, nail hypoplasia/dystrophy **Comorbidities:** Increased risk of coeliac disease, hypothyroidism, horseshoe kidney, ovarian failure
Mixed gonadal dysgenesis (45,X/46,XY mosaicism) 1A.1a.15	I: 1.5 per 10,000 live births [38]	Clinical stigmata of Turner syndrome. Genital phenotype varies widely probably reflecting gonadal developmental disorders. The gonads include bilateral streaks, bilateral dysgenetic testes, or a dysgenetic testis on one side and a streak gonad on the other. Intermediate risk of germ cell malignancy [38].
Neurofibromatosis type 1 (NF1) 1A.1a.16 (#162200)	P: 1/2500-3000 [39] Pr: 0.2-2.3%^	**Skin:** café-au-lait spots, melanotic freckling, neurofibromas **Head:** macrocephaly, Lisch Noduli (eye) Skeleton/muscles: scoliosis **(Co)morbidities:** optic gliomas, epilepsy **Development:** Learning disabilities of varying severity
Noonan syndrome~ 1A.1a.17 (#163950)	P: 1/1000-2500 [40-42]	**Head/neck:** broad forehead, ptosis, hypertelorism, downslanting palpebral fissures, a high-arched palate, and low-set, posteriorly rotated ears, webbed neck **Thorax:** pectus carinatum/excavatum, cardiac murmur (pulmonalis stenosis) **Genitalia:** cryptorchidism
Prader-Willi (-Labhart) syndrome~ 1A.1a.18 (#176270)	P: 1/5525 [43]	Diminished foetal activity, obesity, muscular hypotonia, developmental delay, short stature, hypogonadotropic hypogonadism, small hands and feet.
Silver-Russell syndrome (SRS) 1A.1a.20 (#180860)	I: 1:30,000-100,000 [44]	"A distinct syndromic growth disorder in which prenatal and postnatal growth failure are associated with other characteristic features, including relative macrocephaly at birth, protruding forehead in early life, body asymmetry and substantial feeding difficulties. Almost all children with SRS are born SGA. Postnatal catch-up growth is not seen in the majority of children with SRS"

		[44].
Skeletal dysplasias multiple, e.g. achondroplasia~ (#100800) and hypochondroplasia (#146000) 1A.3a.2	Achondroplasia: P:0.13-0.64/10,000 [45] Pr: 1-9%^	Achondroplasia: Short stature caused by rhizomelic shortening of the limbs, characteristic facies with frontal bossing and midface hypoplasia, exaggerated lumbar lordosis, limitation of elbow extension, genu varum, and trident hand [46] Hypochondroplasia: Short-limbed dwarfism, lumbar lordosis, short and broad bones, and caudal narrowing of the interpediculate distance of the lumbar spine
Heterozygous *SHOX* defects (including Leri-Weill syndrome)~ 1A.3c.1 (#300582)	Pr: 3.8-16.9% [47, 48]	Short stature, mesomelia (short forearm and lower leg), Madelung wrist deformity, cubitus valgus, high-arched palate, muscular hypertrophy [49]
Heterozygous *NPR2* defects 1A.3c.88 (#616255)	Pr: 0-6% (weighted mean 2.0%) [50-55]	Disproportionate short stature and/or phenotypic or radiographic indicators similar to *SHOX* deficiency [52]
Heterozygous *ACAN* defects 1A.3c.88 (#165800)	Pr: 1-2.5% [55-58]	Phenotypic spectrum ranging from mild and proportionate short stature to a mild skeletal dysplasia with disproportionate short stature and brachydactyly. Many affected individuals develop early-onset osteoarthritis and degenerative disc disease [59]
Heterozygous *IHH* defects 1A.3c.88 (#112500)	Pr: 0.5-3% [55, 60]	Mild disproportional short stature with a frequent finding of shortening of the middle phalanx of the fifth finger [60]
Heterozygous *NPPC* defects (*600296)	Pr: 0.3% [61]	Proportionate short stature, small hands, short 4th metacarpal, hypertelorism
Copy number variants 1A.1y	Pr: 13% [62]	Variable
Idiopathic SGA without catch-up growth~ 1A.2	Pr: 0.2-17%^	Variable

For syndromes, MIM codes are added [34]

~ for more details, see [16]

^Percentages based on studies presenting data on diagnostic yield in short children referred to a paediatrician [63-73] (the paper of Lashari et al added a summary of papers by Lindsay et al (1994), Moayeri et al(2004), Bhadada et al (2003) and Colaco et al (1991)).

Supplementary Table 2. Selected secondary growth disorders, which can present with (apparent) isolated short stature

Diagnosis and ICPED code	Incidence/yr (I) Prevalence (P) Prevalence in referred short children (Pr)	Clinical features
GH deficiency#	Total GHD: P: 1:5000 [74] Pr: 1-27% GHD due to PSIS*: I: 1:4,000-10,000 P/14.7-27/100.000 Craniopharyngioma*: I: 0.13-2.0/100,000, P: 1-3/100,000 [34]	Prominent forehead, midfacial hypoplasia, high-pitched voice, lobulated abdominal fat, increased BMI, delayed bone age
GH Insensitivity (Laron syndrome)	?	Clinical hyposomatotropism manifest by short stature, delayed bone age, occasionally blue sclerae and hip degeneration; delayed bone maturation, low IGF1 despite normal or increased levels of GH [46]
Hypothyroidism#	Pr: 0.3-15%^	Fatigue, constipation, slow heart rate, slow release of Achilles tendon reflex
Cushing syndrome#	Pr: 0%^	Increased appetite, hirsutism, buffalo hump, striae, red cheeks, hypertension, increasing BMI SDS
Coeliac disease*	I: 10-17.4/100.000 P: 1:270-1000 [34] Pr: 0.3-15%^	Distended abdomen, abnormal defaecation, anaemia, skin abnormalities
Inflammatory bowel disease (IBD)#	Crohn*: I: 5-9.4/100,000 P: 40-124/100,000 [34]	Intestinal symptoms (abdominal pain, diarrhoea), weight loss.
Haemoglobinopathy	?	Anaemia
Chronic renal failure#	infantile cystinosis*: I: 0.5-1/100,000 P: 0.5/100,000 juvenile nephronophthisis*: I: 0.1-2/100,000 [34]	Hypertension, fatigue
Metabolic bone disorders	?	Variable. Hepatomegaly.
Psychosocial causes	?	Variable
Iatrogenic causes (medication)	?	Variable
Other	?	Variable

* considered as "priority target conditions" [34]

For more details, see[16]

^Percentages based on all available studies presenting data on diagnostic yield in short children referred to a paediatrician [63-73] (the paper of Lashari et al included a summary of papers by Lindsay et al (1994), Moayeri et al(2004), Bhadada et al (2003) and Colaco et al (1991))

Supplementary Table 3. Special points of attention in the physical examination of the child with growth failure

Check	***Interpretation***
Auxology	
Length or height	Calculate height SDS and distance to TH SDS. Calculate change of height SDS over time intervals
Sitting height, arm span	In most dominant (heterozygous) mild forms of skeletal dysplasias mean sitting height/height ratio SDS varies between +1.6 and +2.5, and mean arm span minus height is close to -6 cm. In children with *ACAN* haploinsufficiency mean sitting height/height ratio SDS ≈+1.6 and arm span equals height.
Ratio upper/lower arm, upper/lower leg	Relatively short upper arms and legs (rhizomelia) is suspect for *FGFR3* mutation. Relatively short forearms and lower legs (mesomelia) is suspect for *SHOX* of *NPR2* haploinsufficiency or Robinow S, but is also compatible with hypochondroplasia
Head circumference	Microcephaly is compatible with *IGF1R* and *IGF1* mutations, foetal alcohol S, and multiple dysmorphic syndromes (e.g. Seckel S, MOPD). Relative macrocephaly (in comparison to height SDS) is seen in Silver-Russell S, Turner S, Robinow S, 3M S and *NF1* mutations
Weight for age, weight for height, BMI	Underweight: malnutrition, coeliac disease, cystic fibrosis, chronic intestinal disorders [such as inflammatory bowel disease (IBD)], hypocortisolism, metabolic disorders, SGA, Silver-Russell S. Overweight/obesity: hypothyroidism, Cushing S (centripetal obesity), GH deficiency, hypothalamic disorder, pseudohypoparathyroidism
General impression	
Physical signs of parental neglect or abuse	Emotional deprivation, child abuse
Absent subcutaneous fat	Leprechaunism
Little subcutaneous fat	Progeria
Pigmented naevi	Turner S
Striae	Cushing S
Hirsutism	Coffin-Sirus S, Cornelia de Lange S
Dysmorphic features	Primary growth disorders (syndromes)
Blood pressure	Hypertension in chronic renal failure, Cushing S. Hypotension in hypoadrenalism
Heart rate	Slow heart rate suspect for hypothyroidism
Dermatitis herpetiformis	Coeliac disease
Virilisation	Cushing S
Global impression of the parents (face, body proportions	In case of dysmorphic features and/or abnormal body proportions (sitting height/height, arm span minus height, rhizomelia or mesomelia), suspect dominant syndrome or skeletal dysplasia)
Head	
Alopecia	Progeria
Coarse face	Coffin-Sirus S
Hypoplastic face	Seckel S
Narrow face	Dubowitz S
Facial teleangiectasias	Bloom S
Frontal bossing, mid-facial hypoplasia, triangular face	GH deficiency or insensitivity, Silver-Russell S, 3M S
Round, plethoric “moon” face	Cushing S
Hypertelorism	Aarskog S, Robinow S
Broad nasal bridge	Dubowitz S
Nasal hypoplasia	Hallerman-Streiff S
Prominent nose	Seckel S, Floating Harbor S
Anteverted nares, depressed nasal bridge	3M S
Heavy and continuous eyebrows	Cornelia de Lange S
Supraorbital crease	Dubowitz S
Periorbital fat accumulation	Williams S
Cataract	Hallerman-Streiff S

Epicanthus	Down S, Turner S
Ptosis	Noonan S, Aarskog S, Dubowitz S, Turner S
Almond-shaped eyes	Prader-Willi S
Fundoscopy: retinal abnormalities	Cockayne S
Fundoscopy: papilloedema, visual field defects, optic atrophy	CNS Tumour (e.g. craniopharyngioma) or space-occupying process
Long philtrum	Williams S
Partial anodonty	Williams S
'carp' mouth	Cornelia de Lange S
Large lips	Coffin-Sirus S
Full fleshy lips	3M S
Hypoplasia of the teeth	Hallerman-Streiff S
Prominent lips	Williams S
Mouth ulcers	Coeliac disease
Tonsils	Tonsillar hypertrophy and enlarged adenoid can cause growth failure in infants and toddlers
Voice pitch	High-pitched voice is compatible with GH deficiency or 3M S. Low-pitched voice with hyperandrogenism
Hypoplasia of the jaw	Hallerman-Streiff S, Rubinstein-Taybi S
Micrognathy	Dubowitz S
Narrow mandibula	Turner S
Dysmorphic or rotated ears	Turner S, Noonan S
Neck	
Low posterior hairline	Turner S
Webbed neck	Turner S, Noonan S
Increased dorsal fat pad ('buffalo hump')	Cushing S
Thyroidal size	Enlarged or small thyroid in Hashimoto thyroiditis
Thorax	
Gynaecomastia	prolactinoma
Broad chest	Turner S
Inverted/Hypoplastic or wide-spaced nipples	Turner S
Pectus excavatum	Turner S
Cardiac murmur	Suspect for congenital heart disease: aortic coarctation in Turner syndrome, pulmonary artery stenosis in Noonan S
Abdomen	
Lobulated abdominal fat	GH deficiency
Distended abdomen	Coeliac disease
Hepatomegaly, splenomegaly	Liver disorder, metabolic disorder
Genitalia	
Tanner stages	Assessment of pubertal timing (early, normal, late), assessment of inconsistencies in external pubertal signs (e.g., delayed pubic hair and penile growth in contrast to normal or advanced testicular growth in IGSF1 deficiency)
Micropenis	Hypogonadism, hypopituitarism, various syndromes (e.g. Prader-Willi S, Robinow S, Smith-Lemli-Opitz S)
Shawl scrotum	Aarskog S
Cryptorchidism	Hypogonadism, 45,X/46,XY, Noonan S, various other syndromes (Prader-Willi S, Rubinstein-Taybi S)
Ambiguous genitalia	45,X/46,XY
Skeleton/muscles	
Limb asymmetry	Silver-Russell S
Hip dislocation	Turner S
Proximal muscle weakness	Cushing S
Knee disorder	Turner S

Hyperlaxity	Down S, 3M S
Short arms and legs	Skeletal dysplasias
Madelung deformity	*SHOX* haploinsufficiency
Short forearms	*SHOX* haploinsufficiency, *NPR2* haploinsufficiency, Robinow S
Muscular hypotony or atrophy	Prader-Willi S, Down S, muscle disorder, mitochondrial disorders, glycogenoses
Muscular hypertrophy	*SHOX* haploinsufficiency
Cubitus valgus or ulnar dislocation	Turner S, *SHOX* or *NPR2* haploinsufficiency
Hand/foot	
Small hands and feet	Prader-Willi S, *NPPC* haploinsufficiency
Lymphoedema of hands and feet	Turner S
Hand anomalies	Aarskog S
Hypoplastic nails	Turner S
Syndactyly	Rubinstein-Taybi S, Smith-Lemni-Opitz S
Clinodactyly	Silver-Russell S
Absent toe-nails	Coffin-Sirus S

Abbreviations: MOPD, Microcephalic Osteodysplastic Primordial Dwarfism; S, syndrome; TH, target height

If an abnormal anatomical feature is encountered, one can search the London Medical Database for syndromes associated with that feature. A description and pictures of the most frequent dysmorphic features can be found in Am J Medical Genetics (Special issue: elements of morphology: standard terminology): https://onlinelibrary.wiley.com/toc/15524833/149A/1

Supplementary Table 4. Diagnostic yield (%) in (relatively) high-income countries

	United States 1994 [75]	Taiwan 2002 [66]	Brasil 2005 [67]	Nether-lands 2008 [63]	Greece 2012 [70]	United states 2013 [71]	Nether-lands 2015 [64]	Nether-lands 2016 [65]
n	555	655	99	542	295	235	131	182 (adol)
SGA		**15.3**	**14**	**14.8**	**5.4**		**3.8**	**1.1**
Turner/ girls	3.0	10.1		1.2	1.5		1.8	1.2
Syndromes		3.1	9	1.1	5.1	0.4	3.8	0.6
GHD	2.8	7.9	2	1.1	10.2		1.5	0.6
Hypothy-roidism	0.5	0.3					0.8	0.6
Coeliac disease				1.3	1.0	0.9	3.1	1.1
Other	9.5		4	0.7			3.8	2.7
Total pathology	**14.1**	**21.4**	**15**	**4.8**	**16.9**	**1.3**	**14.8**	**7.1**

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