

OBTAINING INSURANCE COVERAGE FOR HUMAN GROWTH HORMONE TREATMENT FOR IDIOPATHIC SHORT STATURE

In 2003, the Food and Drug Administration (FDA) approved the use of growth hormone (GH) for the long-term treatment of idiopathic short stature (ISS), which the FDA defined as children whose height is less than 2.25 standard deviations (SD) below the mean for age and associated with growth rates unlikely to permit attainment of adult height in the normal range.

To determine whether a child who is short for their age suffers from ISS, the pediatrician or endocrinologist will typically start with a bone age study, which is done by comparing an x-ray of the child's left hand with a book of standards with examples of x-rays of typical bone development at various chronological ages. The significance of the bone age study is that there is a correlation between the degree of skeletal maturation (bone age) and the time period before epiphyseal closure, when the fusion of the growth plates terminates skeletal growth. The greater the difference between a child's bone age and his or her chronological age, the longer the time before epiphyseal fusion will occur and growth will cease. Therefore, the child will have more time to grow and his or her present short stature does not require medical intervention. For example, if the child has a chronological age of seven years old, but the bone age study is read as corresponding to the standard for five years old, this may alleviate any concern about the child's short stature, which will be attributed to constitutional growth delay.

If the bone age study does not show a significant difference between the child's chronological age and his or her bone age, the child's doctor will typically order a GH stimulation test, which measures the child's levels of GH. If those levels are within the normal range, the doctor may diagnose the child as having ISS and commence GH treatment.

GH treatment is expensive and some insurance companies resist paying for it. We have encountered the following problems in obtaining insurance coverage for GH treatment for ISS.

The argument that "medically necessary" GH treatment is limited to classic GH deficiency

Most insurance policies define "medically necessary" treatment as treatment that is "within standards of good medical . . . practice within the organized medical . . . community" (or similar language). Many insurance companies take the position that the only medically necessary GH treatment is for those children who have a subnormal

response to one of the standard GH stimulation tests. However, we are confident that no qualified pediatric endocrinologist would say that limiting GH treatment to children with subnormal responses to the GH stimulation tests is “within standards for good medical practice.”

First, as noted in a leading treatise on pediatric endocrinology, GH stimulation tests are “fraught with numerous technical limitations” and some experts “advocate eliminating provocative GH testing altogether, arguing they do not reliably contribute to the diagnostic algorithm.”¹ The limitations of GH stimulation testing include:

- GH stimulation testing is nonphysiologic because the tests rely upon various drugs to induce GH production and, therefore, do not replicate the normal secretory dynamics of pituitary GH.
- The definition of what constitutes a subnormal response to GH stimulation testing is arbitrary and has changed over time.
- GH assays are of limited accuracy.
- The reproducibility of GH stimulation testing has never been demonstrated.
- Demonstration of “normal” GH stimulation testing does not exclude the possibility of various forms of GH insensitivity, in particular IGF-1 deficiency.

In its 2003 “Update of Guidelines for the Use of Growth Hormone in Children,” the Pediatric Endocrine Society noted that:

[C]onsiderable variability exists in the diagnosis of GH deficiency, which remains a clinical challenge. This is related to the continuum between severe GHD and normality, marked variability in GH assays, arbitrary “cut offs” conventionally used to define GH deficiency on the basis of GH stimulation tests, and the lack of reproducibility of GH stimulation tests.

The Update concluded:

No gold standard exists for the diagnosis of GHD. Although children severely affected by GHD fail GH stimulation tests, there is no doubt that some children with GHD achieve stimulated GH concentrations above the arbitrary cutoffs that have been applied.

¹ Fima Lifshitz (Ed.), *Pediatric Endocrinology*, Vol. 2 (5th Ed. 2007) at 38.

The updated Guidelines then recommended a trial of GH therapy for children with otherwise unexplained short stature who pass GH stimulation tests, but meet other criteria.

Furthermore, in 2007, the Pediatric Endocrine Society conducted a survey of its members “to summarize prevailing attitudes about GH diagnosis and treatment among pediatric endocrinologists.” That survey revealed that over 90 percent of those responding did not believe that GH stimulation tests were the best way to diagnose GH deficiency. Despite that belief, an even greater number of those responding said they “always” (34 %) or “sometimes” (61 %) ordered GH stimulation tests. Why?

Although the prevailing attitude regarding GH stimulation testing is clearly one of fewer in favour, 61 % of respondents note they still perform the tests ‘sometimes’. It is likely that the rationale for performing those tests is to obtain insurance authorization. . . . [I]t is time endocrinologists take a careful look at the motivating factors behind doing stimulation tests, and determine whether the [Pediatric Endocrine Society] constituency as a whole believe they are necessary. If it is agreed that stimulation testing is not the best choice, than endocrinologists must convey this message to insurers.

The survey then discussed the criteria other than GH stimulation tests that the responding doctors actually used in diagnosing GH deficiency and in initiating GH treatment. The survey showed that the most important criteria were the child’s growth velocity and low insulin growth factor – 1 (IGF-1) levels. GH promotes linear growth by regulating the production of IGF-1, synthesized by the liver and other target tissues, which then acts at the epiphyses (growth plates) of long bones to mediate GH’s effect on linear height velocity. A deficiency of either GH or IGF-1 can result in short stature.

Finally, 82 percent of the doctors said that they used the FDA indication for GH treatment of ISS (which necessarily involves GH treatment for children with normal response to GH stimulation testing).

As the prescribing practices of these doctors reflect, GH deficiency as established by a subnormal response to GH stimulation testing is only one of the conditions on the GH-IGF-1 axis that causes short stature. It also shows that limiting GH treatment to children with subnormal responses to the GH stimulation tests is not “within standards for good medical practice” for practicing pediatric endocrinologists.

The argument that GH treatment for ISS is not medically necessary

Some insurance companies take the position that GH treatment for ISS is not medically necessary. However, there is no real question that prescribing GH for a child who meets the FDA indication for GH treatment for ISS is within the standards of “good medical practice” for the pediatric endocrinologist community.

First, as noted above, in the 2007 survey of the members of the Pediatric Endocrine Society, 82 percent of the responding pediatric endocrinologists said that they used the FDA indication in connection with their treatment of ISS.

Second, more recently, the American Academy of Pediatrics conducted a nationwide survey of the factors relied upon by pediatric endocrinologists in deciding whether to initiate and continue GH treatment for ISS. Though the survey did not directly ask whether the responding doctors followed the FDA indication, it showed that for a very short child with a very low predicted adult height, very slow growth velocity (all -3 SD) and family wishing treatment, almost all doctors (93%) would initiate GH treatment. Conversely, most doctors (74%) would not initiate GH for the child whose growth parameters were not as impaired, *i.e.*, current height -2 SD (taller than the FDA indication of -2.25 SD) and growth velocity -1 SD.

Third, how practicing pediatric endocrinologists use the FDA indication for ISS can also be confirmed by reports of the independent medical reviews ordered by the California Department of Managed Health Care (DMHC). If you are insured by a health care service plan regulated by the DMHC and medical treatment has been denied because it was not medically necessary, you can request an independent medical review (IMR) of that decision. An independent doctor retained by a vendor under contract with the DMHC will review the plan’s decision and determine whether the treatment is medically necessary. That decision is then binding on the plan.

The DMHC maintains an on-line database of IMR decisions, which is searchable by type of medical treatment at issue. A search of that database for IMR decisions involving GH treatment for ISS shows that *in every case* where the child met the FDA indication, the independent pediatric endocrinologist determined that the treatment was medically necessary.

All of this is conclusive evidence that GH treatment for a child with ISS is within the standards of “good medical practice” for the pediatric endocrinologist community and, therefore, is medically necessary treatment.

The argument that the child's predicted adult height is above -2.25 SD

Finally, some insurance companies (or their medical reviewers) take the erroneous position that the FDA indication for treatment for ISS requires that the child's "predicted adult height" be less than 5 feet three inches for boys and 4 feet 11 inches for girls. This position is based upon an incorrect interpretation of the FDA's approval for GH use for treating ISS.

The bone age study discussed above can also be used to derive a prediction of a child's final adult height. When the FDA approved the use of GH treatment for ISS in 2003, the approval stated:

This supplemental new drug application provides for the use of [growth hormone] for the long-term treatment of idiopathic short stature, also called non-growth hormone-deficient short stature, defined by height SDS 2.25, and *associated with growth rates unlikely to permit attainment of adult height in the normal range*, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.

The FDA approval does not require that the child have a predicted adult height of less than 2.25 SD, only that the child's height at the time of the ISS diagnosis be less than 2.25 SD. Furthermore, though the approval references "growth rates unlikely to permit attainment of adult height in the normal range," the FDA did not define "adult height in the normal range." Normal ranges in medicine are usually defined as ± 2 SD. However, in its press release announcing its approval of the use of GH for ISS, the FDA said that it restricted its use to children who are even shorter, specifically 2.25 SD below the mean, and stated that this corresponded to an adult height of 5 foot 3 inches in adult men and 4 foot 11 inches in adult women. Based on this reference, some insurance companies mistakenly use these figures as a cut off for "adult height in the normal range." However, this is incorrect because the actual approval clearly does not require that a child's predicted adult height be less than 2.25 SD, only that the actual stature of the child at the time of the ISS diagnosis be less than 2.25 SD below the mean.

Furthermore, reliance on predicted adult height as a strict criterion for GH treatment for ISS is inappropriate given the inaccuracies of such predictions:

All of these methods of predicting adult height are based on data from normal children. None of these systems has been demonstrated to be accurate in children with growth abnormalities. For this type of precision, it would be necessary to develop disease-specific (e.g., achondroplasia, Turner syndrome) atlases of skeletal maturation. Recent retrospective analyses indicate that bone-aged-based adult height predictions slightly under-predict female but often over-predict male children's eventual height.²

If you or someone you know is battling insurance issues regarding to human growth hormone treatment for Idiopathic Short Stature, and you are being denied benefits by your health insurer, please call Kantor & Kantor for a free consultation at 888-569-6013.

We understand, and we can help.

www.kantorlaw.net

² Mark A. Sperling (Ed.), *Pediatric Endocrinology* (3rd Ed. 2008) at 261-262.