Chapter 1. Introduction

The Social Security Administration (SSA) of the Department of Health and Human Services requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, provide the scientific basis for SSA to determine disability claims for children with short stature, with skeletal dysplasias, and with chronic disease in which decreasing growth velocity may be a component. This evidence report is prepared to assist SSA in updating its *Listing of Impairments* and revising its disability policy, as may be appropriate.

This report summarizes the scientific evidence about whether short stature in a child due to a medically determinable cause may be associated with disability, whether skeletal dysplasias in a child may be considered a disability, and whether decreasing growth velocity in a child with a chronic disease may serve as an indicator of severity of the disease. The population of interest includes children age 17 years or younger, both male and female, of all racial, ethnic and socioeconomic groupings.

Scope of the Problem

A range of definitions of short stature among children exists. In general, short stature has been defined as a height less than the 3rd percentile (Plotnick, 1990). This corresponds to a value of 1.9 standard deviations below the mean height (which is commonly rounded up to 2.0). However, many studies use a variety of definitions including height less than the 5th and 10th percentiles (corresponding to 1.65 and 1.3 standard deviations below the mean, respectively). The total number of children who have short stature due to either a medically determinable cause or a skeletal dysplasia as opposed to familial short stature has not been reported. However, by definition, approximately 2.2 million American children have short stature (US Census, 2001).

Causes of short stature in children

There are multiple causes of short stature. The most common causes are familial short stature (FSS) and constitutional growth delay (CGD). FSS occurs when a child has height below the third percentile due to a genetic tendency to short stature in his or her family (Mahoney, 1987). Children with FSS typically reach adult height consistent with their family background. CGD occurs when a child is shorter than would be expected by her or his genetic background and no determinable medical cause of the short stature can be found. Often children with CGD experience a delayed onset of pubertal development and usually obtain normal or near normal adult height (Plotnick, 1990). Neither FSS nor CGD is considered to be due to medically determinable causes in most cases (Attie, 2000). Since it can be difficult to differentiate between these two conditions, the term isolated short stature (ISS), is often used interchangeably for both FSS and CGD.

Medically determinable causes of short stature include abnormalities in the growth hormone axis such as decreased growth hormone production and diminished response to growth hormone. Other endocrine abnormalities such as hypothyroidism and Cushing disease may lead to short stature (Bacon, Spencer, Hopwood, et al., 1990). A variety of genetic disorders including chromosomal disorders,

metabolic disorders and single gene disorders can also result in short stature (Bacon, Spencer, Hopwood, et al., 1990).

Skeletal dysplasias are genetic disorders that result in abnormal formation of part or all of the skeleton. Not all skeletal dysplasia will result in short stature. The skeletal dysplasias most likely to lead to short stature are those that involve formation and growth of the long bones and/or the spine. The most common skeletal dysplasias that typically result in short stature include achondroplasia, hypochondroplasia, and osteogenesis imperfecta (Taybi and Lachman, 1996). There are more than 200 described skeletal dysplasias, many of which may lead to short stature, but each of these conditions individually is quite rare (Online Mendelian Inheritance in Man, 2002).

The presence of a chronic disease in a child has long been known to be a risk factor for decreased growth to a varying degree (Plotnick, 1990). However, the underlying cause of the decreased growth has not been determined in all chronic diseases. Diseases that affect a child's nutritional status (inflammatory bowel disease, celiac disease) may lead to a decrease in growth velocity secondary to caloric and general nutritional insufficiency (Kelts, Grand, Shen, et al., 1979; Oliva and Lake, 1996). Other diseases such as asthma, which do not appear to directly affect nutritional status, have also been reported to lead to decreased growth velocity (Abrams, 2001).

Definition of Disability

The definition of disability in children used for the purposes of this report came from the SSA and was based on a definition passed by Congress in 1996. Under Title XVI, a child under age 18 years will be considered disabled if he or she has a medically determinable physical or mental impairment or combination of impairments that causes marked and severe functional limitations, and that can be expected to cause death or that has lasted or can be expected to last for a continuous period of not less than 12 months (Disability evaluation under Social Security, 1999).

Specific areas of functioning include: 1) acquiring and using information, 2) attending and completing tasks, 3) interacting and relating with others, 4) moving about and manipulating objects, 5) caring for yourself, 6) health and physical well-being. Disability is based on the degree to which the above functions are interfered with. Disability is established if there are marked limitations in at least two areas or there is an extreme limitation in one area of functioning. Where standardized tests of function exist, the regulations define a "marked" degree of functional limitation as more than two but less than three standard deviations below the mean and an "extreme" limitation as three or more standard deviations below the mean. (Disability evaluation under Social Security, 1999).

However, SSA's definition of disability is an administrative one, which is not commonly used by clinicians or researchers. In general, disability is defined differently by different researchers for different diseases. Furthermore, studies of children with short stature frequently focus on differences of ability, rather than on disability per se. Thus, any analysis of the literature to evaluate disability for SSA will be limited by the fact that few studies have primary analyses of disability that correspond to SSA's definition.

Evaluation of children with short stature due to a medically determinable cause

The evaluation of the association of short stature due to medically determinable causes with disability is complicated by the fact that it is often hard to distinguish whether the disability is due directly to short stature or to the underlying medical problem. As an example, Turner syndrome, which is caused by the absence of part or all of one X chromosome in a female, results in short stature in the majority of girls affected. These girls often have difficulties in visual-spatial relationships, but these difficulties are believed to be secondary to their genetic defect and not related to their short stature (Ross, Stefanatos, Roeltgen, et al., 1995). Similarly in Down syndrome, which is caused by chromosome 21 trisomy, children generally have short stature; however the significant mental retardation in these children is not thought to be secondary to their stature (Tolmie, 1997).

Evaluation of children with short stature may be done by a variety of medical specialties including endocrinology, gastroenterology, and genetics and depending on the specialty, different evaluations may be done. In general, research done on children with short stature has tended to focus on intelligence and psychological concerns, which fall into the first three areas of functioning discussed above (acquiring and using information, attending and completing tasks, and interacting and relating with others).

Evaluation of disability among children with short stature due to medically determinable causes is limited in that few studies examine disability per se, but instead compare different levels of ability (e.g. cognitive ability). In addition, direct associations between ability and height are often not reported.

Evaluation of children with short stature secondary to a skeletal dysplasia

Skeletal dysplasias are a relatively heterogeneous group of diseases that cause abnormalities in development of one or more parts of the skeleton. For the most part skeletal dysplasias tend to affect only bony development, specifically metaphyseal or epiphyseal development. However, certain skeletal dysplasias may also have other associated anomalies, such as severe myopia and cleft palate in diastrophic dysplasia, which may impact on a disability evaluation. Most, but not all, skeletal dysplasias will lead to stature below the third percentile. The most common skeletal dysplasias include achondroplasia, hypochondroplasia, osteogenesis imperfecta, and diastrophic dysplasia (Taybi and Lachman, 1996). The research on disability and skeletal dysplasia has tended to focus on structural abnormalities of the bones and short stature and has looked at problems such as difficulties in acquiring and using information, moving about and manipulating objects, caring for self, and health and physical well-being.

Evaluation of disability among children with skeletal dysplasia, as with children with short stature due to medically determinable causes, is limited in that few studies examine disability per se, but instead compare different levels of ability (e.g. cognitive ability). The main exception to this are studies of ambulation and mobility. In addition, direct associations between ability and height and between severity of short stature within a particular skeletal dysplasia are often not reported.

Evaluation of children with decreased growth velocity secondary to chronic disease

Some chronic diseases (e.g., inflammatory bowel disease, asthma, congenital heart disease) have been associated with poor growth in the affected child. The poor growth may lead to height less than the third percentile in some, or the height may stay within the normal range but with a decreased growth velocity (Mahoney, 1987). Of interest is whether decreased growth velocity can be used as a marker to indicate worsening severity of disease. This question does not directly relate to disability.

Certain chronic diseases, such as diabetes or chronic kidney disease, have clearly defined methods of measuring severity of disease (i.e., $HgbA_{1c}$ and glomerular filtration rate, respectively). However, most chronic diseases have less well-defined measures of severity (e.g., asthma, congenital heart disease, sickle cell anemia). Therefore, different studies use different, non-standard definitions of severity, making comparisons across studies difficult. For some chronic diseases, severity of disease may just be a proxy for different categories or sub-types of the disease (e.g., congenital heart disease, juvenile rheumatoid arthritis). Growth may be affected differently by the different categories of the chronic disease, which may not be associated with the "severity" of the disease.

To properly evaluate the association between chronic disease severity and growth, studies must be longitudinal and measure height velocity. However, much of the research on severity of chronic disease has been cross-sectional. Therefore, height, rather than height velocity, has frequently been analyzed.