Guideline for referring short or tall children in preventive child health care

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Guideline for referring short or tall children in preventive child health care

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Abstract

Aim: To develop a guideline for preventive child healthcare professionals in order to improve early detection of pathological disorders associated with short stature (or growth faltering) or tall stature (or accelerated growth).

Methods: We updated the previous Dutch guideline for short stature in children aged 0-9 years and extended it to adolescents (10-17 years), and added a guideline for tall stature, based on literature and input from an expert committee. Specificities were calculated in a cohort of healthy Dutch children aged 0-9 years (n = 970). We investigated the impact of a late onset of puberty on height standard deviation score based on the Dutch growth charts.

Results: Growth parameters of the guideline include height, the distance between height and target height and change of height over time. Other parameters include diagnostic clues from medical history and physical examination, for example behavioural problems, precocious or delayed puberty, body disproportion and dysmorphic features.

Conclusion: Preventive child healthcare professionals now have an updated guideline for referring short or tall children to specialist care. Further research is needed on the diagnostic yield after referral and specificity at field level.

KEYWORDS

children, growth, guideline, height, monitoring

1 | INTRODUCTION

Growth monitoring is an established tool in preventive child health care (PCHC) for the detection of disorders that have an effect on growth.[1] The PCHC professional is expected to refer a child who has an increased risk of a pathological disorder based on the position or shape of the growth curve on the growth chart, taking into consideration relevant diagnostic clues from the medical history and physical examination. If the risk is considered sufficiently high, the child can either be referred to specialised care or requested to come back for a follow-up visit.

Traditionally, PCHC professionals are primarily focused on detecting pathological causes of short stature (or growth faltering). However, there are also disorders associated with tall stature (or

Abbreviations: PCHC, preventive child health care; HSDS, height standard deviation score; TH, target Height.

accelerated growth). In this manuscript, we focus on monitoring height, but measurements of body weight and head circumference also play an important part in establishing the differential diagnosis.

Pathological growth disorders can be subdivided into two groups. The first group is assumed to originate from the epiphyseal growth plate and labelled 'primary growth disorders'.[2,3] Examples of primary growth disorders associated with short stature include a large number of dysmorphic syndromes, such as Turner syndrome, Noonan syndrome, Prader-Willi syndrome and skeletal dysplasias. Examples of primary growth disorders associated with tall stature include Marfan syndrome, Klinefelter syndrome, Sotos syndrome, Fragile X syndrome and Triple X syndrome. The second group is labelled 'secondary growth disorders' and assumed to be caused by a disorder extrinsic to the growth plate. Examples of secondary growth disorders associated with short stature include growth hormone deficiency, coeliac disease and hypothyroidism. Examples of secondary growth disorders associated with tall stature are precocious puberty and hyperthyroidism. For a full list of causes, the reader is referred to International Classification of Pediatric Endocrine Diagnoses.[4,5]

To support PCHC professionals in the decision to refer or measure a child at an additional follow-up visit, a guideline with referral criteria based on scientific research, clinical and parental experience is needed. The first evidence-based referral criteria for short stature between 0 and 9 years of age were developed by a Dutch team.[6] Based on these referral criteria, a guideline for short stature for PCHC for children aged 0-9 years was developed and implemented in the Netherlands in 2010.[7] In a large study comparing the external validity of the Dutch guideline, World Health Organization criteria and Finnish referral criteria for short stature, the authors concluded that the Dutch guideline showed the best performance in terms of sensitivity and specificity.[8] Similarly, in a Dutch study on children with short stature less than 10 years of age, the Dutch guideline compared favourably with the Finnish and United Kingdom guidelines.[9] The Dutch criteria for children aged 3-9 years (Table 1, short stature, 3-9y, second column) and Finnish screening criteria for short stature were also investigated in adolescence.[10] In this age group, the sensitivity to detect pathological growth disorders was good, but the specificity of both guidelines was low, presumably due to the interfering effect of a delayed pubertal growth spurt. Regarding guidelines for children and adolescent with tall stature, several expert opinion reviews have been published [3,11-14]; however, these are primarily aimed at paediatricians and paediatric endocrinologists. PCHC professionals have indicated that they feel a need for a guideline aimed at the screening for pathology associated with tall stature and to identify adolescents with whom a discussion about potential adult height reduction can be considered.[3]

The aim of our study was to update the Dutch PCHC guideline for short stature aged 0-9 years, extend this guideline to adolescents (10-17 years) and create a new guideline for tall stature aged 0-17 years.

Key notes

- Evidence-based referral criteria for short stature in children (0-9 years) have been implemented in the Netherlands since 10 years.
- We updated the referral criteria for short stature in children and extended it to adolescents (10-17 years), and developed referral criteria for tall stature in children and adolescents.
- We recommend preventive child healthcare professionals to refer children who meet the criteria of the guideline to specialist care.

2 | PATIENTS AND METHODS

A committee of experts was set up to evaluate the results of the literature and to discuss the guideline. Members of this committee included scientists, PCHC professionals (nurses and doctors), paediatricians, paediatric endocrinologists, a general practitioner, a doctor's assistant, a nursing specialist, specialists in social medicine and representatives of parents and patient support groups. When there was no relevant literature or cut-off point of growth indicators, we developed new referral criteria according to the opinions of the committee members.

The specificities of new criteria in the age group 0-9 years were then calculated in a cohort of all children born in the years 1989 and 1990 in the municipalities of Landgraaf and Kerkrade, located in the southern part of the Netherlands (n = 970).[6] Most of these children were of Dutch origin with both parents born in the Netherlands. Height standard deviation score (HSDS) was calculated based on the Fourth nationwide growth study.[15] Target height (TH) (SDS) was calculated with previously reported formulas.[16]

At adolescence, growth assessment is complicated because of the concurrent pubertal growth spurt. Several methods have been described to adjust height for pubertal timing.[17-19] However, these methods may not be applicable to the Dutch population, because of their tall stature in comparison with other countries.[20] In order to study the impact of a late onset of puberty on the HSDS position on reference charts of the Dutch population,[20] we calculated the lines representing a HSDS of −2.5 and −2 using Karlberg's formula and the Dutch prepubertal data from the Fourth National Growth Study.[15] The impact of an early onset of puberty on HSDS was not investigated.

3 | RESULTS

Figures 1 and 2 show the referral criteria for short stature and tall stature, respectively. Table 1 explains the development of the algorithms, including the background and several specificities of new criteria.

TABLE 1 Explanation of the development of the referral criteria for short stature and tall stature in different age groups

Guideline (age in years)	Comparison with previous Dutch primary care guideline	New criteria	Background of new criteria
Short stature (0-2 y)	Similar criteria: 1. HSDS< −3 and birthweight ≥ 2500 g 2. Repeatedly HSDS < −2.5 (6-12 months' time interval) and birthweight ≥ 2500 g	None	None
Short stature (3-9 y)	Similar criteria: 1. HSDS < −2.5 2. HSDS < −2 and birthweight and/or −length SDS < −2 for gestation and/or HSDS − THSDS < −1.6 and/or ΔHSDS < −1 Also: Special attention should be given to abnormal body proportions, dysmorphic features and psychosocial short stature	I. HSDS≥ −2 and < −1 and HSDS-THSDS < −2 II: HSDS≥ −2 and ΔHSDS ≥ −2 and < −1 and HSDS-THSDS < −1, additional measurement after 6 months and refer if further HSDS deflection of > 0.5 III: ΔHSDS[a] < −2	Early detection of children with primary and secondary growth disorders who still have a height within the population reference chart. I. To detect Turner syndrome, autosomal recessive conditions and de novo dominant conditions (eg SHOX haploinsufficiency) with a HSDS ≥ −2, particularly if parental height is high. II-III. To detect secondary growth disorders earlier (waiting until HSDS reaches the −2 SDS line would unnecessarily delay the diagnosis). Examples include hypothyroidism, Cushing syndrome and growth hormone deficiency, particularly if caused by an intracranial tumour, for example due to a craniopharyngioma.
Short stature (10-17 y)	Not available	I. HSDS < −2.5	To detect acquired secondary growth disorders in an adolescent with a continuing decrease in HSDS, particularly if this is not consistent with pubertal development. Also, a pathological growth disorder can be present even if HSDS is still within the population range, for example in girls with Turner syndrome caused by a mosaicism, or a slowly growing brain tumour (eg craniopharyngioma).
Tall stature (0-2 y)	Not available	I. HSDS > 3 II. Repeatedly HSDS > 2.5 (6-12 months' time interval) III. HSDS between ≥ 1 and ≤ 2.5 and other clearly present symptoms consistent with pathological causes of tall stature, for example developmental delay, behavioural problems or macrocephaly	To detect Klinefelter syndrome, Marfan syndrome, macrocephalic syndromes or secondary growth disorders (hyperthyroidism and pituitary gigantism).

(Continues)

TABLE 1 (Continued)

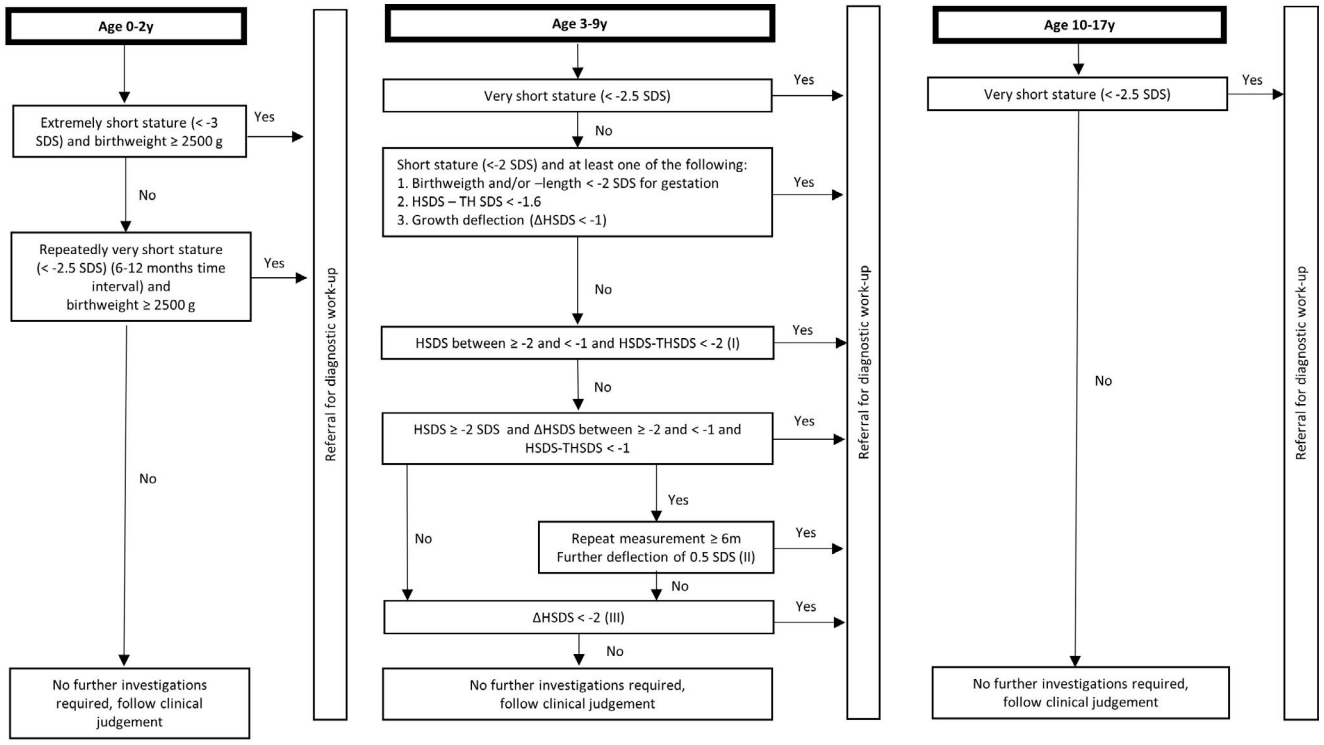
Guideline (age in years)	Comparison with previous Dutch primary care guideline	New criteria	Background of new criteria
Tall stature (3-9 y)	Not available	I. HSDS > 2.5 II. ΔHSDS[a] > 2 III. HSDS > 2 and HSDS-THSDS > 2 IV. HSDS between > 1 and ≤ 2.5 and other clearly present symptoms or signs consistent with pathological causes of tall stature, for example developmental delay in motor and/or speech/language, behavioural problems and macrocephaly. It is also important to investigate secondary sexual characteristics, because precocious puberty is one of the most common causes of accelerated growth	To detect Klinefelter syndrome, Marfan syndrome, macrocephalic syndromes or secondary growth disorders, for example precocious puberty (Tanner stage 2 or more in girls < 8y in and in boys < 9y), hyperthyroidism and pituitary gigantism. IV. For at least two relatively frequent and clinically important syndromes (Klinefelter syndrome and Marfan syndrome), HSDS can be within the (upper half of the) reference range. To decrease the mean age at diagnosis in such patients, we added this criterion.
Tall stature (10-17 y)	Not available	I. HSDS > 2.5 II. HSDS > 2 in combination with late onset of pubertal development or slowly advancing pubertal maturation (ie no breast development at 13y, no menarche at 15y in girls or no testicular growth at 14y in boys). III. When there are concerns about the predicted adult height, a tall adolescent (170 cm in girls and 185 cm in boys) can be referred if the final stage of puberty has not been reached	I-II: To detect Klinefelter syndrome, Marfan syndrome, macrocephalic syndromes or secondary growth disorders (hyperthyroidism and pituitary gigantism). III. In such cases, adult height may be considerably taller than expected based on current HSDS and initial predicted adult height so that specialist care is usually indicated.

[a]ΔHSDS: Difference in HSDS between the current measurement and the measurement from start growth deflection or acceleration, independently of the elapsed time between the measurements.

3.1 | Referral criteria for short stature at age 0-17 years

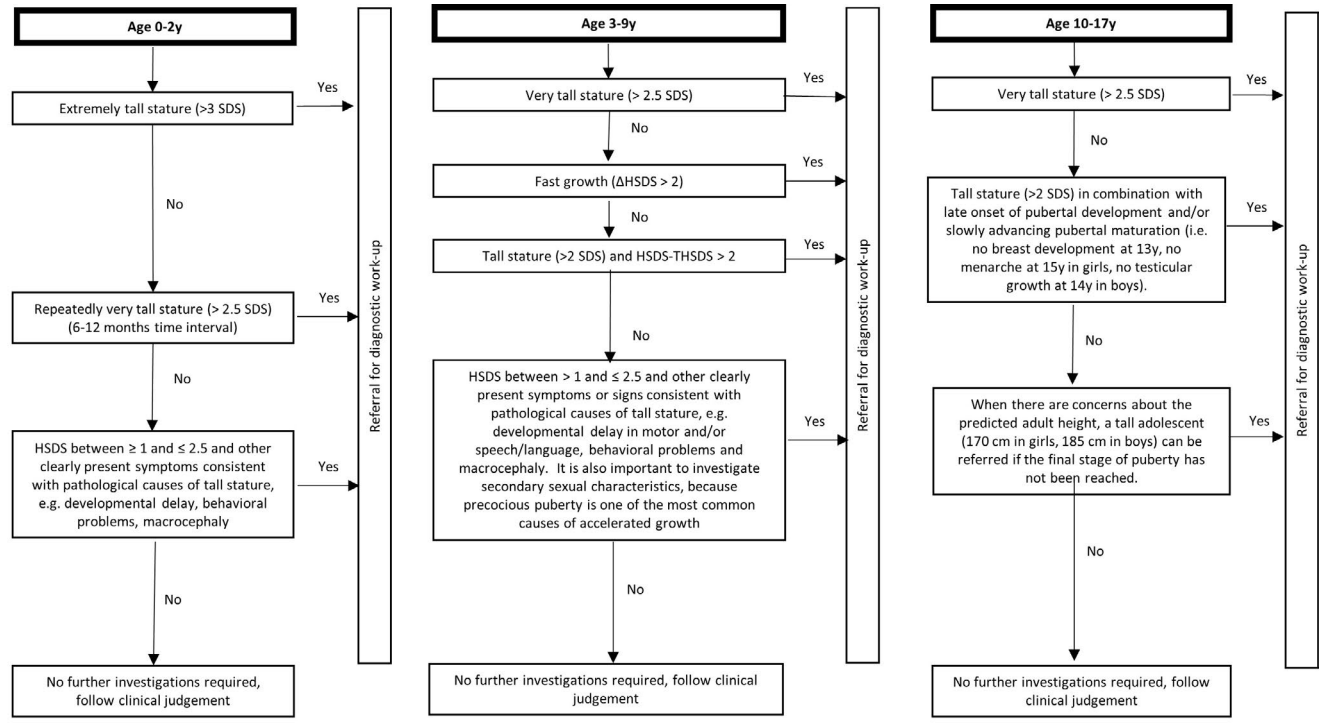
The criteria for infants and young toddlers (0-2 years) have not changed compared to the previous guideline [6,7] (Figure 1, Table 1). On top of the criteria for 3-9 years of age included in the previous version of the Dutch PCHC guideline for short stature,[6,7] three new criteria were added (see I, II and III in Figure 1 and Table 1).

For example, if a child has a HSDS of −1.5 and a THSDS of 1, then his/her HSDS is between ≥-2 and <−1 and HSDS-THSDS is equal to −1.5-1=−2.5 (HSDS is 2.5 SD shorter than THSDS), which is <−2. Therefore, this child should be referred according to criterion I. If a child has a HSDS of −1.1 and a HSDS of 0.4 in the past, and a THSDS of 0, then his/her current HSDS ≥ −2, ΔHSDS is equal to −1.1-0.4=−1.5, which is between ≥-2 and <−1, and HSDS-THSDS is equal to −1.1-0=−1.1, which is <−1. Therefore, this child should have an additional measurement after 6 months. When the child has a further HSDS deflection of > 0.5 (eg a HSDS of −1.7), he/she should be referred according to criterion II. If a child has a HSDS of −1.5 and a HSDS in the past of 1.0, then his/her ΔHSDS is equal to −1.5-1=−2.5, which is below <−2. This child should be referred according to criterion III. Table 1 presents the reasons for adding these criteria. Within the cohort of all children born in the years 1989 and 1990 in the municipalities of Landgraaf and Kerkrade, the specificities of criteria I and III were 99.7% and 99.2%, respectively. The specificity of criterion II could not be calculated, because in the current situation no additional measurement is recommended. For the age group 10-17 years, we applied the method proposed by Karlberg.[19] We found that the HSDS adjusted for a late onset of puberty of −2 was already below −2.5 HSDS in the general Dutch population. We, therefore, did not add a separate criterion for HSDS adjusting for a late-onset or slowly progressive pubertal development.



HSDS: height standard deviation score, THSDS: target height standard deviation score, g:grams, y: year, ΔHSDS: Difference in HSDS between the current measurement and the measurement from start growth deflection or acceleration, independently of the elapsed time between the measurements. Compared to the previous guideline for short stature 0-10y in the Netherlands [13], similar referral criteria were used and 3 new criteria were added (See I, II and III in the figure)

FIGURE 1 Referral criteria for short stature



HSDS: height standard deviation score, THSDS: target height standard deviation score, y: year, ΔHSDS: Difference in HSDS between the current measurement and the measurement from start growth deflection or acceleration, independently of the elapsed time between the measurements

FIGURE 2 Referral criteria for tall stature

3.2 | Referral criteria for tall stature at age 0-17 years

We formulated referral criteria for children with tall stature based on expert opinion and the latest literature on this topic [3,11-14] (Figure 2, Table 1). The diagnostic approach should be focused on the presence of a combination of tall stature with other clinical features.

4 | DISCUSSION

We developed a guideline for PCHC in the Netherlands in order to improve the early detection of disorders that are associated with short stature or tall stature in children aged 0-17 years. Several criteria are evidence-based, while others were formulated based on expert opinion and recent literature.

4.1 | Referral criteria for short stature at age 0-17 years

Research on the previous Dutch guideline for short stature in children aged 0-9 years using 777 children with Turner's syndrome and 3,521 children from the general population showed sensitivities of 76.5%-85.7% and specificities of 98.1%-98.5% between 3 and 9 years of age.[6] Between 0 and 2 years of age sensitivities were considerably lower (14.7%-26.1%), because a high specificity (>99%) was chosen for these young children.[6] In several studies, the Dutch guideline for short stature was externally validated.[8,9] A study in a cohort of Dutch children aged 3-9 years with short stature showed a sensitivity for a pathological growth disorder of 74%.[9] A large study among 341 cases and 3,406 controls compared the external validity of the Dutch guideline for short stature, the WHO criteria and Finnish referral criteria and concluded that the Dutch guideline showed the best performance, although sensitivities were lower (51.8%-54.0%) than in the original study. Specificities were similar (98.4%) as observed in the Dutch studies.[8]

As a result of these studies, the referral criteria of the previous Dutch guideline for short stature in children aged 0-9 years were also included in the newly developed guideline. However, we added three new criteria to the previous Dutch guideline for short stature aged 3-9 years to improve the early detection of children with primary and secondary growth disorders who still have a height within the population reference chart. The new Criterion I was aimed at improving the sensitivity of detecting a primary growth disorder, particularly in children with tall parents, without substantially lowering the specificity. There is good evidence that the height of young girls with Turner syndrome can stay within the reference range for quite some years,[2] and even in childhood, girls with Turner syndrome can show a stable growth curve within the lower half of the population range.[2] Theoretically, a similar growth pattern can be expected in multiple other syndromes, particularly autosomal recessive conditions and de novo dominant syndromes.

Previous research showed that the distance between HSDS and THSDS is a more sensitive criterion than HSDS itself.[6] This criterion is less suitable for early detection of one of the recently uncovered dominant forms of skeletal dysplasia if these are inherited from one of the parents. If one of the parents of a short child is short, and particularly if he or she (or the child) shows body disproportion, the PCHC professional should refer the child to specialist care, even if HSDS is within the reference range and similar to THSDS. Such pattern can, for example, be seen in children with haploinsufficiency of SHOX, NPR2, ACAN or IGF1R.[2]

The new criteria II and III were developed in an effort to achieve an earlier diagnosis of secondary growth disorders. Examples of such disorders include hypothyroidism, Cushing syndrome and growth hormone deficiency (particularly if caused by an intracranial tumour, for example due to a craniopharyngioma). In children with such disorder, particularly if they have tall parents, height can remain within the reference range for a number of years, given a mean HSDS deflection of 1 SDS/year in such children.[21,22]

The detection of pathological causes of short stature is complicated at adolescence, because of the concurrent pubertal development, and large individual variation in the timing of the pubertal growth spurt. The shape of the growth curve of a child with a pathological condition cannot be easily distinguished from that of a late maturing but otherwise healthy adolescent. Our study shows that methods to adjust HSDS for a late onset of puberty may not be helpful in the Dutch population. A Dutch study among 182 adolescents aged 10 to < 18 y with a suspicion of a growth disorder showed that the sensitivity of the Dutch referral criteria developed for 3-9 years was 85%, which was higher than the age-appropriate Finnish referral criteria (62%).[10] However, for both guidelines specificity was low because of the interfering effect of delayed puberty. After intensive discussions in the committee, a cut-off point of −2.5 HSDS was chosen for the 10-17 years, although this referral criterion has a low status regarding level of evidence. Future studies of the growth curves of children with acquired growth hormone deficiency due to brain tumours in comparison with growth curves of children with delayed puberty ('constitutional delay of growth and puberty') will be needed to improve the referral criteria in this age group.

In the interpretation of growth during adolescence, but also at other ages, it is important to take notice of pubertal status and other clinical features.[4] For example, body disproportion and dysmorphic features are strong indicators of a primary growth disorder. For the early detection of Turner syndrome, the PCHC professionals should check for a combination of a typical growth pattern (early growth deflection followed by stabilisation of HSDS until early adolescence and a further decrease in HSDS, and a large distance between HSDS and THSDS), absence of pubertal development and presence of typical dysmorphic features (so-called 'Turner stigmata'). Although criteria for this 10-17 age group have now been formulated, we expect that if the proposed referral criteria in the

younger age groups are applied, the majority of pathologic growth disorders can be detected before 10 years of age, because the associated growth deflection and clinical features are usually already apparent then.

4.2 | Referral criteria for tall stature at age 0-17 years

Various expert-based algorithms for the diagnostic approach of a child or adolescent with tall stature by the paediatrician or paediatric endocrinologist have been reported.[3,11-14] In the few studies on the diagnostic yield of pathological causes of tall stature, the prevalence appeared to be low.[3] In the recently published guideline for general paediatricians [2] much emphasis was laid on early detection of Klinefelter syndrome and Marfan syndrome, for which an early diagnosis is of paramount importance.

For an early diagnosis of these and other pathological disorders associated with tall stature, adequate and early referral by PCHC professionals is needed, but so far guidelines for referral are lacking. A challenge is that the growth pattern of all clinically relevant disorders shows a considerable overlap with the reference population.[3] Therefore, PCHC professionals should be alert on the presence of diagnostic clues for the most prevalent and relevant primary growth disorders (Klinefelter syndrome, Marfan syndrome, macrocephalic syndromes) or secondary growth disorders (precocious puberty, hyperthyroidism, and pituitary gigantism).[3,11-14] For example, suspicion of Klinefelter syndrome (usually caused by an XXY karyotype) should be aroused if the PCHC professional sees a boy who is relatively tall for his THSDS, showed a short period of growth acceleration between 5 and 8 years and has some motor or speech delay or behavioural problems. Suspicion of Marfan syndrome can come from a combination of a relatively tall stature with some of the elements of the Marfan syndrome systemic score according to the Revised Ghent criteria.[3,23] For an early detection of the rare dysmorphic syndromes associated with relatively tall stature, a checklist may be useful, including developmental delay, macrocephaly and dysmorphic facial features.[3]

5 | LIMITATIONS

With the exception of the Dutch guideline for short stature in children aged 0-9 years, which was subject to validation, referral criteria for short adolescents and tall children and adolescents were based on expert opinions, and consequently, further research is needed to investigate the diagnostic yield of multiple priority target conditions and specificity at field level. This may vary between countries, because of differences in children's healthcare management. Key factors that may impact the validity includes the number of visits to PCHC, the child's age at a visit and the growth charts used in clinical practice.

6 | RECOMMENDATIONS

We recommend PCHC professionals to refer children who meet the criteria of the guideline to specialist care. The criteria of the guideline consist of cut-off points for standardised (SDS) height and parental height so that the guideline can also be applied to children and adolescents of non-Dutch origin in and outside the Netherlands if ethnic- or country-specific growth references are used. We recommend a training for PCHC professionals and digital tools in applying the referral criteria.

Finally, no algorithm or digital tool can fully replace clinical judgement. A thorough medical history should include a check for developmental delay in motor or speech/language, behavioural problems, precocious or delayed puberty, symptoms of emotional deprivation and disorders in the family (also undetected in case of a very short or tall parent). Besides an accurate height measurement and collection of previous height data, a full physical examination should include an assessment of body weight for height, head circumference and its relationship to height (documenting microcephaly or relative macrocephaly),[24] a visual impression of body proportions (relation between trunk and extremities), dysmorphic features and any other physical signs consistent with pathological causes.

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CONFLICT OF INTEREST

There were no conflicts of interest.

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