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Growth monitoring for short stature: update of a systematic review and economic model

D Craig, D Fayter, L Stirk and R Crott

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Growth monitoring for short stature: update of a systematic review and economic model

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Abstract

Growth monitoring for short stature: update of a systematic review and economic model

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Objectives: The aim of the project was to compare different screening rules and/or referral cut-offs for the identification of children with disorders of short stature. We undertook an update of a previous systematic review and economic model that addressed the same question.
Data sources: Sources searched included MEDLINE, EMBASE, Science Citation Index, Social Science Citation Index, Conference Proceedings Citation Index – Science/Social Science & Humanities, Cochrane Library 2009 Issue 4, Office of Health Economics Health Economic Evaluations Database, and the NHS Economic Evaluation Database.
Review methods: The review was conducted as an update to our previous assessment in 2007. Searching covered January 2005 to November 2009 with no language or publication restrictions. Two reviewers examined full papers for relevance. Data extraction was conducted by one reviewer and independently checked by a second. In addition, searches were conducted to identify quality of life or utility papers to inform the economic evaluation. We developed a probabilistic decision analytic model to estimate the costs and quality-adjusted life-year (QALY) gains from the perspective of the UK NHS and personal social services. The model was a cohort model, assuming a homogeneous population of 5-year-olds at baseline.
Results: One study was included in the systematic review. The study was not UK based, but had been identified in the brief as relevant to the UK setting. The study's authors examined the performance of a number of rules to determine sensitivity and specificity of referral for short stature in four patient groups and three reference groups in the Netherlands. They derived an algorithm for referral based on the optimal rules. No new studies were located that provided appropriate quality of life or utilities data for the economic model. The model was based on the previous assessment which was updated to better reflect current UK clinical practice. We compared two alternative monitoring strategies, one of which was based on the study identified in our systematic review (Grote strategy); the other was based on UK consensus (UK strategy). We identified that the UK strategy was the least effective and least costly, with a mean gain of 0.001 QALYs at a mean cost of £21. The Grote strategy was both more expensive and more effective, with a mean cost of £68 and a mean QALY gain of 0.042. The incremental cost-effectiveness ratio was £1144 per QALY gained.
Conclusions: This assessment contributes further knowledge, but does not provide definitive answers on how to deliver growth monitoring. In particular, we were unable to ascertain current practice in the UK for growth screening. Further, we were unable to evaluate through the use of identified studies and modelling an optimal referral cut-off and

age at which to screen. We identified a number of research questions that would further inform referral strategies, which in summary would involve further primary and secondary data collection.

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Glossary

Auxology The science or study of growth.

Cost-effectiveness acceptability curve (CEAC) A graphical summary of the uncertainty in the cost-effectiveness estimates. It shows the probability that an intervention is cost-effective compared with the alternative for a range of maximum monetary values.

Confidence interval (CI) The range of uncertainty about an estimate of a treatment effect. It is the range of values above and below the point estimate that is likely to include the true value of the treatment effect. Ninety-five per cent CI indicates that there is a 95% probability that the CI calculated from a particular study includes the true value of a treatment effect.

Discount rate The percentage rate required to allow the calculation of the present value of future costs and benefits.

Dysmorphic feature A difference of body structure that is suggestive of a congenital disorder, genetic syndrome or birth defect. A dysmorphic feature can be a minor and isolated birth defect or one of a combination of features indicating a serious multisystem syndrome.

Growth monitoring The process of checking, observing or keeping track of height and/or weight measurement for a specific period of time or at specified intervals.

Incidence The number of new cases of a specific condition occurring during a certain period in a specified population.

Prevalence The proportion of people in a population who have a given disease or attribute at a given point in time.

Quality of life (health-related quality of life) A concept incorporating all the factors that might affect an individual's life, including factors such as the absence of disease or infirmity as well as others that might affect their physical, mental and social well-being.

Quality-adjusted life-year (QALY) An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Screening A health service in which members of a defined population, who do not necessarily perceive they are at risk of a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment.

Sensitivity In diagnostic/screening tests, a measure of a test's ability to correctly identify people with the disease or condition of interest.

Sensitivity analysis An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was carried out. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Skeletal dysplasias A heterogeneous group of > 200 disorders characterised by abnormalities of cartilage and bone growth, resulting in abnormal shape and size of the skeleton and disproportion of the long bones, spine and head.

Specificity In diagnostic/screening tests, a measure of a test's ability to correctly identify people who do not have the disease or condition of interest.

Utilities Values that represent the strength of an individual's preferences for specific health-related outcomes.

List of abbreviations

CEAC	cost-effectiveness acceptability curve
CRD	Centre for Reviews and Dissemination
GHD	growth hormone disorder
HSDS	height standard deviation score
HTA	*Health Technology Assessment*
ICER	incremental cost-effectiveness ratio
ISS	idiopathic short stature
NCMP	National Child Measurement Programme
NICE	National Institute for Health and Clinical Excellence
PWS	Prader–Willi syndrome
QALY	quality-adjusted life-year
QoL	quality of life
SD	standard deviation
SDS	standard deviation score
SF-36	Short Form questionnaire-36 items
SGA	small for gestational age

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Early detection and diagnosis of causes of short stature are desirable to maximise height gain and to minimise the impact of any underlying health condition. However, children are frequently diagnosed late. A previous technology assessment indicated that a growth monitoring programme could help identify children who have been missed or failed to present in clinical practice. However, further research is needed to investigate the most effective and cost-effective approach to growth monitoring.

Objectives

The aim of this assessment was to compare different screening rules and/or referral cut-offs for the identification of children with disorders of short stature by updating a systematic review and economic model.

Methods

We undertook a systematic review to identify studies that compared growth monitoring/screening strategies. As this review was conducted as an update to our previous assessment [Fayter D, *et al.* A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions. *Health Technol Assess* 2007;**11**(22)], searching covered a range of databases from January 2005 to November 2009 with no language or publication restrictions. As part of our search strategy, we aimed to identify new studies containing quality of life/utilities data to utilise in the economic model. Two reviewers examined full papers for relevance. One reviewer extracted data and one checked the data and authors were contacted for supplementary information where required. We summarised the results narratively.

We developed a probabilistic decision analytic model to estimate the costs and quality-adjusted life-year (QALY) gains. The model adopted the perspective of the UK NHS and personal social services. The price year was 2009 and an annual discount rate of 3.5% was used. The model was a cohort model, assuming a homogeneous population of 5-year-olds at baseline.

Results

One study was included in the systematic review of referral strategies. The study's authors examined the performance of a number of rules to determine sensitivity and specificity of referral for short stature in four patient groups and three reference groups in the Netherlands. They derived an algorithm for referral based on the best-performing rules.

No new studies were located that provided appropriate quality of life or utilities data for the economic model.

The model was based on the previous assessment, which was updated to better reflect current UK clinical practice. We compared two alternative monitoring strategies, one of which was based on the study identified in our systematic review (Grote strategy); the other was based on UK consensus (UK strategy). We identified that the UK strategy was the least effective and least costly with a mean gain of 0.001 QALYs at a mean cost of £21. The Grote strategy was both more expensive and more effective, with a mean cost of £68 and a mean QALY gain of 0.042. The incremental cost-effectiveness ratio (ICER) was £1144 per QALY gained. We tested a range of assumptions in sensitivity analyses. Under no scenario did the ICER exceed £8000.

Discussion

We conducted a thorough systematic review of the literature on referral for short stature in children of primary school age. However, we identified just one relevant study. We conclude from this that there is a lack of evidence on appropriate referral strategies. We also found a lack of evidence in relation to quality of life and utility gains in children with short stature, particularly linking gains in height to utilities.

The model structure and the lack of evidence affects the robustness of our economic model findings owing to the large number of assumptions required.

Conclusions

This assessment contributes further knowledge, but does not provide definitive answers on how to deliver growth monitoring. In particular, we were unable to evaluate an optimal referral cut-off and age at which to screen. The results obtained are logical in the sense that referring more children results in a higher detection rate and thereby a higher ICER. Our assessment suggests that from the strategies we have evaluated the Grote strategy appears to be a cost-effective option given current willingness-to-pay thresholds. We identified a number of research questions that would further inform referral strategies, which in summary would involve further primary and secondary data collection.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

General background

The role of growth monitoring

Assessment of a child's height and weight is well established as an indicator of his or her general health and well-being. Such assessment can also lead to the identification of treatable disorders in the apparently normal child. Early detection and diagnosis of causes of short stature help to optimise final adult height and minimise the impact of any underlying health condition. However, children are frequently diagnosed at a late age.[1]

A growth monitoring or screening programme could potentially identify a number of children with various treatable causes of abnormal growth who have been missed or failed to present in current practice. Our previous systematic review[2] found that growth monitoring (usually conducted as a one-off screening exercise) could give an additional yield of undiagnosed height-related conditions. Such a programme could also lead to the additional detection of other undiagnosed conditions for which short stature is a secondary presentation.[2]

Conditions related to short stature

Assessment of a child's stature does not aim to detect a single pathology. There are a number of conditions that may present as slowed growth/short stature. The European Society for Paediatric Endocrinology classification distinguishes between primary and secondary growth disorders and idiopathic short stature (ISS).[3] Primary growth disorders include clinically-defined syndromes such as Turner's and Cornelia de Lange, children who are small for gestational age (SGA) with failure to catch up, and skeletal dysplasias. Secondary growth disorders include malnutrition, disorders in organ systems (e.g. renal or liver), primary or secondary growth hormone disorder (GHD), other endocrine disorders such as poorly controlled diabetes mellitus, metabolic disorders, psychosocial conditions such as anorexia nervosa or emotional deprivation, and iatrogenic causes such as chemotherapy.

Conditions in which short stature is often the only or most significant presenting feature are GHD and Turner's syndrome. In GHD, an absence or insufficient production of growth hormone leads to slowed growth and results in short stature. Estimates of prevalence range from 1 in 3500 to 1 in 7000.[4] Early diagnosis is beneficial to maximise final height; if left untreated, GHD results in a reduced adult height, an average of 4.7 standard deviations (SDs) below the mean.[5] With treatment, final height can be within 1 SD of the norm.[5] Turner's syndrome is a chromosomal disorder affecting 1 in 2000 live female births that leads to short stature and infertility among other medical issues.[6] It may be, but is not always, associated with a number of characteristic physical features. For a female with Turner's syndrome, the average height in adulthood if left untreated is 143–147 cm, much more than 2 SDs below the normal female height.[5] Growth hormone can be used to increase height to within 1 SD of the normal mean height.[5] In addition to these two conditions, there is recent evidence that an important number of children with coeliac disease may present with short stature in the absence of the expected gastrointestinal complaints.[7] Once identified, with appropriate dietary guidance these children's growth may be optimised.

In the UK, growth hormone (somatropin) is currently offered for the promotion of growth to those with GHD, Turner's syndrome, chronic renal failure and Prader–Willi syndrome (PWS – a complex genetic disorder present from birth, characterised by excessive appetite, low muscle tone, emotional instability, immature physical development and learning disabilities).[8] However, at the time of writing, the provision of growth hormone was under review.[9] Further conditions under consideration included those born SGA with subsequent growth failure at 4 years of age or later and those with a genetic disorder known as short stature homeobox-containing gene deficiency.

However, identifying children with disorders manifesting with short stature is not done merely to treat their growth disorder. It also allows for management and treatment of any underlying condition. In the case of Turner's syndrome this might include treatment of cardiovascular disease[10] in addition to management of issues around fertility and sexual development. Thus, the early identification of children with disorders of short stature might help to prevent future health issues.

Current status of growth monitoring

Historically, growth monitoring practices have varied across the UK.[11] However, the National Child Measurement Programme (NCMP) was established in 2005. Currently, children in the UK have their height screened in reception year (aged 4–5 years) and in year 6 (aged 10–11 years) as part of this programme.[12] Figures for 2008–9 showed that 90% of those eligible had a valid measurement.[13] Children's measurement is overseen by health-care professionals and undertaken in school by trained staff. Primary care trust staff then enter the data into the NCMP Upload Tool. The aims of the programme are to inform local planning and delivery of services for children and to gather population-level surveillance data to allow analysis of trends in weight. The programme also offers parents and carers feedback on their child's height and weight. The focus of the programme, then, is on combating overweight and obesity rather than on identifying individual children of short stature. To our knowledge, no evaluation of the impact of the programme on referral for short stature has been undertaken. The impact of the programme on the detection of disorders of stature is, hence, unknown.

Across the world there is wide variation on growth monitoring policies and practices.[14] Indeed, organised growth monitoring is not universally available across the developed world.[14] Hence, the exact role of growth monitoring programmes in identifying short stature-related disorders is still unclear. Best practice, particularly in terms of referral, has not yet been determined.

Referral criteria

Height varies within a given population, and a child's height is measured relative to a population norm for age and sex. Diagnosis of abnormal growth is usually based on a child's measurement outlying recommended centiles on an appropriate growth chart. Many children whose measurement is found to lie outside the 'normal' range will have no underlying pathology, but a small number will be identified with a pathological cause of their short stature. An ideal growth monitoring programme should have sufficient sensitivity to detect those with short stature due to pathology. However, specificity needs to be considered in order to minimise the number of unnecessary referrals. There is clearly a trade-off between sensitivity and specificity.

For children age ≥ 4 years, the UK uses the UK 1990 charts.[15] UK consensus guidelines produced in 2004 recommended a single height and weight measurement taken at or around time of school entry and that the 0.4th centile for height should be used to initiate referral.[16] The performance of this strategy is unknown.

There is little consensus on referral criteria and diagnostic work-up of children with short stature across industrialised countries.[17] In a survey of paediatric endocrinologists from 36 countries, Grote *et al.*[17] concluded that there was a lack of evidence-based guidelines on referral and that new evidence-based guidelines were necessary with better sensitivity and specificity. Their further work examined the performance of different rules on different patient and reference groups in the Netherlands, leading to the development of a new algorithm for referral.[18] This algorithm has not been evaluated in other settings and populations.

Relationship of this study to previous research

Our previous systematic review and economic model identified the potential utility and cost-effectiveness of growth monitoring but were limited, particularly in terms of the economic model, by the available literature.[2] The previous model compared a one-off screening exercise at age 5 years with no monitoring. For the monitoring strategy it was assumed that all pupils below a certain threshold would be referred to a paediatrician or endocrinologist. For the no-monitoring strategy it was assumed that children would be referred on an ad hoc basis by either a GP or concerned parents. The model then proceeded to evaluate diagnosis and treatment of any underlying condition found by either strategy. Different referral cut-offs were not compared. The referral yields of those identified were pooled to obtain the probability of referral or an underlying condition.

This project was commissioned in the knowledge that at least one alternative screening strategy has been developed and published.[18] It was, therefore, anticipated that the availability of further research on strategies for referral would now offer an opportunity to develop the earlier model to address a more specific decision problem: from one that compares monitoring with no monitoring to one that compares at least two different screening rules and/or referral cut-offs. Accordingly, this assessment aimed to identify and synthesise studies that compare referral strategies and/or screening rules. The economic model was to be updated to take into account the different screening strategies with the aim of identifying an optimal referral strategy.

Chapter 2

Aims and objectives

Aim

To compare different screening rules and/or referral cut-offs for the identification of children with disorders of short stature.

Objectives of the assessment

The primary aim of the report was to update the earlier economic model to reflect new monitoring strategies. The two main objectives were:

- to update a previous systematic review in order to identify and synthesise studies that compare referral strategies and/or screening rules for growth monitoring[2]
- to revisit the structure of the economic model and update it to reflect the inclusion of identified strategies.

Chapter 3

Methods

Systematic review of referral strategies

A systematic review was undertaken following the principles recommended by the Centre for Reviews and Dissemination's (CRD's) guidance[19] and the quality of reporting of meta-analyses statement.[20] We used similar search criteria to our previous systematic review, but conducted a newly more focused search for studies that compared growth monitoring/screening strategies. As this review was conducted as an update of our previous review, searching covered January 2005 to November 2009. To ensure that all relevant sources of data were located, searches were not restricted by language, date of publication or study design (see *Appendix 1* for full details of the search strategies used). The results of all searches were imported into ENDNOTE XI (Thomas Reuters, CA, USA) bibliographic software and deduplicated.

Titles and abstracts were examined for relevance, and all potentially relevant papers were ordered. Two researchers independently examined full papers for relevance based on the inclusion criteria below. An EXCEL 2007(Microsoft Corporation, Redmond, WA, USA) spreadsheet was used to record decisions, and disagreements were resolved by consensus. Studies that did not fulfil all of the criteria were excluded with documented reasons and are listed in *Appendix 2*. Published and unpublished studies reported in any language were eligible for inclusion provided they met the following inclusion criteria:

- *Population* Studies of children of primary school age (ages 4–11 years) in Western Europe (including Scandinavian countries), North America or Australia/New Zealand (excluding studies of aboriginal populations) were eligible. Studies that also included overlapping age groups outside the prespecified range were also eligible.
- *Intervention and comparator* Studies comparing one or more growth monitoring or screening strategies for referral for short stature were eligible. Strategies that involved serial height measurements (monitoring) or a single measurement (one-off screening) were included.
- *Outcomes* Studies that examined rates of appropriate referral, sensitivity and specificity of the growth monitoring/screening strategies for the detection of short stature-related conditions were eligible.

A data extraction form was developed and studies were data extracted by one reviewer and checked by a second. Authors were contacted with any queries. Data from multiple publications of the same study were extracted and reported as a single study. Data extracted from the studies were tabulated and discussed in a narrative synthesis.

Literature search for quality of life data and utilities

In our previous systematic review[2] we identified a number of studies investigating quality of life (QoL) in children with a variety of growth-related conditions. However, only two provided data that could be used in the economic model.[21,22] Data from these studies were supplemented by expert opinion to derive quality-adjusted life-year (QALY) gains from detecting and treating children with a growth problem early as a result of monitoring when compared with detecting and treating children late on an ad hoc basis assuming no growth monitoring.[2] For this project, we conducted an update of the searches for QoL data with the aim of obtaining utility data for use in the updated economic model. Searches were undertaken as part of the overarching search for studies for the systematic review of referral strategies using the same date restrictions (see *Appendix 1*).

Economic model

A probabilistic decision analytic model, in the form of a decision tree, was developed to estimate the costs and QALYs of the identified referral strategies over a 12-year time horizon. The model adopted the perspective of the UK NHS and personal social services. The price year was 2009 and an annual discount rate of 3.5% was used. When necessary, costs were inflated using the UK health sector pay and prices inflation factor. The model was a cohort model, assuming a homogeneous population of 5-year-olds at baseline. All modelling was performed using TREEAGE PRO (TreeAge Software Inc., Williamstown, MA, USA) and following, where feasible, the National Institute for Health and Clinical Excellence (NICE) guidelines.[23]

Chapter 4

Results

Studies identified in the literature search for referral strategies

The search strategies identified 2861 references. These were screened as described in *Chapter 3*, and 133 full copies of papers were obtained and assessed for inclusion in the main review. *Figure 1* shows the flow of studies through the review process and numbers excluded at each stage.

One study, published in three papers,[14,18,24] met the inclusion criteria for the systematic review of referral strategies. Data extraction for this study can be found in *Appendix 4*, and the results of the study are briefly discussed in *Results of the systematic review of referral strategies*. One hundred and thirty publications were excluded from the review and their bibliographic details can be found in *Appendix 2*.

Studies identified in the literature search for quality of life and utilities

Our updated search identified 24 publications investigating QoL in relation to short stature (see *Appendix 3*).[25–48] However, none of the studies provided appropriate, useable data for inclusion in the economic model. A brief overview of the identified studies is given here.

Seven QoL studies were identified for Turner's syndrome.[25–31] Of these, three had used Short Form questionnaire-36 items (SF-36) as a tool to measure QoL.[27–29] All but one of the studies had evaluated the impact of growth hormone on QoL. Although height was an issue, generally the evidence identified suggested that other factors, such as infertility and sexual functioning and development, affected QoL more than final height gain.

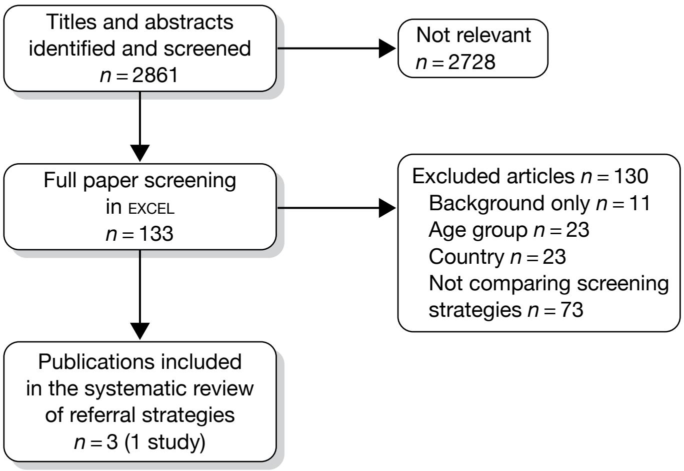
Titles and abstracts identified and screened n = 2861
Not relevant n = 2728
Full paper screening in EXCEL n = 133
Excluded articles n = 130
Background only n = 11
Age group n = 23
Country n = 23
Not comparing screening strategies n = 73
Publications included in the systematic review of referral strategies n = 3 (1 study)

FIGURE 1 Flowchart of study selection.

Three studies were identified that evaluated QoL for individuals diagnosed with growth hormone disorder.[32–34] Two used a condition-specific assessment tool,[32,33] the third a generic paediatric tool.[34] These studies also looked at the impact of growth hormone treatment on QoL and presented mixed results. It was not clear, however, that final height gain was linked to QoL. We identified nine papers that looked at QoL in other growth-related conditions treated with growth hormone.[36–44] Again these presented a variety of results, but only limited evidence that there is a strong link between QoL and final height gain. Several of the studies called for further research into the links between QoL and short stature and the tool with which this is evaluated.

Results of the systematic review of referral strategies

The results presented in this section are based on one study published in three papers.[14,18,24] Grote *et al.* conducted a study in the Netherlands that aimed to establish evidence-based guidelines for growth monitoring on a population basis. The authors examined the performance of a number of auxological rules to determine sensitivity and specificity of referral for short stature. They used four patient groups and three reference groups, and analysed data separately for children aged 0–3 and 3–10 years. We reported results for the 3- to 10-year age group only as this group is within the population covered by this review.

The four patient groups comprised 777 girls with Turner's syndrome, 27 new patients with a pathological reason for short stature, 216 children with cystic fibrosis and 120 with coeliac disease. Two of the three reference populations related to the 3- to 10-year age groups and comprised 1370 Dutch children. Ethnically appropriate growth charts were used.[49–52] Only measurements before diagnosis or start of diet (coeliac disease cohort) were taken into account. The majority of children had more than one measurement (full details are given in *Appendix 4*). Parental height was imputed where missing and a child's target height was calculated with an additional correction for secular trend. There was no discussion on the organisation of health services in the Netherlands required to undertake monitoring.

The performance of three rules was analysed separately and in combination. The rules were 'short for target height', 'very short' and 'height deflection'. 'Short for target height' represented the distance between the height standard deviation score (HSDS) and target height of > 2 SDs together with an HSDS of –2, –1.5 or –1. The 'very short' rule was set at an HSDS < –2.5 and the 'height deflection' rule was a deflection of 1 SD over an undetermined time interval combined with HSDS of –2, –1.5 or –1. The authors then refined the rules and tested the performance of the referral criteria with the best test characteristics on the patient and reference samples (*Table 1*).

TABLE 1 Performance of Grote *et al.*'s[14,18,24] referral strategies

		True positives				False positives	
Rule		TS (%)	SSP (%)	CF (%)	CD (%)	Limburg reference sample	ZHN reference sample[a]
1 Short for target height	HSDS – THSDS < –2 and HSDS < –2	76.9	58.8	8.0	27.3	0.7	1.1
2 Very short	HSDS < –2.5	74.0	58.8	4.0	18.2	0.9	0.8
3 Height deflection	Change in HSDS < –1 and HSDS < –2	13.4	17.6	0.0	18.2	0.1	0.8
Combination	Rules 1, 2, 3	85.7	76.5	8.0	27.3	1.5	1.9

CD, coeliac disease; CF, cystic fibrosis; SSP, short stature due to pathology; THSDS, target HSDS; TS, Turner's syndrome.

[a] ZHN reference sample: children born 1985 and 1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn, the Netherlands.

The authors concluded that distance to target height was the most important criterion. In combination with the other rules, the sensitivity was 85.7% for girls with Turner's syndrome and 76.5% for those with short stature due to pathology at a low false-positive rate of 1.5%–1.9%. They devised an algorithm (*Figure 2*) based on these rules.

Decision model overview

The initial aim of the model was to compare all relevant growth screening/monitoring algorithms for the population of interest. The systematic review found only one such algorithm, Grote *et al.*, which has been presented above.[18] The earlier systematic review did not identify any studies meeting this inclusion criterion, therefore only one algorithm was evaluated.[2] For the remainder of this report this algorithm will be referred to as the 'Grote strategy'. The comparator in the model was referral at < 0.4th centile, which is considered, in this analysis, to represent current UK practice. The comparator will be referred to as the 'UK strategy'. Current UK practice was based on the current NICE guidance for referral. It should be noted that it is not clear at the time of compiling this report whether this guidance has been evaluated in the UK setting.

The structure of the decision tree was principally based on the previous model,[2] although some changes were implemented to better reflect current treatment pathways in the general paediatric setting. The main change was the restructuring of the order of clinical testing. This was done to reflect the fact that in clinical practice children do not appear to move from initial investigatory tests to growth hormone provocation testing. There is a period of delay while growth velocity is considered. This is now reflected in the model structure. In addition, no-monitoring was no longer considered as a relevant comparator and therefore was not included in the model. This reflects current guidance, which we have assumed represents current practice in the UK setting. A graphical depiction of the model structure is presented in *Figure 3*.

The time horizon of the model was 12 years, long enough for a referred child to reach puberty, although we accept that, in some of the conditions evaluated, this time frame might vary. On average, this was considered an appropriate assumption and is consistent with the earlier model.[2] A lifetime horizon may have been more appropriate, allowing for all costs and outcomes of these

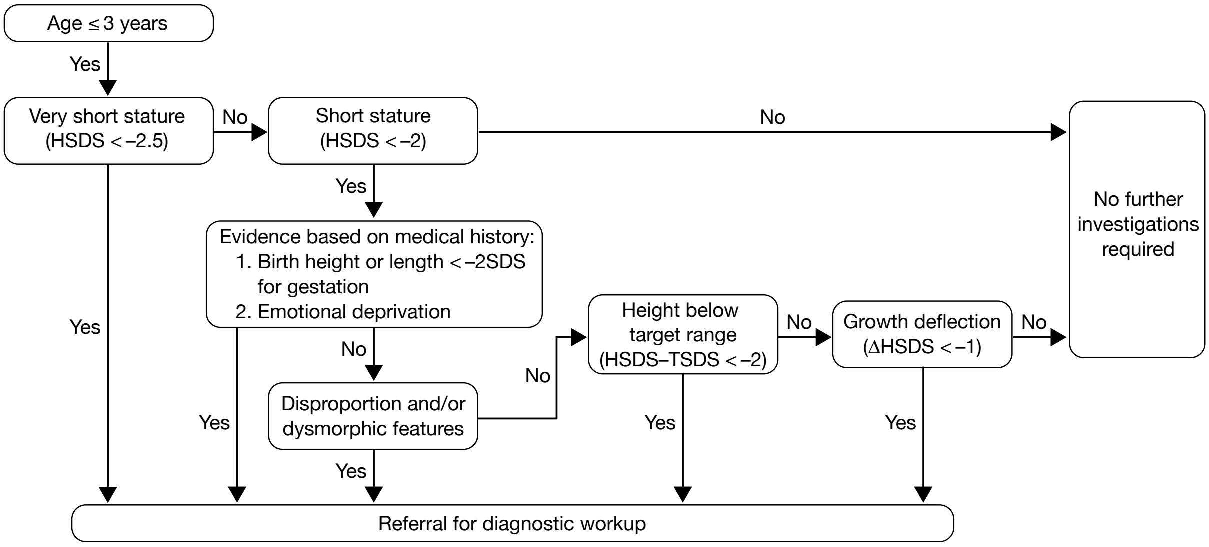
Age ≤ 3 years
Yes
Very short stature (HSDS < –2.5)
No
Short stature (HSDS < –2)
No
No further investigations required
Yes
Evidence based on medical history:
1. Birth height or length < –2SDS for gestation
2. Emotional deprivation
Yes
No
Yes
Disproportion and/or dysmorphic features
No
Height below target range (HSDS–TSDS < –2)
No
Growth deflection (ΔHSDS < –1)
No
Yes
Yes
Yes
Referral for diagnostic workup

FIGURE 2 Grote *et al.*[18] algorithm. Reproduced from *Arch Dis Child*, Grote *et al.*, volume 93, pages 212–17, 2008, with permission from BMJ Publishing Group Ltd.

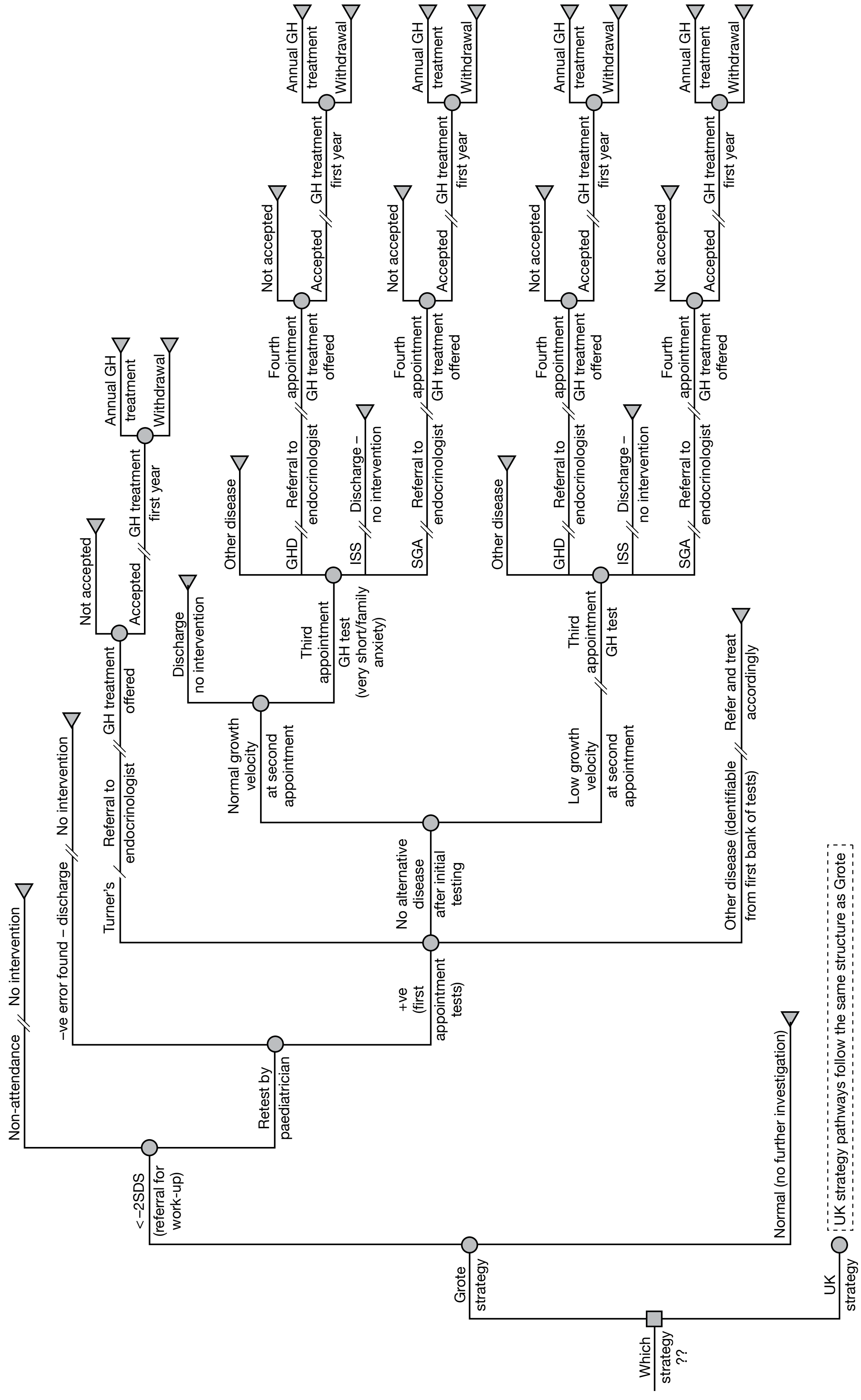
Which strategy ??
Grote strategy
UK strategy
< −2SDS (referral for work-up)
Normal (no further investigation)
Non-attendance
No intervention
Retest by paediatrician
−ve error found – discharge
No intervention
+ve (first appointment tests)
Turner's
Referral to endocrinologist
GH treatment offered
Not accepted
Accepted
GH treatment first year
Annual GH treatment
Withdrawal
No alternative disease after initial testing
Other disease (identifiable from first bank of tests)
Refer and treat accordingly
Normal growth velocity at second appointment
Discharge no intervention
Third appointment GH test (very short/family anxiety)
Low growth velocity at second appointment
Third appointment GH test
Other disease
GHD
ISS
SGA
Referral to endocrinologist
Discharge – no intervention
Fourth appointment GH treatment offered
Not accepted
Accepted
GH treatment first year
Annual GH treatment
Withdrawal
UK strategy pathways follow the same structure as Grote

FIGURE 3 Model structure.

lifelong conditions to be captured. However, given the data limitations, any extrapolation to a lifetime may have led to even more spurious results. The conditions of interest were Turner's syndrome, ISS, SGA and GHD. These were considered to be the most likely conditions to be identified through monitoring and as such, in our model, other less likely, although still extremely important conditions, have been combined under the umbrella of 'other identifiable conditions'. Of the conditions being evaluated, treatment was considered only for those children diagnosed with Turner's syndrome, GHD or SGA. Children with a diagnosis of ISS are assumed to receive no treatment. Children diagnosed with what we have classified as 'other identifiable condition' at initial assessment are not considered past this point in our model. Consequently, no treatment for this population was considered. Further, treatment was not considered for those children who were fully assessed and were diagnosed at a later point in time with a growth-related condition that was not Turner's syndrome, SGA or GHD. Treatment options considered in the model were limited to growth hormone. This does not reflect clinical practice and was a major limitation to the modelling. However, owing to time and data limitations, attempting to consider all other relevant treatment options was not plausible. This is likely to have the most impact on treatment for Turner's syndrome. The outcomes considered were number of cases of each condition diagnosed and QALY. The input parameters for the model were obtained from a variety of sources, including the previous model,[2] published literature and expert opinion. In addition, a number of assumptions were required; these will be presented in full. The following sections outline details of the model structure, inputs and analyses.

Owing to the lack of data with which to populate this model and the number of assumptions required, the following analysis should be considered speculative and we would advise that it is not used to inform resource allocation decisions. However, it is hoped that the analysis will inform discussion and further research.

Referral strategies

The screening/monitoring strategies were assumed to be applied in the school setting by a trained nurse. The UK strategy, referral < 0.4th centile, is considered to be a one-off screen. The child is measured and, if his or her height falls below the cut-off, he or she is referred directly to a paediatrician in a secondary health-care setting. Details of this strategy were derived from the previous assessment.[2] However, from discussions with clinical experts it would seem that it is more likely that referral would come via the child's GP and not directly from a nurse. We identified no new evidence to inform a re-estimate for this referral rate. As the only evidence available to us was the referral rate from the previous assessment, which implied that the monitoring/referral was conducted by a trained nurse, we have assumed the same.

To facilitate the inclusion of the Grote strategy in the model, some simplification of the algorithm was required. The algorithm refers those children < -2.5 standard deviation score (SDS) directly for diagnostic work-up, and those between < -2.5 SDS and < -2 SDS to a further screen based on medical history, birth height or length, emotional deprivation, disproportion and dysmorphic features, target height (based on parents' height) and growth deflection (change in HSDS < 1). As it was not possible to identify from the Grote research the link between final diagnosis and the cut-off for referral, we have combined the algorithm into one screen in which all children < -2 SDS were referred for further testing. Despite correspondence with the author of the strategy, it was not possible to obtain enough detail to allow us to unpick the different elements of the algorithm. Additionally, despite no clear indication from the authors' reporting, but in an attempt to reflect what might occur in the UK setting, we have assumed that the algorithm will be applied in the school setting by a trained nurse and that referral will be directly to a paediatrician in a secondary health-care setting. However, given the nature of some of the information required (i.e. medical history), it is not clear that the full algorithm could be applied by a community/school nurse without an intermediate step of a referral to a GP being introduced. These are simplifying assumptions that hugely affect the results obtained. A different set of assumptions are likely to produce different results. Owing to data limitations we were not in a position to analyse alternative sets of structural and organisational assumptions. No discussion of service delivery or organisation in the Netherlands was provided in the Grote papers or via e-mail requests.[14,18,24]

Clinical pathways

The clinical pathway for both referral strategies being compared is outlined below. On referral, an outpatient appointment with a paediatrician is sent. Children will either attend or not attend this appointment. Those children who do not attend exit the model and are not considered further, although they do incur the cost of the initial screen. Those who attend the appointment are assessed by a paediatrician for correct referral. Incorrect referrals, which are assumed to occur as a result of measurement error at initial screen, are discharged and not considered further in the model. Estimates to inform these model parameters were derived from the literature.[2] It should be noted that non-attendance at appointments is likely to incur a cost to the NHS. This additional cost has not been considered in this analysis. Incorrect referrals also incur costs; these children who are discharged incur the cost of the resources that they have consumed (i.e. the cost of referral and the cost of outpatient appointment/retest). Correct referrals undergo a bank of investigatory tests, which include blood tests, urine tests, height, weight, medical history and chromosome tests. The results of these tests determine one of three possible outcomes: (1) a diagnosis of Turner's syndrome; (2) a diagnosis of 'other identifiable conditions' such as renal disorders, cystic fibrosis or coeliac disease; or (3) a diagnosis of no identifiable condition, which results in a referral for further assessment.

Those children who have received a diagnosis of Turner's syndrome continue on through the model with a referral to an endocrinologist, who will be in a position to offer growth hormone treatment. The growth hormone treatment can be either accepted or declined. This is the only treatment option considered in the model. Those children declining treatment will incur the costs and benefits accrued to date, but are assumed to be discharged and not considered further in the model. Those who accept undergo treatment for a period of 12 years (the time horizon of the analysis) and accrue costs and benefits throughout this time. During the 12-year period it is assumed that some children will withdraw from treatment. For simplicity it has been assumed that those that withdraw will do so at the halfway point (6 years) and consequently incur half of the costs and benefits of those who complete the 12-year treatment.

Those children who receive a diagnosis of 'other identifiable condition' do not go any further in the model and are assumed to exit the model at the point of diagnosis. They incur the cost of the monitoring and testing undertaken to get them to this point, but no further evaluation of their conditions or the subsequent appropriate treatment is undertaken in this model.

Those with 'no other identifiable condition' continue in the model and are referred on for a second appointment with the paediatrician. The focus of the second appointment is growth velocity. The model structure allows children to be split into two cohorts, those with normal growth velocity and those with low growth velocity as measured at the initial assessment appointment and a second appointment over a 6-month time frame. The model structure for the two groups differs slightly. For those children with normal growth velocity there is a possibility of discharge with no further testing, although externalities, such as parental concern, may lead to a growth hormone provocation test, the result of which can be a diagnosis of 'other' disease, GHD, ISS or SGA. Unlike those children with normal growth velocity, all children with low growth velocity undergo a growth hormone provocation test, the results of which can lead to the same four diagnosis categories: other, GHD, ISS and SGA.

Post diagnosis, the normal growth velocity and the low growth velocity branches are the same. The 'other' conditions incur costs of referral and diagnosis, but are not considered further in the model. In addition, they achieve 1 year's worth of utility gain to reflect any benefit in QoL that may be realised as a consequence of being active in the health-care system. The other three conditions are offered growth hormone treatment and the model structure allows them to accept or decline. As with the Turner's syndrome branch, those who accept will undergo treatment for a period of 12 years, the time horizon of the model. During the 12-year period it is assumed that some children will withdraw from treatment. For simplicity it has been assumed that those who withdraw will do so at the halfway point (6 years) and consequently incur half of the costs and benefits of those who complete the 12-year treatment.

Outcomes

Usually a QALY is obtained by means of allowing an accrual of the life expectancy multiplied by the utility value over the relevant time horizon. The primary model outcome is QALYs gained. These aggregated QALY gains were taken from the previous *Health Technology Assessment* (HTA) journal publication.[2] They were based on two published studies[21,22] and clinical opinion. Using an aggregated estimate of lifetime QALY gains as an outcome is not a commonly used method and the results presented in this analysis can be interpreted as the gains in QALYs for each intervention. Despite limitations we have used this approach for a number of reasons. The systematic searches of a number of sources identified a number of QoL studies, but no suitable utilities for the population being evaluated. Further, it was not clear that the use of adult utilities or other such proxies would be any improvement on the QALY gains that had previously been published.[2] It is worth noting that the authors of the earlier report suggest that QALY gain was linked to achieving a more normal height. This belief was based on identified studies and expert opinion which they used to augment the literature and help estimate utility gains. However, it is not clear from the review of QoL studies that we undertook that this link is supported by the QoL evidence. A summary of the review of QoL studies has been presented in *Appendix 3*.

The aggregate QALY gain for each of the conditions is presented in *Table 2*. Any withdrawal from treatment was assumed to take place at the halfway point, and consequently children received half of the QALY gain. No treatment is assumed to result in no QALY gain.

Clinical data

Data to populate the model were derived from a variety of sources. All clinical parameters are presented in *Table 3*. The systematic review provided data on the algorithm which informed the Grote strategy. Data for the comparator UK strategy were taken from the earlier model.[2] Further referral rates for the Grote strategy were obtained from an unpublished doctoral thesis[14] whose authors tried to assess, retrospectively, the proportion of (correct) referrals that would be generated when screening the general population of children. This was achieved by applying an

TABLE 2 Quality-adjusted life-year gains

Status	QALY gain	Status	QALY gain
Turner's		***ISS***	
No treatment	0	No treatment	0
Treatment	5	***SGA***	
Stop treatment	2.5	No treatment	0
GHD		Treatment	3.12
No treatment	0	Stop treatment	1.56
Treatment	5	***'Other'***	
Stop treatment	2.5	Treatment	3.26

TABLE 3 Probability estimates

Probability	Estimate	Distribution	Source
UK referral	0.0075	Beta	Fayter *et al.*[2]
Grote referral	0.023	–	Theoretical
Attendance	0.9	Beta	Fayter *et al.*[2]
Non-attendance	0.1	Beta	Fayter *et al.*[2]
Referral error	0.18	Beta	Fayter *et al.*[2]
Turner's syndrome	0.08	Dirichlet	Expert opinion
No alternative condition	0.942	Dirichlet	Expert opinion
Other condition	0.05	Dirichlet	Expert opinion
Normal growth velocity	0.75	Triangular	Expert opinion
Low growth velocity	0.25	Triangular	Expert opinion
Discharge (normal growth)	0.9	Triangular	Expert opinion
Test (normal growth)	0.1	Triangular	Expert opinion
Given low growth velocity			
Other condition	0.025	Dirichlet	Grote[14]
GHD	0.016	Dirichlet	Grote[14]
ISS	0.779	Dirichlet	Grote[14]
SGA	0.183	Dirichlet	Grote[14]
Given normal growth velocity			
Other condition	0.025	Dirichlet	Grote[14]
GHD	0.016	Dirichlet	Grote[14]
ISS	0.779	Dirichlet	Grote[14]
SGA	0.183	Dirichlet	Grote[14]
Accepting growth hormone treatment			
GHD	0.91	Triangular	Fayter *et al.*[2]
Turner's syndrome	0.83	Triangular	Fayter *et al.*[2]
SGA	0.71	Triangular	Fayter *et al.*[2]
Withdrawal from growth hormone treatment			
GHD	0.093	Triangular	Fayter *et al.*[2]
Turner's syndrome	0.17	Triangular	Fayter *et al.*[2]
SGA	0.03	Triangular	Fayter *et al.*[2]

algorithm, retrospectively, to two databases of general population children measurements. Details of this are discussed in *Results of the systematic review of referral strategies*.

The Grote calculations showed that this would lead to an overall referral rate for further assessment in a specialised setting of between 1.5% and 1.9% of all children between 3 and 10 years old, demonstrating a sensitivity of between 85.7% and 76.5% depending on the disease. However, the prevalence of organic diseases linked to growth deficiency is very low in the population of children to be screened. For example, incidence at birth of Turner's syndrome is estimated to be around 1 in 2000 or only 0.05%, i.e. 5/10,000 live births.[6] This means that assuming no case was discovered prior to screening, to detect four cases of Turner's syndrome (5 × 0.85) in a population of 10,000 children one has to refer 200 of the children (2%) to a specialised clinic. Even with an overall prevalence of organic disease of 5% we would still have to refer 200 children for further appraisal, of whom approximately 38 (50 × 0.765) would be diagnosed, while the rest (162 children) would be classified as SGA or ISS. In our model the

Grote strategy refers all children < 2 SDS for further assessment. The theoretical perfect referral rate would be 2.3%; this can be easily calculated using a normal distribution curve and *z*-tables. The details of the Grote analysis were not well presented and it is not clear that population retrospectively analysed is representative of the population whom we wish to evaluate. We therefore took the decision to use the theoretical perfect referral rate as the base case and assess the impact of the alternative referral rate in sensitivity analyses.

The base-case error rate (18%) was assumed to be the same for both strategies and was based on UK data used in the previous HTA report.[2] We also assumed that the rate of non-attendance (10%) was the same for both strategies; this, like many other parameters, was taken from the previous model.[2] The probabilities of 'other' disease, no identifiable disease and Turner's syndrome were derived from two sources: the previous HTA report[2] and expert opinion. The probability of normal or low growth velocity was derived from expert opinion. Although the importance of growth velocity appears to have been acknowledged in the Grote strategy, owing to the way in which it was presented and the means by which we have incorporated it into the model, it was not possible to obtain any data from the Grote publications to help inform these two parameters. We, therefore, had no choice but to use expert opinion to obtain estimates; these, like other parameters, are tested in sensitivity analyses. The distribution of diagnosed conditions (other, GDH, ISS and SGA) was derived from Grote.[14] As previously mentioned, the Grote publications[14,18,24] did not provide information on growth velocity status. To facilitate modelling, we have assumed in the base case that the distribution of diagnosed conditions is the same for both low and normal growth velocity branches. In reality, this may not be the case and it is probable that those children with normal growth velocity are less likely to be diagnosed with GHD and more likely to be diagnosed with ISS. This has been tested in sensitivity analyses. Finally, the probability of accepting growth hormone treatment when offered and the probability of withdrawing from that treatment were taken from the previous HTA report.[2] The actual reasons for withdrawal were not documented in the previous assessment and we found no further evidence to allow us to adjust or confirm the rates. Owing to this uncertainty we assessed a zero withdrawal rate in sensitivity analysis.

Resource and cost data

The unit costs of the consultations and diagnostic tests are presented in *Table 4*. All costs were inflated to 2009. The model assumes that a trained nurse conducted the initial screen; the cost of this was taken from the previous assessment.[2] To reflect the more complex nature of the Grote

TABLE 4 Unit cost data

Unit cost	Estimate	Distribution	Source
Urine test	4.83	Fixed	Fayter *et al.*[2]
Cost per outpatient attendance first contact face to face	264	Gamma	*NHS reference costs*[53]
Cost per outpatient attendance subsequent contact face to face	188	Gamma	*NHS reference costs*[53]
Specialist community nurse per patient contact (1 hour)	73.00	Gamma	PSSRU[54]
Community nurse per patient visit (1 hour)	65.00	Gamma	PSSRU[54]
Blood tests (for full blood count, chemical profile, thyroid and IGF)	53.01	Gamma	Takeda *et al.*[55]
Pituitary function test (glucagon, insulin stress test) includes 2 hours nurse time	215.66	Gamma	Takeda *et al.*[55]
Growth hormone provocation test (an additional nurse for 8 hours plus eight blood tests)	377.55	Fixed	Bryant *et al.*[56]
Chromosome test (blood karyotype)	198.69	Fixed	Bryant *et al.*[56]
Drug cost per mg	23.18	Fixed	Takeda *et al.*[55]

IGF, insulin-like growth factor; PSSRU, Personal Social Services Research Unit.

strategy, the cost of the UK strategy was increased one and a half times in the base case. This assumption was tested in sensitivity analysis.

The resource use associated with each of the clinical diagnosis treatment pathways is presented in *Table 5*. The condition diagnosed dictates the number of appointments attended and the additional tests undertaken. Once a diagnosis has taken place there are additional resource implications for growth hormone treatment of GHD, Turner's syndrome and SGA. These, along with some unit costs, were taken directly from Takeda *et al.*,[55] a recently conducted HTA report on treatment with growth hormone.

Drug doses are dependent on weight and the dose per kg per day/week/year for each of the conditions is presented in *Table 6*. The average weight of children at each age was used to derive an annual cost of treatment for each of the 12 years. Average weights and appropriate dose for each condition were derived from data presented in Takeda *et al.*[55] As previously stated, discounting was conducted at 3.5%.

Dealing with uncertainty

The evidence base from which the data to inform this model have been drawn was extremely limited. To address some of this uncertainty, a number of one-way sensitivity analyses were

TABLE 5 Resource use

Annual administration and monitoring resources	GHD	Turner's syndrome	SGA
No treatment (monitoring			
Outpatient visit	2	2	2
Blood test	1	1	1
Growth hormone treatment (year 1)			
Specialist nurse home visit	1 hour	1 hour	1 hour
Community nurse home visit	4 hours	4 hours	4 hours
Outpatient visit	2	2	2
Blood test	1	1	1
Pituitary function test	0.1	0	0
Growth hormone treatment (11 subsequent years)			
Outpatient visit	2	2	2
Blood test	1	1	1
Hand X-ray	1	1	1
Pituitary function test	0.1	0	0
End of treatment			
Outpatient visit	1	1	1

TABLE 6 Drug doses

Dose	SGA	GHD	Turner's syndrome
mg/kg/day	0.035	0.025	0.045
mg/kg/week	0.245	0.175	0.315
mg/kg/year	12.74	9.1	16.38

conducted to enable us to assess the impact that a change in one of the parameters has on the model results. In addition to the univariate (one-way) sensitivity analysis, a probabilistic sensitivity analysis was performed to incorporate parameter uncertainty into the cost-effectiveness analysis. Appropriate parameter distributions were chosen, according to the nature of the variables, for those input parameters for which suitable data were available. These distributional assumptions could not be validated, as no data were available. An alternative set of distributional assumptions would produce a different set of results. Cost-effectiveness acceptability curves (CEACs) and scatterplots were used to present summaries of uncertainty. CEACs assess the probability of each option being cost-effective according to different willingness to pay per unit of health benefit obtained (in this instance per QALY gain). As the referral rate for the Grote strategy was theoretical, this was incorporated as a point estimate and no distribution was applied.

Model results

The highly speculative base-case deterministic results presented in *Table 7* show that the UK strategy was the least effective and the least costly, producing a mean gain of 0.001 QALYs at a mean cost of £21. The Grote strategy was found to be both more expensive, with a mean cost of £68, and more effective, with a mean QALY gain of 0.042. The incremental cost-effectiveness ratio (ICER), which is defined as the ratio of the change in costs (incremental cost) and the change in effects (incremental effect) of the intervention, is £1144 per QALY gained. The result is logical: if one strategy refers more children there is a higher cost in processing and testing those referrals, but it is more likely that cases will be identified, hence the higher benefit. Any decision on whether a strategy is cost-effective is dependent on the decision-makers' willingness to pay. It is widely accepted that the current UK threshold is between £20,000 and £30,000. The low cost of monitoring suggests that as long as cases are being identified and treated, it is likely to look like a cost-effective option. The issue of late versus early detection was not addressed in this model, but is an issue that will hugely affect the benefits of any monitoring programme.

The number of health conditions diagnosed in a cohort of 100,000 children is presented in *Table 8*. These figures were obtained by tracking final diagnosis in the model. They have been presented to highlight the potential difference in diagnostic yield between the two alternative strategies.

Sensitivity analysis

Owing to the paucity of clinical data, we were unable to address all of the model uncertainties. We have attempted to deal with those that were highlighted as uncertainty by differing clinical estimates. However, in some instances no clinical evidence was available, which made dealing with uncertainty more problematic. A summary of the univariate sensitivity analyses conducted is presented here. In addition, several scenarios were evaluated.

TABLE 7 Model results

Intervention	Cost	Incremental cost	QALY gain	Incremental QALY gain	ICER (£/QALY gain)
UK strategy	£21		0.001		
Grote strategy	£68	£46	0.042	0.041	1144

TABLE 8 Health condition yield

Health condition	UK strategy	Grote strategy
Other identifiable conditions	14	85
Turner's syndrome	4	14
Normal growth velocity		
GHD	0	3
ISS	20	91
SGA	8	28
Other	2	3
Low growth velocity		
GHD	2	8
ISS	74	334
SGA	25	158
Other	3	6

The original model[2] appeared to estimate that the probability of being diagnosed with 'other condition' after initial referral and initial investigatory tests was 40%. Discussions with our clinical advisor suggested that this was more likely to be around 5%. As it was difficult to ascertain whether 40% was an accurate estimate of diagnosis of 'other condition' at this stage of the clinical pathway, a decision was made to use 5% in our base case. Those children who fall into this diagnostic category do not incur any further costs or benefits in this model. The alternative rate was assessed in sensitivity analysis (1) and the results are presented in *Table 9*.

As expected, the mean cost of each strategy reduces, as do the incremental costs and benefits of the Grote strategy compared with the UK strategy. This in turn leads to the slightly higher ICER of £1524 per QALY gain.

The structure of our model splits children into those who achieve normal growth velocity and those who achieve low growth velocity at a second appointment. We believe that growth velocity is an extremely important component of the monitoring process. Growth velocity was not considered in the previous model and we found no evidence in the systematic review to allow us to inform what proportion of the children would be normal/low, what proportion of those who had normal growth velocity would receive a growth hormone provocation test, or what the distribution of diagnosed conditions would be for these two different populations. To address these separate issues we conducted a number of analyses using slightly different scenarios.

1. We assumed that all children in our cohort had normal growth velocity.
2. We assumed that all children in our cohort had low growth velocity.
3. We assumed that all children in our cohort with normal growth velocity who received a growth hormone provocation test received a diagnosis of ISS.

The ranges of the estimates obtained from these analyses are presented in *Table 10*, sensitivity analysis (2). Variation of these individual estimates does have an impact and, as might be expected, assuming that all children have a low growth velocity leads to a higher ICER, almost £8000. Again, this is well within the £30,000 threshold that is generally accepted to be the UK upper value of willingness to pay per QALY gained. Further investigation into to the role of growth velocity in monitoring is warranted.

As we have assumed a theoretical referral rate of 2.3% for the Grote strategy, we assessed what the impact might be of reducing that referral rate to 1.5% in line with the retrospective evaluation that Grote conducted. As can be seen from the results of sensitivity analysis (3), presented in *Table 11*, the ICER is slightly reduced compared with the result of the base case, a reflection of the lower number of children being referred and incurring costs and benefits.

The cost of monitoring using the Grote strategy was based on an assumption that the application of the Grote algorithm would be more resource intensive than the UK strategy. We increased the cost of the UK strategy, which was taken from the previous report,[2] by one and half times for the base case. We increased this further in sensitivity analysis (4) to assess what the impact might be if the cost of the Grote strategy were three times that of the UK strategy. As can be seen from the results presented in *Table 12*, the benefits achieved by each strategy remain the same, while the cost of the Grote strategy and the ICER increase accordingly.

Probabilistic analysis

The results of the probabilistic model, which by assigning distributions to all parameters allows the parameter uncertainty to be propagated throughout the model, are presented in the following section. We performed the analysis with 100,000 Monte Carlo simulations, which allowed us to assess the robustness of the base-case results to parameter uncertainties. The results of the analysis were plotted as an incremental cost-effectiveness scatter plot (*Figure 4*). The plot

TABLE 9 Sensitivity analysis results (1)

Intervention	Cost	Incremental cost	QALY gain	Incremental QALY gain	ICER (£/QALY gain)
UK strategy	£19		0.001		
Grote strategy	£58	£39	0.026	0.026	1524

TABLE 10 Sensitivity analysis results (2)

Intervention	Cost range	Incremental cost range	QALY gain range	Incremental QALY gain range	ICER (£/QALY gain) range
UK strategy	£17–£34		0.0005–0.0026		
Grote strategy	£52–£115	£35–£81	0.0138–0.0511	0.0112–0.0506	690–7194

TABLE 11 Sensitivity analysis results (3)

Intervention	Cost	Incremental cost	QALY gain	Incremental QALY gain	ICER (£/QALY gain)
UK strategy	£21		0.001		
Grote strategy	£47	£25	0.027	0.026	976

TABLE 12 Sensitivity analysis results (4)

Intervention	Cost	Incremental cost	QALY gain	Incremental QALY gain	ICER (£/QALY gain)
UK strategy	£21		0.001		
Grote strategy	£75	£54.00	0.042	0.041	1329

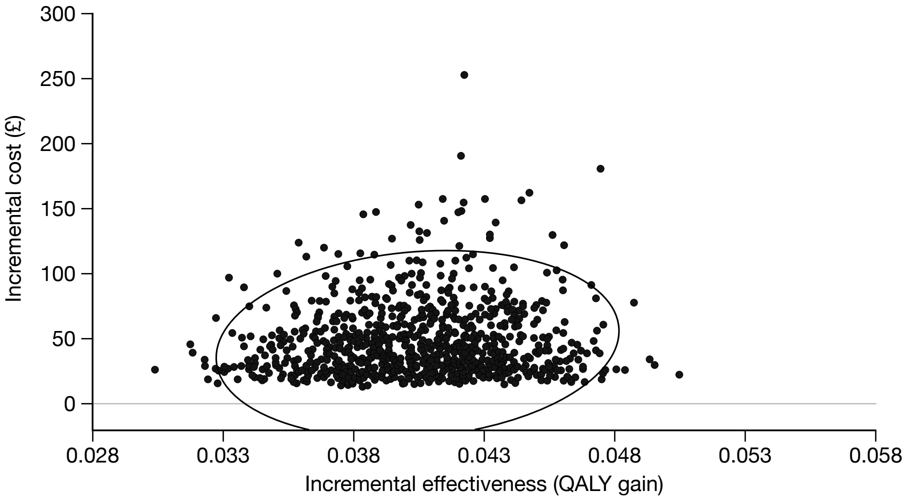

FIGURE 4 Scatter plot.

shows us the distribution of the incremental costs, incremental benefits and joint cost–effect distribution. It has been obtained by randomly and repeatedly drawing from the distributions that we assigned to the model parameters. The estimates obtained are then plotted on the cost-effectiveness plane. A cost-effectiveness plane is divided into four quadrants, with each quadrant having a different interpretation for the economic evaluation. All of the estimates obtained from this analysis fall into the north-east quadrant of the plane, showing that all of the sampled estimates have positive costs and effectiveness. This corresponds to the other results presented. The figure also shows the 95% confidence ellipse, which reflects the uncertainty in the simulated estimates.

The scatter plot shows the incremental cost and effect estimates for the Grote strategy compared with the UK strategy. For each sample of the probabilistic analysis the difference in expected costs and effects is plotted. The axes represent incremental costs and effects. It is clear from the spread that the base-case results (incremental cost £46 and incremental effects 0.041) fall centrally within the cloud.

From this scatter plot a CEAC has been generated (*Figure 5*). The CEAC, which is derived from the joint uncertainty, shows the probability that the Grote strategy is a cost-effective choice compared with the UK strategy, across a range of willingness-to-pay thresholds. The aim of the CEAC is to visually represent the uncertainty, which is presented as the probability that each alternative has the greatest net benefit as a function of willingness to pay. The CEAC is constructed by means of counting how many simulations fall below and to the right of a line with a slope set equal to a willingness-to-pay threshold value. The slope of the line is initially set to equal zero and the proportion of points estimated; the line is then adjusted counterclockwise to represent alternative threshold values. Plotting these points on a graph gives us the CEAC.

The CEAC clearly shows that at lower willingness-to-pay threshold values, there is a probability (declining from 1 to 0.5) that the UK strategy will be a cost-effective strategy. As the willingness-to-pay threshold increases there is a switch, and the probability of the Grote strategy being the most cost-effective strategy becomes higher, again ranging between 0.5 and 1, but this time increasing. The switch point on the willingness–to-pay axis corresponds to the base-case ICER, the switch point on the probability axis occurs at 50%, suggesting that the underlying distribution of the incremental net benefit is symmetrical.

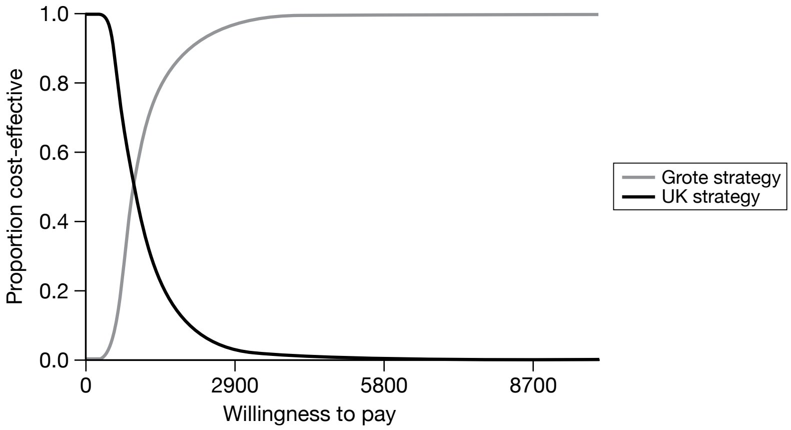

FIGURE 5 Cost-effectiveness acceptability curve.

Chapter 5

Discussion

Summary of findings

This assessment presents an updated systematic review and economic model to investigate referral strategies for the identification of disorders of short stature in primary school-aged children. We located just one relevant study, published by Grote *et al.*[18] This study assessed the performance of a number of referral rules and resulted in an algorithm for referral for investigation of short stature. We simplified and adapted the algorithm presented in this study for the economic model and compared it with the UK consensus for referral for short stature. We labelled the strategies 'the Grote strategy' and 'the UK strategy' respectively. The systematic review found no studies of QoL that could inform the model utilities.

The economic model, which was highly speculative, found that the UK strategy was the least effective and least costly with a mean gain of 0.001 QALYs at a mean cost of £21. The Grote strategy was both more expensive and more effective, at a mean cost of £68 with a mean QALY gain of 0.042. The ICER was £1144 per QALY gained. This figure is well within the accepted current UK threshold for willingness to pay.

Assessment methods and limitations

We conducted a thorough systematic review of the evidence published since our last assessment.[2] Thus we can be confident in stating that there is a lack of evidence on referral as witnessed by the fact that we could identify only one relevant study.[18] Our analysis of this study was extremely limited and, despite our efforts, we were unable to obtain all of the supplementary details from the authors. The algorithm identified and assessed in this study was theoretical and does not reflect current practice in the authors' country (the Netherlands). All evaluations of the algorithm were retrospective in nature and much of the detail that would have aided transparency and replication was not available to us. It is also not possible to assess just how generalisable these data are to the UK setting.

The economic model structure was updated to better reflect current clinical practice regarding diagnosis and treatment post referral. We assumed that monitoring would be implemented in schools and undertaken by a trained nurse in the school setting. The nurse would be responsible for referring children directly to the paediatrician. This reflects the approach used in the earlier model, but it is not clear that if implemented this would be the most appropriate means of delivery for a monitoring programme. In practice, a two-stage referral approach comprising a referral by a trained nurse to a GP and the GP referring on after some form of further assessment may be more appropriate. The GP would be acting as a gatekeeper to the paediatrician. While this may not change the number of referrals from the nurse, it would affect the clinical pathway and the number of referrals to the paediatrician. We could find no evidence regarding the delivery and organisation of monitoring programmes. The service delivery of the Grote strategy was not discussed. The clinical/diagnostic pathways that formed the structure of our model were based on expert opinion on the clinical pathways followed in a general UK paediatric setting. We acknowledge that practices vary both across the UK and across the world. However, we believe that our structure is a reasonable reflection of a typical pathway. It would have been prudent to model alternative structures in an attempt to assess the impact of different clinical pathways. However, given the data limitations and a lack of evidence surrounding alternative pathways this did not seem a viable option.

We made every attempt to identify new effectiveness evidence from the literature to populate the model. However, this update relied heavily on the evidence identified in the earlier assessment.[2] We further limited our analysis by including only growth hormone treatment, but a full assessment of all alternative treatments for these conditions was not possible within the scope of this analysis. We did not fully review all of the evidence for growth hormone treatment effectiveness and the associated resource implications; instead we obtained this information from a recently published HTA report which specifically aimed to assess these factors.[55] While these reports may have limitations, we believe that they represent the best available evidence.

We identified a number of studies of QoL in the population of interest. However, none was suitable to inform the economic model. This was largely due to a lack of utility or QoL data that could be mapped to utilities. Hence utility outcomes, which are presented as aggregate QALY gains, are based on the previous model[2] and expert opinion. These QALY gains appear to hinge on the assumption that there is a link between height gain and enhanced QoL. However, the evidence found in our review of these studies did not present clear evidence of such a link. We therefore suggest that the link between height gain and QALY remains unclear.

The lack of high-quality evidence entailed making a number of simplifications and assumptions in relation to the economic model, all of which led to less robust and highly speculative findings. We undertook a large number of sensitivity analyses, both one-way and probabilistic. Under no scenario did the ICER exceed £8000 (an extreme scenario where all children referred for a second assessment had low growth velocity). However, in order to conduct these analyses we were required to make further assumptions about our uncertainty around point estimates; these were made with the help of clinical guidance, but remain uncertain. While there are many methods available to help deal with parameter uncertainty, the number of assumptions that sometimes have to be made to facilitate these methods can add additional uncertainty. We have tried to clearly and transparently report our analysis, but we have been unable to address all of the uncertainties that have been identified.

The underlying lack of evidence has affected all aspects of the project including the type of modelling that could be undertaken. Given a better evidence base, the use of a Markov model would have allowed us to assess referral at different ages, diagnosis at different ages, disease progression, treatment effects related to progression and the associated utilities. The data to populate such a model are not currently available and the evidence identified would suggest that we are a long way from being able to undertake such a model.

Some steps could be taken to try to assess some of the uncertainties in the evidence identified. For example, the Grote algorithm was developed using retrospective analysis of already diagnosed children and this influenced our decision to use the theoretical referral rate in the base case of the model. However, a retrospective evaluation of UK children may be possible, and this would reduce some of the uncertainty around whether the different populations who have been retrospectively evaluated are comparable to the UK general population of children being screened. This may also help to overcome the lack of transparency regarding the Grote strategy. To overcome any issues with comparability of populations, as the Grote strategy was evaluated on confirmed cases, we used a theoretical referral rate based on the evidence and tested the referral rate from Grote in sensitivity analysis. Therefore, we have made some assumptions about the comparability of the populations, but have been unable to test these assumptions any further.

There are several options available that may help reduce some of the uncertainties surrounding what we have identified. However, the only way to address the uncertainties surrounding the evidence is to conduct further research. There are a number of key issues that remain unclear, including the age at which monitoring should commence, who should undertake the monitoring, what the cut-off point for referral should be set at and how important is growth velocity? These are fundamental issues that require answers.

Chapter 6

Conclusions

Implications for service provision

Both this report and the previous assessment[2] suggest that monitoring for short stature is a cost-effective option. Further, we know that some monitoring already takes place in the form of the NCMP, but the primary focus of this programme is not on identifying children with short stature. What remains unclear is how monitoring for short stature and the type of monitoring undertaken by the NCMP might be linked. We have identified limited evidence to support any particular strategy for short stature monitoring and no evidence for the implementation or delivery of such a programme. Our economic modelling is highly speculative and does not provide any useful additional information with which to inform a decision about which monitoring programme to use.

We hope that this report contributes further knowledge, but we acknowledge that it does not provide definitive answers. In particular, we were unable to establish current practice or evaluate optimal referral cut-offs and age(s) at which to screen. The results obtained are logical in the sense that referring more children results in a higher detection rate and thereby a higher ICER, but they cannot be interpreted as definitive answers.

Given that the NCMP is a well-established service, consideration should be given to the impact of incorporating growth monitoring and referral for short stature. This does not negate the decision of which referral strategy is optimal and further research would still be required to answer this question.

Suggested research priorities

In our previous assessment[2] we suggested long-term research on growth monitoring in the form of controlled trials comparing growth monitoring with no growth monitoring. We also suggested studies of diagnostic accuracy following up both children found to be short and those found to be normal. We have identified some research priorities that may help inform the evidence base and these are listed below. However, our previous long-term research priorities recommended in the previous assessment[2] remain valid.

- Conduct an assessment of current referral sources for short stature (i.e. GP, school nurse, parents).
- Conduct a retrospective data analysis of a large sample of UK children currently referred for short stature to assess the identification rate of diagnosis of disease.
- Survey current clinical referral pathways and diagnostic work-up and final diagnosis for children referred for short stature.
- Survey the attitudes of health-care professionals, parents and children to a national growth monitoring programme to identify possible barriers to implementation.
- Investigate the feasibility of integrating growth monitoring for short stature into the NCMP.

- Monitor any introduction of a programme for quality assurance to decrease referral errors and false negatives.
- Undertake an assessment of QoL and utilities for children diagnosed with disorders of short stature, preferably at referral and during and after treatment.

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Contribution of authors

Dawn Craig contributed to all aspects of the economic modelling, including model structure, data inputs, analysis and report writing. Dawn also contributed to aspects of the clinical review.

Debra Fayter contributed to all stages of the clinical review and provided input to the economic model.

Lisa Stirk devised the search strategy, carried out the literature searches, maintained the library of references and wrote the search methodology sections of the report.

Ralph Crott contributed to all stages of the project, commented on drafts of the report and had overall responsibility for the project.

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Appendix 1

Search strategy

Child growth update

Limits – records added to database since 2005.

No language limits.

MEDLINE (Ovid) – 4 November 2009

1424 records found.

Search terms

1. (short$adj2 (stature$or child$or girl or girls or boy or boys)).ti,ab.
2. low stature$.ti,ab.
3. (growth adj2 (retard$or fail$or decreas$or delay$or deficien$or restricted or abnormal)).ti,ab.
4. reduced height.ti,ab.
5. (stunting or stunted).ti,ab.
6. (growth hormone adj (deficien$or disorder$)).ti,ab.
7. turner$syndrome.ti,ab.
8. Turner Syndrome/
9. juvenile hypothyroidism.ti,ab.
10. or/1-9
11. exp child/
12. child$.ti,ab.
13. (school-age$or schoolage$).ti,ab.
14. schoolchild$.ti,ab.
15. (boy or boys or girl or girls).ti,ab.
16. or/11-15
17. (monitor$or measur$or diagnos$or screen$or referr$or surveill$or guideline$).ti,ab.
18. Mass Screening/
19. 17 or 18
20. 10 and 16 and 19
21. exp Life-Tables/
22. Quality-of-Life/
23. Health-Status/
24. exp Health-Status-Indicators/
25. (health measurement$scale$or health measurement$questionnaire$).ti,ab.
26. (standard gamble$or categor$scal$or linear scal$or linear analog$or visual scal$or magnitude estmat$).ti,ab.
27. (rosser$classif$or rosser$matrix or rosser$distress$).ti,ab.
28. (index of wellbeing or index of well being).ti,ab.
29. (quality of wellbeing or quality of well being or qwb).ti,ab.
30. (rating scale$or multiattribute$health ind$or multi attribute$health ind$).ti,ab.
31. (health utilit$index or health utilit$indices).ti,ab.
32. (multiattribute$theor$or multi attribute$theor$).ti,ab.

33. (multiattribute$analys$or multi attribute$analys$).ti,ab.
34. (multiattribute$utilit$or multi attribute$utilit$).ti,ab.
35. (health utilit$scale$or classification of illness state$or (15d or 15-d) or 15 dimension).ti,ab.
36. (health state$utilit$or (12d or 12-d) or 12 dimension).ti,ab.
37. euroqol.ti,ab.
38. well year$.ti,ab.
39. health utilit$scale$.ti,ab.
40. (utilit$approach$or health gain or (hui or hui2 or hui3)).ti,ab.
41. (qol or (5d or 5-d) or 5 dimension).ti,ab.
42. (quality of life or eq-5d or eq5d or hrqol).ti,ab.
43. (qualy or qaly or qualys or qalys).ti,ab.
44. quality adjusted life year$.ti,ab.
45. life year$gain$.ti,ab.
46. willingness to pay.ti,ab.
47. (person trade off$or person tradeoff$).ti,ab.
48. (time trade off$or time tradeoff$).ti,ab.
49. (hye or hyes).ti,ab.
50. health$year$equivalent$.ti,ab.
51. theory utilit$.ti,ab.
52. life table$.ti,ab.
53. health state$.ti,ab.
54. utility value$.ti,ab.
55. or/21-54
56. 10 and 16 and 55
57. 20 or 56
58. Developing Countries/or exp Africa/or exp Asia/or exp South America/
59. (third world or 3rd world).ti,ab.
60. (developing world or developing countr$or developing nation$).ti,ab.
61. or/58-60
62. 57 not 61
63. animal/not (animal/and human/)
64. 62 not 63
65. (editorial or letter or case reports).pt.
66. 64 not 65
67. (2005$or 2006$or 2007$or 2008$or 2009$).ed.
68. 66 and 67

EMBASE (Ovid) – 4 November 2009

1537 records found.

Search terms

1. short stature/or turner syndrome/
2. growth hormone deficiency/
3. (short$adj2 (stature$or child$or girl or girls or boy or boys)).ti,ab.
4. low stature$.ti,ab.
5. (growth adj2 (retard$or fail$or decreas$or delay$or deficien$or restricted or abnormal)).ti,ab.
6. reduced height.ti,ab.
7. (stunting or stunted).ti,ab.
8. (growth hormone adj (deficien$or disorder$)).ti,ab.
9. (turner$syndrome or juvenile hypothyroidism).ti,ab.
10. or/1–9

11. child/or boy/or girl/or handicapped child/or hospitalized child/or preschool child/or school child/
12. child$.ti,ab.
13. (school-age$or schoolage$).ti,ab.
14. schoolchild$.ti,ab.
15. (boy or boys or girl or girls).ti,ab.
16. or/11-15
17. (monitor$or measur$or diagnos$or screen$or referr$or surveill$or guideline$).ti,ab.
18. mass screening/or developmental screening/
19. 17 or 18
20. 10 and 16 and 19
21. life table/
22. exp "quality of life"/
23. exp health status/
24. health survey/
25. (health measurement$scale$or health measurement$questionnaire$).ti,ab.
26. (standard gamble$or categor$scal$or linear scal$or linear analog$or visual scal$or magnitude estmat$).ti,ab.
27. (rosser$classif$or rosser$matrix or rosser$distress$).ti,ab.
28. (index of wellbeing or index of well being).ti,ab.
29. (quality of wellbeing or quality of well being or qwb).ti,ab.
30. (rating scale$or multiattribute$health ind$or multi attribute$health ind$).ti,ab.
31. (health utilit$index or health utilit$indices).ti,ab.
32. (multiattribute$theor$or multi attribute$theor$).ti,ab.
33. (multiattribute$analys$or multi attribute$analys$).ti,ab.
34. (multiattribute$utilit$or multi attribute$utilit$).ti,ab.
35. (health utilit$scale$or classification of illness state$or (15d or 15-d) or 15 dimension).ti,ab.
36. (health state$utilit$or (12d or 12-d) or 12 dimension).ti,ab.
37. euroqol.ti,ab.
38. well year$.ti,ab.
39. health utilit$scale$.ti,ab.
40. (utilit$approach$or health gain or (hui or hui2 or hui3)).ti,ab.
41. (qol or (5d or 5-d) or 5 dimension).ti,ab.
42. (quality of life or eq-5d or eq5d or hrqol).ti,ab.
43. (qualy or qaly or qualys or qalys).ti,ab.
44. quality adjusted life year$.ti,ab.
45. life year$gain$.ti,ab.
46. willingness to pay.ti,ab.
47. (person trade off$or person tradeoff$).ti,ab.
48. (time trade off$or time tradeoff$).ti,ab.
49. (hye or hyes).ti,ab.
50. health$year$equivalent$.ti,ab.
51. theory utilit$.ti,ab.
52. life table$.ti,ab.
53. health state$.ti,ab.
54. utility value$.ti,ab.
55. or/21-54
56. 10 and 16 and 55
57. 20 or 56
58. developing country/or exp Africa/or exp Asia/or exp South America/
59. (third world or 3rd world).ti,ab.
60. (developing world or developing countr$or developing nation$).ti,ab.

61. or/58-60
62. 57 not 61
63. nonhuman/or animal/
64. human/
65. 63 not (63 and 64)
66. 62 not 65
67. (editorial or letter).pt.
68. case report/
69. 67 or 68
70. 66 not 69
71. (2005$or 2006$or 2007$or 2008$or 2009$).em.
72. 70 and 71

Science Citation Index (Web of Knowledge) – 4 November 2009

1460 records found.

Social Science Citation Index (Web of Knowledge) – 4 November 2009

132 records found.

Conference Proceedings Citation Index – Science/Social Science & Humanities – 4 November 2009

107 records found.

Search terms

ts="juvenile hypothyroidism"
ts="turner* syndrome"
ts=("growth hormone deficien*" or "growth hormone disorder*")
ts=(stunting or stunted)
ts=reduced height
TS=("growth retard*" or "growth fail*" or "decreas* growth" or "delay* growth" or "growth deficien*" or "restricted growth" or "abnormal growth")
TS=low stature*
ts=("short* stature*" or "short* child*" or "short* girl" or "short* girls" or "short* boy" or "short* boys")
#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
ts=(boy or boys or girl or girls)
ts=schoolchild*
ts=("school-age*" or schoolage*)
ts=(child or children)
#13 OR #12 OR #11 OR #10
ts=(monitor* or measur* or diagnos* or screen* or referr* or surveill* or guideline*)
#15 AND #14 AND #9
Ts=("theory utilit*" or "life table*" or "health state*" or "utility value*")
Ts=(hye or hyes or "health* year* equivalent*")
Ts=("time trade off*" or time tradeoff* or "person trade off*" or "person tradeoff*" or "person trade off*" or "person tradeoff*")
Ts=("life year* gain*" or "willingness to pay")
Ts="quality adjusted life year*"
Ts=(qualy or qaly or qualys or qalys or "quality of life" or "eq-5d" or eq5d or hrqol)
Ts=(qol or 5d or "5-d" or "5 dimension")
Ts=("utilit* approach*" or "health gain" or hui or hui2 or hui3)
Ts="health utilit* scale*"

Ts=(euroqol or "well year*")
Ts=("health state* utilit*" or 12d or "12-d" or "12 dimension")
Ts=("health utilit* scale*" or "classification of illness state*" or 15d or "15-d" or "15 dimension")
Ts=("multiattribute* utilit*" or "multi attribute* utilit*")
Ts=("multiattribute* analys*" or "multi attribute* analys*")
Ts=("multiattribute* theor*" or "multi attribute* theor*")
Ts=("health utilit* index" or "health utilit* indices")
Ts=("rating scale*" or "multiattribute* health ind*" or "multi attribute* health ind*")
Ts=("quality of wellbeing" or "quality of well being" or qwb)
Ts=("index of wellbeing" or "index of well being")
Ts=("rosser* classif*" or "rosser* matrix" or "rosser* distress*")
Ts=("standard gamble*" or "categor* scal*" or "linear scal*" or "linear analog*" or "visual scal*" or "magnitude estmat*")
Ts=("health measurement* scale*" or "health measurement* questionnaire*")
#38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17
#39 AND #14 AND #9
#40 OR #16
Ts=("developing world" or "developing countr*" or "developing nation*" or "third world" or "3rd world" or africa or asia or india or china or "south america")
#41 NOT #42
#43 AND Document Type=(Article)

Cochrane Library 2009 Issue 4 – 16 November 2009

Records found:

- Cochrane Database of Systematic Reviews – 10
- CENTRAL – 146
- Database of Abstracts of Reviews of Effects – 0
- NHS Economic Evaluation Database – 0
- HTA database – 0.

Search terms

#1 (short* near/2 (stature* or child* or girl or girls or boy or boys)):ti,ab,kw or (low stature*):ti,ab,kw or (growth near/2 (retard* or fail* or decreas* or delay* or deficien* or restricted or abnormal)):ti,ab,kw or (reduced height):ti,ab,kw or (stunting or stunted):ti,ab,kw
#2 (growth hormone deficien* or growth hormone disorder*):ti,ab,kw or (turner* syndrome):ti,ab,kw or (juvenile hypothyroidism):ti,ab,kw
#3 MeSH descriptor Turner Syndrome explode all trees
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Child explode all trees
#6 (child*):ti,ab,kw or (school age* or schoolage*):ti,ab,kw or (schoolchild*):ti,ab,kw or (boy or boys or girl or girls):ti,ab,kw
#7 (#5 OR #6)
#8 (monitor* or measur* or diagnos* or screen* or referr* or surveill* or guideline*):ti,ab,kw
#9 MeSH descriptor Mass Screening, this term only
#10 (#8 OR #9)
#11 (#4 AND #7 AND #10)
#12 (#11), from 2005 to 2009

Office of Health Economics Health Economic Evaluations Database – 16 November 2009

One record found.

Search terms

‘short stature’ or ‘short child’ or ‘short children’ or ‘short girl’ or ‘short girls’ or ‘short boy’ or ‘short boys’ or ‘low stature’ or ‘growth retardation’ or ‘growth retarded’ or ‘growth failure’ or ‘decreased growth’ or ‘growth delay’ or ‘delayed growth’
‘growth deficiency’ or ‘restricted growth’ or ‘abnormal growth’ or ‘reduced height’ or stunting or stunted or ‘growth hormone deficiency’ or ‘growth hormone disorder’ or ‘growth hormone disorders’ or ‘turners syndrome’ or ‘turner syndrome’ or ‘juvenile hypothyroidism’
AND
child or children or ‘school age’ or ‘school aged’ or schoolage or schoolaged or schoolchild or schoolchildren or boy or boys or girl or girls
AND
monitor* or measur* or diagnos* or screen* or referr* or surveill* or guideline*

NHS Economic Evaluation Database

No records found.

Search terms

#1 (short* near/2 (stature* or child* or girl or girls or boy or boys)):ti,ab,kw or (low stature*):ti,ab,kw or (growth near/2 (retard* or fail* or decreas* or delay* or deficien* or restricted or abnormal)):ti,ab,kw or (reduced height):ti,ab,kw or (stunting or stunted):ti,ab,kw
#2 (growth hormone deficien* or growth hormone disorder*):ti,ab,kw or (turner* syndrome):ti,ab,kw or (juvenile hypothyroidism):ti,ab,kw
#3 MeSH descriptor Turner Syndrome explode all trees
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Child explode all trees
#6 (child*):ti,ab,kw or (school age* or schoolage*):ti,ab,kw or (schoolchild*):ti,ab,kw or (boy or boys or girl or girls):ti,ab,kw
#7 (#5 OR #6)
#8 (monitor* or measur* or diagnos* or screen* or referr* or surveill* or guideline*):ti,ab,kw
#9 MeSH descriptor Mass Screening, this term only
#10 (#8 OR #9)
#11 (#4 AND #7 AND #10)
#12 (#11), from 2005 to 2009

Appendix 2

Studies excluded from the systematic review of referral

Abdullah N, Drummond P, Gray N, Al-Khalidi O, Barry R, Cheetham T. Short stature: increased in children with severe learning disability. *Child Care Health Dev* 2009;**35**:266–70.

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Appendix 3

Studies identified in the quality of life and utilities literature search

Twenty-four references published between 2005 and 2009 were retrieved relating to QoL. All were ordered, but none was found to be suitable for use in the economic model. A brief overview of the studies is provided.

Turner's syndrome

Study details	Population	Study design	QoL instruments	Major findings
Li *et al.* (2007)[25]	TS	A systematic review and economic evaluation of GH treatment	NA	GH improves final height, but the effect on QoL is unclear (only two studies). Economic evaluation based on one study using time trade-off for better height found that GH was not cost-effective, but it was concluded that ethically GH should be provided to enable final height gain
Sutton *et al.* (2005)[26]	97 US girls and women with TS and 21 parents	Qualitative study	NA	The major challenges for girls and women across the lifetime in order of importance were infertility, short stature, sexual development and functioning and general health issues. The participants were keen to have an early diagnosis
Carel *et al.* (2005)[27]	568 GH-treated patients	French population-based registry (StaTur study)	SF-36 (French) and GHQ-12	HRQoL similar in adult women with TS treated with GH in childhood and the general population. Factors associated with low HRQoL scores: cardiac and otological involvement, induction of puberty after age of 15 years and higher expectations from GH treatment. Adult height or height gain had no influence on HRQoL
Carel *et al.* (2006)[28]	566 GH-treated patients	French population-based registry (StaTur study) follow-up	Coopersmith's Self-Esteem Inventory and Social Adjustment Scale Self-Report, SF-36 (French) and GHQ-12	Height was not associated with self-esteem and social adjustment
Bannink *et al.* (2006)[29]	Study of 49 women with TS, former participants in two GH studies	Survey	Dutch SF-36 and TNO/AZL Adult Quality of Life[a]	Satisfaction with height and breast development had significant positive influence on several HRQoL scales including social and physical functioning
Lagrou *et al.* (2006)[30]	30 women aged 18–23 years old with TS diagnosed at an early age, treated in childhood with GH and oestrogens if indicated	Case–control study with age-matched reference group of 44 non-TS students	Young Adult Self Report, Self Perception Profile for College Students and Bodily Attitude Scale	TS patients did not report more behavioural and emotional problems than non-TS females except for attention problems. Reported fewer problems on some subscales. Did not differ on body satisfaction, but perceived themselves as less socially competent. BMI was related to Body Attitude Scale score, but height was not related to any of the evaluated psychosocial parameters
Kilic *et al.* (2005)[31]	11 Turkish girls 9–17 years old with TS (not all treated with GH and/or oestrogen), FSS and healthy controls	Matched control comparative study	Children's Depression Inventory, State-Trait Anxiety Inventory for Children and Piers-Harris Children's Self Concept Scale	TS girls reported lower self-concept and self-esteem and higher state anxiety than normal controls

BMI, body mass index; FSS, familial short stature; GH, growth hormone, GHQ, General Health Questionnaire; HRQoL; health-related quality of life; NA, not applicable; TS, Turner's syndrome.

[a] TNO/AZL questionnaire for adults health-related quality of life.

Growth hormone disorder only

Study details	Population	Study design	QoL instruments	Major findings
Hoybye *et al.* (2007)[32]	353 adults with childhood-onset GH deficiency categorised by GHD aetiology	Retrospective review	QoL Assessment of GHD in Adults Questionnaire	After 2 years of treatment with GH, QoL improved in all three groups categorised by GHD aetiology (non-organic disorder, organic pituitary disease and brain tumour), although to a lesser degree in patients in the brain tumour group
Attanasio *et al.* (2005)[33]	66 adults with severe GHD in transition to adulthood	Based on 2-year RCT of GH treatment at two doses versus no treatment	Specially developed QoL questionnaire for adult patients with GHD (QLS-H)	Overall baseline QoL was not compromised during the transition period, but dimensions related to age-specific psychological problems were worse than for healthy participants and appeared to respond positively to GH treatment
Sheppard *et al.* (2006)[34]	22 patients aged 8–16 years with diagnosis of IGHD or AGHD following malignancy	Before-and-after 6-month study	Pediatric Quality of Life inventory comprising eight items on physical functioning and 15 on a psychosocial subscale (completed by parents and children) and Parent only Strengths and Difficulties Questionnaire covering psychosocial adjustment	Children with AGHD (below population norms at baseline) improved significantly over a 6-month period on QoL measures. Children with IGHD, who were comparable to population norms at baseline, improved but not significantly. Authors concluded that the benefits of GH for QoL needed to be evaluated independently for different diagnostic groups
Sandberg (2006)[35]	NA	Commentary on Sheppard *et al.*[34]	NA	NA

AGHD, growth hormone disorder; GH, growth hormone, IGHD, idiopathic isolated growth hormone disorder; NA, not applicable; QLS-H, Questions on Life Satisfaction-Hypopituitarism; RCT, randomised controlled trial.

Other conditions

Study details	Population	Study design	QoL instruments	Major findings
Bertella *et al.* (2007)[36]	13 GH-treated adult PWS patients and their parents	Survey	SF-36, Psychological General Well-Being Index	Significant results in relation to improvements from baseline on both QoL scales in both physical and psychological well-being
Tanaka *et al.* (2009)[37]	Japanese children (aged 4–15 years) with ISS (116) or GHD (127) naive to GH treatment	Case–control	Japanese Child Behaviour Checklist (CBCL/4–18) consisting of 118 multiple choice questions answered by primary caregiver	QoL is impaired in Japanese children owing to short stature
Brutt *et al.* (2009)[38]	Children and adolescents with GHD or ISS	Literature review	Description of generic, condition-specific and treatment-specific QoL tools	There is a need for further research into the development of a new QoL instrument to assess short stature
Bullinger *et al.* (2009)[39]	Children and adolescents with GHD or ISS	Follow-up literature review to Brutt *et al.*[38]	Description of generic, condition-specific and treatment-specific QoL tools	There is a need for further research into the relationship of QoL and short stature
Visser-van Balen (2005)[40]	38 adolescents with ISS or SGA	3-year RCT comparing GH/GnRHa treatment with no intervention	Parental interview, Child Behaviour CheckList completed by parents, Silhouette Apperception Technique (parents and adolescents), Adolescent self report on Dutch version of Self Perception Profile for Children (CBSK) and for Adolescents (CBSA), Dutch version of Stait Trait Anxiety Inventory for Children (ZBV-K), KDVK (short depression questionnaire for children) and Dutch Personality questionnaire-Junior (NPV-J)	The observation of some adverse psychological consequences as reported by adolescents shows that it is useful to monitor psychosocial functioning during combined GH/GNRHa treatment in adolescents with ISS or SGA. It is uncertain whether any positive effects of expected gain in final height can sufficiently counterbalance possible short-term negative effects

Study details	Population	Study design	QoL instruments	Major findings
Visser-van Balen (2007)[41]	30 adolescents with ISS or SGA	Follow-up to previous study[40] on average 5.5 years after cessation of treatment	Semi-structured interviews of young adults and their parents on social circumstances, height-related psychosocial stressors and psychosocial functioning and well-being, Self-Perception Profile for Young Adults (Dutch version), Dutch version of the State-Trait Anxiety Inventory (ZBV)	In the long term, and independent of hormone treatment, adequate psychosocial adjustment is expected for those with short stature
Bannink *et al.* (2005)[42]	Adolescents born SGA mean age 15.8 years (standard deviation 2.1 years) treated with GH (44) or untreated (28)	Comparative study	Self-reports of the Children's quality of Life Short Stature Module (TACQOL-S) disorder-specific questionnaire and the generic Child Health Questionnaire (CHQ)	Adolescents born SGA treated with GH had better QoL than untreated group according to a disorder-specific questionnaire. The authors advise the use of a disorder-specific questionnaire for measuring QoL in children with short stature in addition to a generic questionnaire which did not reveal differences in QoL
Storch *et al.* (2005)[43]	26 children with short stature (pathological, unknown and not related to pathology) and 32 children with DM1	Comparative study	Child Behaviour Checklist, children's Depression Inventory, Social Anxiety Scale for Children – Revised and Asher Loneliness Scale administered to child and parent	Parents of children with short stature rated their children as having more social, thought and attention problems and exhibiting greater delinquent behaviour than parents of children with DM1. No diagnostic differences in child or parent-rated internalising symptoms were found
Norrby *et al.* (2006)[44]	199 Swedish children aged 9–16 years with diagnoses of asthma (53), diabetes (48), short stature (51) and juvenile chronic arthritis (47)	Comparative study	Child Health questionnaire child form and Parent form (others used for validation of this questionnaire)	Short stature group had the highest QoL of the four groups

GH, growth hormone; GnRHa, gonadotropin-releasing hormone analogue; DM1, diabetes mellitus type 1; RCT, randomised controlled trial.

General papers

Study details	Population	Study design	QoL instruments	Major findings
Zlotkin and Varma (2006)[45]	Children with short stature	Literature review	NA	There are effects of GH therapy on GHD children beyond the increase in final adult height. These factors should be taken into consideration when GH is prescribed for them
Voss (2006)[46]	Children with ISS	Literature review	NA	There is no compelling evidence to show an association between short stature and cognitive and psychosocial maladaptation or dysfunction
Christensen *et al.* (2007)[47]	14,416 adults	2003 Health Survey for England (HSE03)	EQ-5D	Short adult stature is significantly correlated with HRQoL. The largest deficit in HRQoL was seen in those with the greatest deficit in height relative to the population norm
Sandberg and Colsman (2006)[48]	Children with short stature	Literature review	NA	Clinicians should consider incorporating a psychosocial component in the diagnostic evaluation of short stature (follow-up to previous study[40])

EQ-5D, European Quality of Life-5 Dimensions (also known as EuroQol quality of life questionnaire); GH, growth hormone; HRQoL, health-related quality of life; NA, not applicable.

Appendix 4

Included study data extraction

Study details

Study reference

Grote *et al.* (2008)[18]

Related publications

Grote *et al.* (2008)[24]

Grote (2007)[14]

Objective

To establish evidence-based guidelines for growth monitoring on a population basis

Country

The Netherlands

Growth charts

Dutch, Turkish and Moroccan reference data[49–52]

Note

In this study results are analysed in two age groups (0–3 years and 3–10 years). Results from the 0- to 3-year age group are not extracted as they are outside the target population age range of this review

Participant characteristics

Patient group 1, TS

777 girls with TS from three sources: The National Registry of Growth Hormone Treatment in Children of the Dutch Growth Foundation all receiving GH treatment (316 girls selected born between 1968 and 1996), 87 TS girls born between 1973 and 1988 from Sophia Children's hospital and 374 girls described by Rongen *et al.*[60] (see van Buuren *et al.*[57])

Patient group 2, SSP

27 new patients referred for short stature to the outpatient clinics of the general paediatric departments of two hospitals (Erasmus MC – Sophia Children's Hospital, Rotterdam and Spaarne Hospital, Haarlem) between January 1998 and December 2002[a] with a pathological reason for short stature[b]

Patient group 3, CF

216 patients with CF collected from three major CF clinics Erasmus MC – Sophia Children's Hospital, Rotterdam ($n = 166$), University Hospital Maastrict ($n = 30$) and Juliana Children's Hospital in The Hague ($n = 20$)

Patient group 4, CD

120 patients with CD from a study by Damen *et al.*[58] ($n = 60$) and a study by Boermsma *et al.*[59] ($n = 60$)

Reference sample 1, SMOCC

2151 participants obtained from a nationally representative cohort (SMOCC) providing length and weight data up to the age of 2.5 years

Reference sample 2, Limburg

970 participants (a cohort born in the years 1989 and 1990 in Landgraaf and Kerkrade)

Reference sample 3, ZHN[c]

400 participants (sample of children born between 1985 and 1988 attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn)

Methods and analysis

Number of measurements per child

Only measurements before or at age of diagnosis or start of diet (CD cohort) were taken into account

Age 3–10 years

Number of children measured once or more or twice or more, and mean number of measurements per child in brackets in each group[18]

Sample	≥ 1	≥ 2
TS	524 (5)	472 (6)
SSP	17 (3)	13 (3)
CF	25 (2)	14 (3)
CD	22 (4)	16 (5)
SMOCC	NA	NA
Limburg	958 (3)	893 (4)
ZHN	361 (4)	339 (4)

Target height calculation

Parental height missing data (4–58%) was imputed (full details of the model parameters are in the paper)

Target height was calculated by Tanner's method with an additional correction for secular trend

Target height (boys) = [(FH + MH + 13)/2] + 4.5

Target height (girls) = [(FH + MH – 13)/2] + 4.5

Referral threshold(s)

Based on evidence from the literature, three auxological criteria were created:

1. *'Short for target height'* Distance between HSDS and target height of > 2 SDs with cut-off points for HSDS of –2, –1.5 or –1 SDS
2. *'Very short'* HSDS < -2.5 (approximately 0.6th centile)
3. *'Height deflection'* Deflection of 1 SDS over an undetermined time interval combined with HSDS <-2, –1.5 or –1

All rules were analysed separately and in combination with the others. If a child had only one measurement, the child could not comply with criteria on deflection or repetition and was assumed to be non-referred

Results and conclusions

Referral criteria with the best test characteristics

1. *Short for target height* HSDS – target height SDS < -2 and HSDS < -2
2. *Very short* Length SDS < -2.5 and HSDS < -2.5
3. *Height deflection* Change in HSDS < -1 and HSDS < -2

Sensitivity of auxological rules for the four different patient groups (true positives)[18]

Rule	TS (%)	SSP ()	CF (%)	CD (%)
Short for target height	76.9	58.8	8.0	27.3
Very short	74.0	58.8	4.0	18.2
Height deflection	13.4	17.6	0.0	18.2
Combination	85.7	76.5	8.0	27.3

Estimated percentages of referrals in the three reference groups (false positives)[18]

Rule	Limburg	ZHN
Short for target height	0.7	1.1
Very short	0.9	0.8
Height deflection	0.1	0.8
Combination	1.5	1.9

An algorithm was presented to show implementation of the rules

Authors' conclusions

The proposed guidelines show high sensitivity at an acceptably low false-positive rate in 3- to 10-year-old children. Distance to target height is the most important criterion. The algorithm proposed appears to be suitable for industrialised countries but needs further testing in other populations and does not replace clinical judgement

CD, coeliac disease; CF, cystic fibrosis; FH, father's height; MH, mother's height; NA, not applicable; SDS, standard deviation score; SMOCC, Social Medical Survey of children Attending Child Health Clinics; SSP, short stature due to pathology; TS, Turner's syndrome.

[a] Grote *et al.*[24] specifically examined accuracy of referral for short stature according to the Dutch consensus guidelines[61] and also considers diagnostic work-up. Seven hundred and forty-two children were identified, of whom 200 were excluded from analysis as their cause of growth retardation was already known, their records were missing or they had a reason for referral other than short stature. The referrals of 542 children were examined (59 < 3 years old); 76.4% were correctly referred, 5.6% were not classifiable and 18% were not correctly referred. Seven children were referred for other reasons in addition to short stature: anaemia (2), coughing (2), delayed closure of fontanel (1), health check after adoption (1), poor weight gain (1) and poor food intake (1). Five had dysmorphic features at the time of referral, six had already been seen for referral, of whom two were referred for second opinion on short stature. None of the children had been pre-investigated for short stature. One child with a pathological cause of short stature was incorrectly referred and had a height SDS of –1.7 SDS at referral and had been referred owing to short stature and anaemia. The rule combining 'short for target height and for the population' (HSDScorr) was most complied with, followed by absolute height and height deflection.

[b] The 27 patients identified represented a finding of a pathological cause for short stature in 5% of the patients referred. Conditions identified were as follows: GHD (7), CD (7), TS (3), other [10 of which Noonan's (1), Léri-Weill (1), anaemia (3), skeletal diseases (4), emotional deprivation (1)].

[c] ZHN reference sample: children born 1985 and 1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn, the Netherlands.

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We look forward to hearing from you.

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