Chapter 2. Methodology

This evidence report is based on a systematic review of the literature. A series of teleconferences was held with the science partner representatives from the Social Security Administration (SSA), the American Academy of Pediatrics (AAP), the internal technical experts from the Evidence-based Practice Center (EPC), and a representative of the Disability Law Center to formulate the key questions addressed by this report. A comprehensive search of the medical literature was conducted to identify the evidence available to address the questions.

Detailed information about each study used in the systematic review was abstracted. The results are presented in evidence tables. Information directly pertinent to answer each aspect of the key questions addressed is presented in summary tables within the Results section (Chapter 3). A list of abbreviations is presented in Appendix 2.

Key Questions Addressed by the Evidence Report

The EPC staff, pediatric experts, and representatives of SSA arrived at consensus on three key questions following discussions and between-meeting solicitation of comments from the group members. The key questions were refined to ensure that the answers would be useful to SSA, would be of interest to the technical experts, would be appropriate for literature review, and would likely be available in the literature. The final key questions are:

1. Is short stature (height < 5th percentile) as a result of a medically determinable impairment associated with severe functional limitations, according to, but not limited to, SSA's definition of disability?

2. What is the evidence that short stature (height < 5th percentile) due to a skeletal dysplasia is disabling according to, but not limited to, SSA's definition of disability? If so, are children disabled by virtue of their size or other features of their conditions?

3. What is the evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of an underlying disease? Is such a process likely to be disabling?

For all key questions, the populations of interest are boys and girls under age 18 years who have short stature. Children of all ethnicities, nationalities, racial, and socioeconomic groups were included.

For key questions 1 and 2, short stature was defined as height less than the 5th percentile (or less than –1.67 standard deviations (SD) below the mean) for age. However, given the variability of definitions of short stature in the literature, we accepted definitions of short stature up to the 25th percentile.

For key questions 1 and 2, disability was defined based on SSA definitions published in "Disability Evaluation Under Social Security" (Disability Evaluation Under Social Security, 1999), as discussed in the Introduction. The list of impairments provided by SSA was reviewed to determine the possible disabilities of interest. However, SSA's definition of disability is based on a need to determine an administrative definition to comply with Federal law. Clinicians and researchers, though, use various definitions of ability and disability to care for patients. Thus,

very few studies have examined the association between short stature and (SSA-defined) disability, per se. This report therefore focuses on assessments of functional limitations, as defined by study authors. Objective and teacher- or clinician-scored assessments were included. Parent or child determinations of functional ability were excluded.

Question 1. Definition of short stature as a result of medically determinable impairment.

The primary categories (or causes) of short stature considered included isolated or idiopathic short stature, constitutional growth delay, growth hormone deficiency, multiple hormone deficiency, Russell-Silver syndrome, and Turner syndrome. No predetermined definitions for each of the causes of short stature were used; instead, definitions used by study authors were accepted. Studies that focused on children with Down syndrome were not reviewed as SSA already defines such children as disabled from birth.

The associations between short stature due to medically determinable impairment and functional ability included academic achievement, intelligence, academic advancement, visual motor skills, psychomotor development, and teacher-graded behavioral problems.

Question 2. Definition of short stature as a result of skeletal dysplasia.

The primary skeletal diseases resulting in short stature considered included osteogenesis imperfecta, achondroplasia, diastrophic dysplasia, and other skeletal dysplasias. No predetermined definitions for each skeletal dysplasia were used; instead, definitions used by study authors were accepted.

The associations between short stature due to skeletal dysplasia and functional ability included academic achievement, intelligence, psychomotor development (visual-motor skills, motor development, and motor development patterns), neuromuscular function, ambulation and mobility, limb range of motion, spinal curvature, hearing loss, respiratory dysfunction (sleep apnea and pulmonary function), and psychological outcomes.

Question 3. Chronic disease and linear growth velocity

Attention was paid to addressing the association between disease severity and decreased linear growth velocity. Thus, only studies that categorized children with chronic diseases by disease severity and that also directly compared height to disease severity were included. Studies that investigated only the association between disease presence and height were not reviewed. No predetermined definitions of disease severity were used; instead definitions used by study authors were accepted. To capture the full range of data available on growth in children with chronic disease, we included both studies that evaluated height velocity as well as height alone.

The review focused on chronic diseases that either are associated with, or may result in, disability, as defined by SSA. We did not review studies that evaluated the association between treatment for chronic disease and height, unless sufficient data were available to answer the primary question. Thus, studies of steroid use for gastrointestinal and most other diseases were generally excluded. For studies of children with asthma, we excluded those that explicitly examined the effect on growth of steroid use. However, we included studies that used medication

requirement (including steroids) as a marker of severity, since this was a common method of analysis. Cancer and cardiac diseases requiring surgery were not considered because separating the effect on height of treatment from the underlying disease is not possible.

Search Strategies

Systematic searches were performed for full journal articles of original data. The primary search for the literature review consisted of a MEDLINE® search from 1966 through February 2001, with updates through October 2001. Supplemental searches were also performed in ERIC, PsycInfo, Healthstar and Embase. Additional studies were identified from reference lists of review and primary articles, and from domain experts.

Development of the search strategies was an iterative process that included input from domain experts. Keywords from known relevant studies were used to refine and focus the final search strategies used.

The details of the literature searches performed in MEDLINE® are presented in Appendix 1. The primary search strategy for key questions 1 and 2 retrieved articles with the keywords or text words developmental bone diseases, growth disorders, body height, or short stature, along with variations of disability, limitation, handicap, or impairment (Appendix Table 1, lines 1-11). The primary search strategy for key question 3 retrieved articles with the keywords or text words developmental bone diseases, short stature, skeletal dysplasia, growth velocity, retardation, delay and restriction, and growth disorders (Appendix Table 1. lines 12-50). Studies that focused on growth disorders that do not cause short stature, that affect neonatal development or that are rapidly fatal were not included. These topics included fetal development, pregnancy, failure to thrive, facial bones, thanatropic dysplasia, and various forms of gigantism or other bone diseases that do not cause short stature. To capture additional studies of common chronic diseases that affect growth, supplemental searches were performed for heart diseases, arthritis, and asthma in children, as summarized in Appendix Table 2.

Only articles that included human children under age 18 years and that were published in English were included. Case reports, review articles, commentaries, letters, and abstracts were excluded.

Study Selection

Pediatrician domain experts and EPC staff manually screened the titles and abstracts of the search results to identify potentially useful articles to address each of the key questions. A set of minimum inclusion criteria were used in this initial screening: primary articles reporting original data on at least 10 children that provided primary or secondary evaluation of growth failure and had a primary or secondary outcome of a potential functional limitation. Studies could be cross-sectional or longitudinal, prospective or retrospective, comparative or not. Full articles of abstracts found potentially useful were retrieved for more careful evaluation.

Data Abstraction

Data abstraction forms were developed in an iterative process by EPC staff with the pediatrician experts. The forms were designed to capture information of various aspects of the

primary articles. Individual forms were developed for each key question. Forms included study setting, demographics (including such information as age, height, sex, race, and socioeconomic status), eligibility criteria, number of subjects, study design, funding source, relevant measurements and outcomes evaluated, statistical methodology, results, potential biases, and study quality.

Pediatrician domain experts performed all the data abstraction. Abstractors were trained by the EPC staff. As part of the training, each Team Member abstracted three studies in duplicate with the Team Leader and meetings were held to discuss discrepancies. After training, all remaining studies were abstracted by one pediatrician. All abstracted data were reviewed by two members of the EPC staff when data were transferred to evidence and summary tables.

Articles that reported data on the same or overlapping sets of children were grouped together in the evidence and summary tables, or noted to contain duplicate data, to avoid duplication of results. One study author (RHH Engelbert) was contacted by email to clarify the overlap of a number of studies.

Summary Tables

Summary tables were created to describe studies reviewed for each topic. The tables describe the strength of the evidence according to four dimensions: study size, study sample applicability, results, and methodological quality. For questions 1 and 2, studies are grouped first by study sample disease type. Within each section, studies are ordered first by methodological quality (best to worst), then by study size (largest to smallest). For question 3, studies are grouped first by methodological quality, then by applicability of study sample to children with the given chronic disease, then by study size.

Study Quality

Methodological quality (also known as internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of design types were evaluated, a three-level classification of study quality, used in previous reports, was modified. All studies were graded on the following scale:

- ● Good quality. Least bias. Results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; prospective design, clear description of the population and setting; proper measurement techniques; appropriate statistical and analytic methods; no reporting errors; no obvious bias.
- ◐ Fair quality. Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria of category A. It has some deficiencies but none likely to cause major bias.
- ○ Poor quality. Significant bias likely that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

In general, studies that reported data relevant to multiple topics of interest were given the same quality rating for each topic; however, some studies were rated differently for different topics, depending on the quality of the data for each topic. For example, a study may have

performed a complete and valid statistical analysis of intelligence but may not have performed a statistical analysis of academic achievement. The study may therefore receive a lower quality rating for its analysis of academic achievement than for intelligence.

Applicability

Applicability (also known as generalizability or external validity) addressed the issue of whether the study sample is sufficiently broad so that the results of the study can be generalized to the population of interest at large. The study population is typically defined by the eligibility criteria. Restrictive eligibility criteria (e.g., single sex, limited range of disease severity) or small sample size may reduce the applicability of a given study.

For questions 1 and 2 the applicability of each study is described by the type of disease causing short stature. The few studies that had particularly restrictive eligibility are noted in each table's footnotes. For certain disability topics (e.g., hearing loss and ambulation) where separate results are reported for different sub-populations of children, columns were added to the tables to describe the populations. For each study, the mean, median, or threshold height (generally expressed in age and sex standard deviations from the mean, or standard deviation score (SDS) were recorded.

For question 3, where all studies within a given table evaluate children with the same (or similar) diseases, a designation for applicability was assigned to each article, according to the following three-level scale:

- 🧍🧍🧍 Study is representative of all children with the given chronic disease. Study sample includes both sexes, the full range of disease severity, a sufficient number of subjects. There are no substantial eligibility restrictions.
- 🧍🧍 Sample is representative of a relevant sub-group of children with the given chronic disease. There were eligibility restrictions that may limit the applicability, such as single sex, disease severity, or co-morbidities.
- 🧍 Sample is representative of a narrow subgroup of children with the given chronic disease. There were substantial eligibility restrictions that limit applicability.

To complement the applicability scale, each table has a column describing the diseases of the study population.

Study Size

The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to have wide applicability, depending on eligibility criteria. However, large study size does not guarantee applicability.

Results

The type of results available is determined by each study's design, the purpose of the study, and the question(s) being asked. Therefore, the results presented vary across summary tables. For

questions 1 and 2 most summary tables present either the mean test results of a given test or the prevalence of a given condition. When necessary, the test or condition evaluated in each study is included. When available, the results for a control group are also included. Summary tables for question 3 include separate columns for association of disease severity with height and with height velocity. For appropriate topics in questions 1 and for all topics in question 3, associations are described with the following arrows:

- ⬆ Statistically significant positive association between severity of chronic disease and height or height velocity. More severe chronic disease associated with growth retardation. If statistical analysis was not reported, but a large clinical difference in growth based on disease severity was, statistical significance was assumed to be likely. This symbol was used only in studies evaluated for question 3.

- ⬇ Statistically significant negative association between ability and disease causing short stature. This symbol was used only in studies evaluated for visual-motor skills in question 1.

- ⇧ Trend toward positive association between severity of chronic disease and height or height velocity. Some indication that children with more severe chronic disease may be associated with growth retardation. However, association either is not statistically significant or statistical analysis was not reported. This symbol was used only in studies evaluated for question 3.

- ⇔ No association between severity of chronic disease and height or height velocity. This symbol was used only in studies evaluated for question 3.

Limitations

While literature searches were intended to be comprehensive, they may not have been exhaustive. As noted above, search strategies were limited to focus on studies likely to be relevant. Searches were limited to English language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts and studies found in reference lists were included in the review.