

CLINICAL PRACTICE

Short Stature in Childhood — Challenges and Choices

David B. Allen, M.D., and Leona Cuttler, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

From the Division of Pediatric Endocrinology and Diabetes, American Family Children's Hospital, University of Wisconsin School of Medicine and Public Health, Madison (D.B.A.); and the Center for Child Health and Policy and the Division of Endocrinology and Diabetes, Rainbow Babies and Children's Hospital, Case Western Reserve School of Medicine, Cleveland (L.C.). Address reprint requests to Dr. Allen at the University of Wisconsin School of Medicine and Public Health, H4/448 CSC, Dept. of Pediatrics, 600 Highland Ave., Madison, WI 53792-4108, or at dballen@pediatrics.wisc.edu.

N Engl J Med 2013;368:1220-8.

DOI: 10.1056/NEJMcp1213178

Copyright © 2013 Massachusetts Medical Society.

A family seeks evaluation and treatment of short stature in their 11.5-year-old son. He previously was in the 3rd percentile for height, but his growth rate has slowed during the past 2 years, and his height is now just below the 1st percentile (Fig. 1). His mother is 5 ft 0 in. (152 cm), and his father is 5 ft 6 in. (167 cm). The child's size at birth was normal. His medical history and a review of systems are unremarkable. His physical examination is normal and shows prepubertal development. The complete blood count, erythrocyte sedimentation rate, thyrotropin, tissue transglutaminase antibody, and insulin-like growth factor I (IGF-I) levels and growth hormone levels after provocative testing are normal. His skeletal maturation (bone age) is approximately 9 years, and his predicted adult height is 5 ft 5 in. (165 cm) plus or minus 1.3 in. (3.3 cm).¹ How should his condition be managed?

THE CLINICAL PROBLEM

Short stature in childhood is a very common reason for referral to pediatric endocrinologists. Although evaluation for growth-inhibiting disorders is often indicated, most children with short stature are essentially healthy. Testing for growth hormone secretion often does not clearly distinguish isolated growth hormone deficiency from idiopathic short stature. Treatment with recombinant human growth hormone can increase the adult height of children with idiopathic short stature by 1.2 to 2.8 in. (3.0 to 7.1 cm), with wide variation in the incremental gain.²⁻⁵ In 2003, the Food and Drug Administration (FDA) approved human growth hormone treatment for children with idiopathic short stature and height below the 1st percentile (-2.25 SD). Accordingly, at least 500,000 children in the United States (i.e., approximately 1% of children 4 to 13 years of age)⁶ were considered to have a condition for which there is available, effective, and expensive treatment (approximately \$10,000 to \$60,000 per patient per year).³ The FDA approval gave rise to controversies, uncertainties, and inconsistencies regarding therapeutic options that often overshadow the problem of short stature itself.

STRATEGIES AND EVIDENCE

EVALUATION

Clinicians who evaluate children with short stature must consider many potential causes (Fig. 2).⁷ Although evaluation is needed to rule out disorders such as true growth hormone deficiency and hypothyroidism, the Turner syndrome, and chronic diseases, the majority of children with short stature ultimately receive a diagnosis of



An audio version
of this article is
available at
NEJM.org

KEY CLINICAL POINTS

SHORT STATURE IN CHILDHOOD

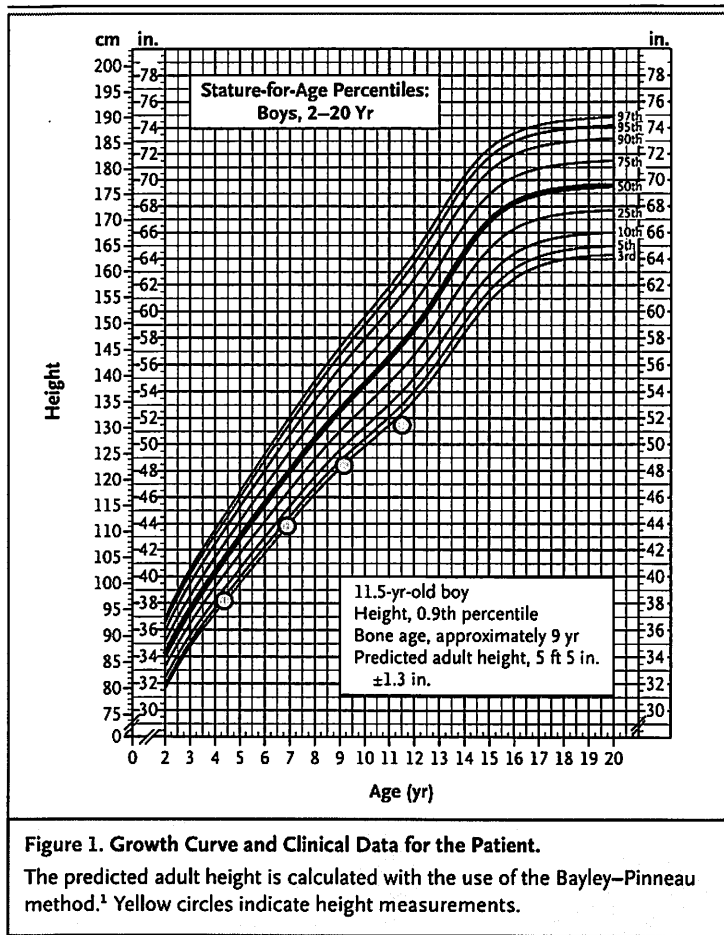
- Thorough evaluation of short stature in childhood is warranted when the child's height deficit is severe (<1st percentile for age), the growth rate is abnormally slow (<10th percentile for bone age), the predicted height differs significantly from midparental height, or the body proportions are abnormal.
- Human growth hormone treatment increases the growth rate, modestly increases adult height, and has been shown to be safe thus far, but it is expensive and the long-term risk:benefit ratio for essentially healthy children remains uncertain.
- Observation and reassurance are reasonable for most children with short stature, given the lack of good evidence linking short stature with psychological harm or showing a long-term psychosocial benefit with growth-enhancing therapy.
- Low-dose oral oxandrolone is an effective and relatively inexpensive option for growth acceleration, but it has not been shown to increase adult height.

idiopathic short stature due to physiological variants such as familial short stature, constitutional delay of growth and puberty (CDGP), or both. In general, a growth rate that is abnormally slow for chronologic and bone age should prompt a thorough examination and possible laboratory evaluation. Growth patterns in a child that differ markedly from the midparental height (estimated by averaging the two parents' sex-specific height percentiles) are also of concern, although these estimates are less accurate when parental-height percentiles are more disparate and are based on the assumption that parental height was not itself diminished by a growth-restricting condition. A family history of late onset of puberty and the age at attainment of adult height may suggest a slowed "tempo" of growth and development (as in CDGP). A history of intrauterine growth restriction should also be assessed, since about 15% of children with this condition continue to have short stature throughout life.⁷

Physical examination should assess for the following: abnormal body proportions (e.g., an increased ratio of the upper to lower body segment, calculated by comparing the height in a sitting position with the height in a standing position, which suggests bone dysplasia or the Turner syndrome); characteristics that suggest genetic conditions (e.g., lymphedema or a low posterior hairline, both of which occur in the Turner syndrome, or a murmur related to pulmonic-valve stenosis, which occurs in the Noonan syndrome); or findings (e.g., goiter) that suggest hypothyroidism. Poor weight gain (i.e., weight gain that

is disproportionate to height gain) may suggest a nutritional disturbance or chronic disease. Although children with true growth hormone deficiency may have classic physical findings such as increased subcutaneous fat, most present primarily with attenuated growth from infancy (congenital growth hormone deficiency) or later (acquired growth hormone deficiency).

Familial short stature, CDGP, or both are the most common causes of short stature. However, when the height for age is less than the 1st percentile, the growth rate is less than the 10th percentile for bone age, the predicted adult height¹ differs significantly from the midparental height, or the body proportions are abnormal, laboratory evaluation is warranted (Fig. 2). Screening laboratory studies target potential hormonal disorders (e.g., with measurement of thyroid hormone levels), renal disorders (with measurement of electrolyte and creatinine levels), inflammatory and immune disorders (with measurement of the erythrocyte sedimentation rate and tests for tissue transglutaminase antibodies), and hematologic disorders (with a complete blood count). Genetic testing for specific syndromes may be indicated by physical findings or simply by a growth pattern and height projection that differ significantly from those in other members of the family. Assessment of the growth hormone-IGF-I axis begins with measurement of the serum IGF-I level, but since levels increase rapidly with the onset of puberty, results must be interpreted relative to bone age rather than to chronologic age. A normal IGF-I level for bone age



rules out severe forms of growth hormone deficiency but not necessarily milder forms.⁸ Measurement of growth hormone levels after provocation with various agents is the classic method for assessing growth hormone deficiency, but the interpretation of the results is complicated by variation in testing procedures and the unclear sensitivity and specificity (and variation among countries) of cutoff levels used for diagnosis. The diagnostic value of low stimulated growth hormone levels (especially 5 to 10 ng per milliliter, with levels of >10 ng per milliliter conventionally thought to indicate adequate growth hormone secretion) is controversial. Moreover, relatively low growth hormone levels during late childhood may return to normal levels after puberty begins⁹ or with sex-steroid priming.¹⁰

A low IGF-I level and low provoked growth hormone level (e.g., <5 ng per milliliter) in a child with attenuated growth strongly suggest growth hormone deficiency. Magnetic resonance imaging of the pituitary gland and hypothalamus can

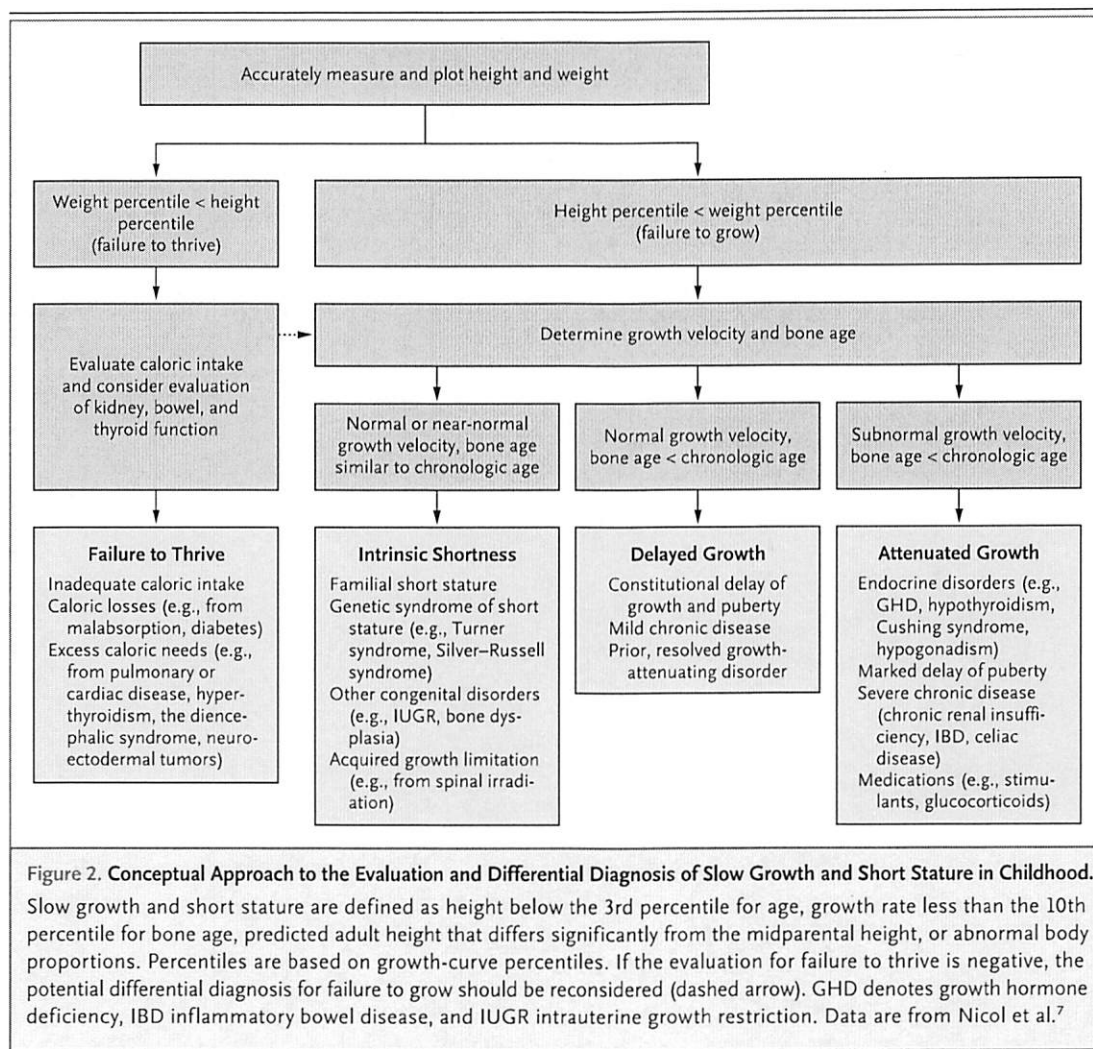
be helpful in such children, since abnormal findings such as diminished pituitary size or ectopic or absent posterior pituitary enhancement further support this diagnosis.¹¹ In the large majority of short children, however, the history and examination are unrevealing, and tests yield equivocal or normal results. These children are generally considered to have short stature that is not related to growth hormone deficiency — idiopathic short stature due to physiological variants (i.e., familial short stature, CDGP, or both). Familial short stature and CDGP are commonly included under the umbrella of idiopathic short stature.¹²

MANAGEMENT

Children with short stature that is not related to growth hormone deficiency may receive markedly different recommendations for management options that vary in complexity and costs and for which the relative benefits and risks are uncertain. Management decisions often depend on the primary care physician's decision about whether to refer the child to a specialist to rule out a pathologic cause of short stature, the pediatric endocrinologist's perspective on the use of growth-promoting medications, insurance coverage,¹³⁻¹⁶ and parents' concern that their child is noticeably shorter than other children or is teased because of his or her size. Their potentially valid concern — “my child is short and needs help to be taller” — ranges in meaning from “will my child be disabled by short stature as an adult?” to “will short stature be a disadvantage in my child's social life and career?”¹⁷ to “would my child feel better at a more normal height?”¹⁸

Once the child is referred to an endocrinologist, decisions regarding treatment depend on the perspectives of the physician and family regarding whether short stature is a disorder or disability warranting medical treatment and, if so, whether the therapeutic goal should be faster growth during childhood or a normal, increased, or maximum attainable adult height. The responsible use of resources and concerns about long-term safety are additional considerations.^{15,19}

The rationale for treating short stature in childhood includes increasing height and alleviating psychosocial disability while maintaining favorable risk:benefit and cost:benefit ratios. Selection among management options may therefore depend on the degree to which each one meets these goals.



Observation and Reassurance with No Treatment

Observation is a reasonable strategy for most children with familial short stature or CDGP.²⁰ Although a child may be teased or feel sad about being short, comparisons of children with short stature that is not related to growth hormone deficiency with taller peers^{21,22} and psychosocial assessment of short adults²³ indicate that psychological stress can be²² but is not predictably²¹ related to stature. Furthermore, increases in the growth rate and height resulting from androgen²⁴ or human growth hormone treatment (including increases in one double-blind, placebo-controlled trial)²⁵ have not predictably improved psychosocial well-being, even when the surrogate measure of final height was increased.^{26,27} Without treatment, although short stature as compared with the stature of peers may temporarily worsen in

late childhood because of delayed puberty (Fig. 3), psychological distress can be addressed with counseling,²⁹ and predicted adult height (and height eventually achieved) will probably approximate the low end of the normal range of target height that is consistent with parental heights.

Height-Promoting Treatment with Human Growth Hormone

FDA approval of human growth hormone for children with idiopathic short stature³⁰ implies that the cause of short stature and the growth hormone secretory status are not critical factors in decisions about whether such children should be treated.³¹ Data from randomized, controlled trials,⁴ observational dose-response studies,⁵ and systematic reviews² indicate that human growth hormone therapy in children with idiopathic short

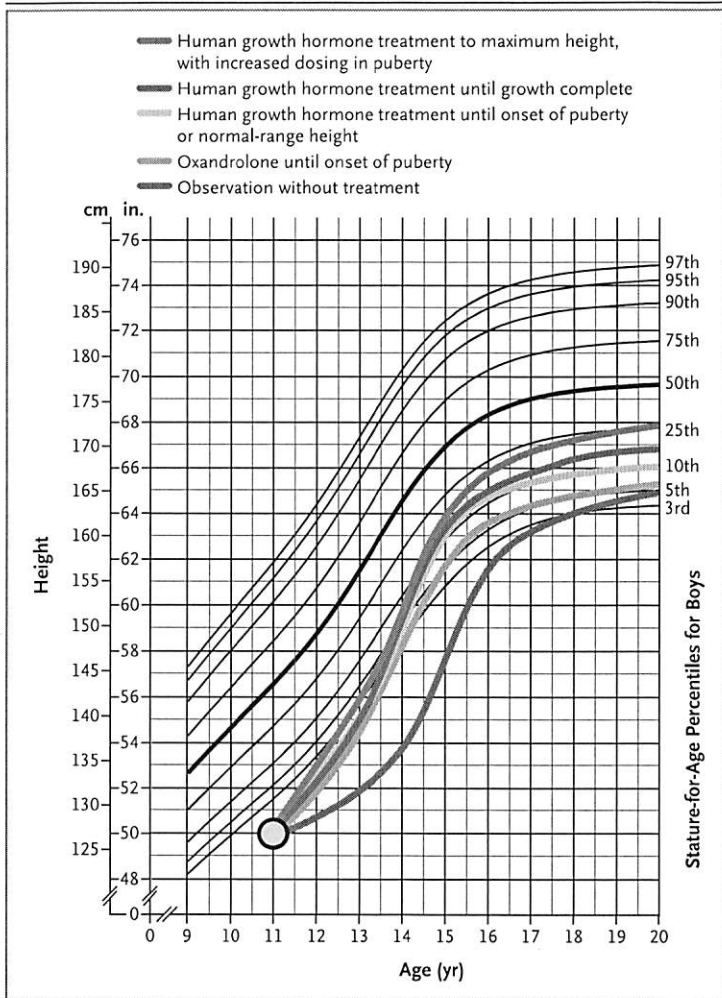


Figure 3. Approximate Projections of the Growth Trajectory and Adult Height Associated with Various Treatments for Short Stature.

In the child in the case vignette, approximate projections are plus or minus 1.3 in. (3.3 cm) according to the Bayley–Pinneau predictions of adult height at 11.5 years of age with a bone age of 9 years¹ and are based on published reports of the effects of the treatments. The curve for oxandrolone (orange) assumes an increase in the growth rate to approximately 3.1 in. (7.9 cm) per year until the onset of puberty.²⁴ The curve for human growth hormone treatment until completion of growth (green) assumes an average reported increment in height gain for idiopathic short stature plus approximately 0.4 in. (1.0 cm) per year of treatment.^{3,4} The curve for human growth hormone treatment until the onset of puberty (yellow) assumes normal pubertal growth after discontinuation of human growth hormone treatment at the onset of puberty. The curve for human growth hormone treatment to maximum adult height (blue) assumes an additional increment of 1.4 in. (3.6 cm) of height (as compared with standard-dose human growth hormone therapy) due to 2.5 years of high-dose human growth hormone treatment (0.7 mg per kilogram of body weight per week).²⁸

stature increases the growth rate and mean adult height by 1.2 to 2.8 in., or approximately 0.4 in. (1.0 cm) per year of human growth hormone treatment.^{2,4,5,12} The response is variable and is influ-

enced positively by younger age at baseline, delay in skeletal maturation,⁴ and taller parents (and negatively by shorter parents).²

Human growth hormone is administered subcutaneously at a dose of 0.2 to 0.375 mg per kilogram of body weight per week. Daily administration of human growth hormone is superior to less frequent administration.³² Dose modulation may influence the effect; doses at the higher end of this range^{32,33} and adjustment of the dose to achieve high-normal IGF-I levels³⁴ lead to faster growth and perhaps to taller adult height,³⁵ although this has not been assessed in randomized trials. In one controlled trial, doubling the dose of human growth hormone during puberty until epiphyseal closure further increased near-final height (Fig. 3).²⁸ Treatment is typically continued until completion of growth or until the child grows to a height subjectively considered to be satisfactory by the child, family, and physician. Alternatively, since most children with equivocal results of growth hormone tests have normal endogenous growth hormone secretion and sustained normal growth to normal height after the onset of puberty,³⁶ a 4-to-6-month period without human growth hormone (with reinstatement of therapy if growth slows abnormally) can be considered when signs of puberty are evident³¹ (Fig. 3). The effect of such an approach on adult height has not been examined in randomized trials.

Extensive clinical experience indicates that the risks of adverse effects from human growth hormone during treatment (e.g., occurrences of intracranial hypertension, glucose intolerance, or a slipped capital femoral epiphysis) are low.³⁷ However, safety data from postmarketing surveillance studies probably underestimate risks associated with higher doses of human growth hormone and changing risk factors (e.g., an increased prevalence of obesity, which carries a higher risk of diabetes) and do not inform post-treatment metabolic risks or the risk of cancer.³⁸⁻⁴⁰ A long-term follow-up study from France involving persons who had growth hormone deficiency or idiopathic short stature or who were small-for-gestational-age infants showed an increased standardized mortality rate of 1.33 after human growth hormone treatment, as compared with the general population in France⁴¹; assessment of cause-specific mortality identified increased risks of death attributable to bone cancer and

Table 1. Estimated Average Adult Height, Psychological Benefit or Harm, and Cost Associated with Various Management Options for Short Stature for the Child in the Case Vignette.*

Treatment	Estimated Adult Height in Inches (± 1.3 in.)	Psychological Benefit or Harm	Estimated Treatment Cost
No medication	65	Uncertain	No cost for drug with or without cost for counseling
Low-dose androgen (i.e., oxandrolone)	65	Uncertain	Oxandrolone, 2.5 mg/day, \$2,920/yr \times 2.5 yr = \$7,300
Human growth hormone until onset of puberty	66	Uncertain	Human growth hormone at dose for idiopathic short stature (0.375 mg/kg/wk) \times 2.5 yr = \$76,050
Human growth hormone until normal range (e.g., 5th percentile) of adult height	66	Uncertain	Human growth hormone \times 4 yr = \$133,087
Human growth hormone until completion of growth	66–67	Uncertain	Human growth hormone \times 5 yr = \$176,962
Human growth hormone until maximum attainable height	68	Uncertain	Human growth hormone at dose for idiopathic short stature \times 2.5 yr plus "pubertal" dose of human growth hormone (0.7 mg/kg/wk) \times 2.5 yr = \$264,420

* To convert the values for inches to centimeters, multiply by 2.54. Costs of therapy were based on estimates of weight derived from the 3rd percentile for age: a mean of 28 kg from 11 up to 13 years of age, 36 kg from 13 up to 15 years, and 45 kg from 15 to 16 years. Medication costs, obtained from Epocrates Online, were \$50 per milligram of human growth hormone (the lowest current available per-milligram cost listed was \$50 to \$75 per milligram) and \$8 per 2.5-mg tablet of oxandrolone.

circulatory system disorders among persons who received growth hormone and an increased risk of death with a dose of human growth hormone that was higher than 0.35 mg per kilogram per week. However, a similar surveillance study from Belgium, the Netherlands, and Sweden did not confirm these findings.⁴² In addition, human growth hormone treatment for idiopathic short stature is expensive (conservatively estimated at \$35,000 to \$50,000 per inch of height gained).^{3,43} Higher-dose regimens and a longer duration of treatment increase costs and may also increase risks³⁰ (Table 1).

Other Treatments to Increase Growth

For short peripubertal boys, growth-promoting alternatives to human growth hormone are low-dose androgen therapy with injectable testosterone and low-dose androgen therapy with oral oxandrolone (e.g., 1.25 to 2.5 mg per day). Both regimens are relatively low in cost, and though they are not FDA-approved for growth acceleration, they increased the growth rate by 1.2 to 2.0 in. (3.0 to 5.1 cm) per year for 1 to 3 years in controlled trials.^{44,45} To avoid accelerated estrogen-mediated epiphyseal maturation, oxandrolone (not aromatized to estrogen) is theoretically preferred over testosterone when the bone age is less than 11 years. Oxandrolone is usually discontinued after a documented increase in endogenous testos-

terone; long-term follow-up studies indicate that treatment is followed by normal pubertal growth and eventual attainment of an adult height equal to or slightly greater than⁴³ the predicted height before treatment (Fig. 3). Extensive clinical experience indicates that the risks of low-dose androgen treatment (e.g., adverse hepatic or lipid effects) are low.^{24,44,45}

Aromatase inhibitors (which reduce estrogen production and delay skeletal maturation) have been used experimentally in boys to prolong pubertal growth and increase height, but they are more expensive and have less of a growth-accelerating effect than androgens, and actual adult height gains⁴⁶ have fallen short of prior predictions of 1.6 to 2.4 in. (4.1 to 6.1 cm).⁴⁷ In view of concerns about potential adverse effects of estrogen deficiency during pubertal growth, including vertebral-body deformities,⁴⁶ aromatase inhibitors cannot be recommended for treatment of short stature outside of investigative studies.

AREAS OF UNCERTAINTY

Decisions regarding the treatment of short stature that is not related to growth hormone deficiency are complicated by uncertainties about the adverse consequences of short stature, appropriate therapeutic goals, and risk:benefit and cost:benefit ratios. The assumption that short

stature is predictably associated with psychological distress is challenged by studies that show only minor difficulties in behavioral adaptation and normal psychological function in children^{21,48} and adults²³ with short stature. It is therefore unclear whether or how to include psychosocial factors in determining therapeutic objectives.

If treatment is instituted, should the goal be acceleration of short-term growth or increased adult height? If the goal is the latter, should the aim be an adult height within the statistically normal range (e.g., the 5th to 10th percentile, which is approximately 5 ft 5 in. to 5 ft 6 in. (165 to 167 cm) for men and approximately 5 ft 0 in. to 5 ft 1 in. (152 to 155 cm) for women), a height matching that of other members of the family, or the tallest height that is safely attainable? These different goals are associated with markedly different costs; the last 1 to 3% of potential height gain may increase the total expenditure by 20%.¹⁹ Without evidence that the surrogate measure of increased height improves patient well-being,²⁵ various treatment strategies cannot be differentiated according to quality-of-life outcomes.

Finally, more data are needed to inform our understanding of the potential risks of long-term therapy with human growth hormone. Given evidence supporting a role of the growth hormone and IGF-I system in the pathogenesis of various cancers,⁴⁸ more data (preferably from large international collaborative studies with appropriate controls) are needed to identify and measure any long-term disease risks associated with the use of human growth hormone.^{40,48}

GUIDELINES

Guidelines and consensus statements on the treatment of short stature that is not related to growth hormone deficiency in children are available from professional societies, including the Growth Hormone Research Society, Pediatric Endocrine Society, and European Society for Paediatric Endocrinology.^{12,49} These recommendations review FDA guidelines, interpretation of growth hormone stimulation tests and IGF-I levels, possible doses and the risks and benefits of human growth hormone treatment, and aspects of treatment follow-up. However, they do not specify how to select among therapeutic options for short stature, the goals and cost-effectiveness of medi-

cal intervention, and when or whether to discontinue treatment.

CONCLUSIONS AND RECOMMENDATIONS

The peripubertal boy described in the vignette is markedly short but otherwise appears to be healthy. Although his growth pattern in earlier life and predicted height match those expected on the basis of parental heights, his slowed growth rate and the severity of his short stature warrant screening studies to rule out underlying disease and frank growth hormone deficiency. Normal findings on these tests support a diagnosis of idiopathic short stature (familial short stature combined with and exacerbated by CDGP). Options for treatment of idiopathic short stature should be discussed with the child and his parents; these options include observation and reassurance, human growth hormone therapy, and low-dose androgen therapy. Observation is a reasonable strategy that is supported by the lack of good evidence linking short stature with psychological harm or showing a long-term psychosocial benefit of growth-enhancing therapy, and the expectation of eventual achievement of adult height approximating midparental height. Alternatively, human growth hormone treatment has been shown to increase the growth rate and, to varying and albeit generally modest degrees (1.2 to 2.8 in.), eventual adult height. Although human growth hormone treatment has a strong safety record thus far, it is costly, requires daily injections, and could have adverse effects in the future that are relevant to treatment decisions for an otherwise healthy child.⁵⁰ A third option is low-dose, oral oxandrolone treatment, which also stimulates growth and has a relatively low cost but no proven salutary effect on eventual attained height. Thus, management options for short stature are widely disparate, with important implications with respect to cost and complexity of care.¹⁵

Whereas height augmentation has a role in some cases of short stature that is not related to growth hormone deficiency and in particular may benefit children with extreme, disabling short stature, benefits of treatment are uncertain for the vast number of otherwise healthy children with marginal short stature who are likely to reach a relatively short but normal adult height. Further-

more, for children who are treated, appropriate treatment goals and the most appropriate duration of therapy remain controversial. Thus, for a child such as the one described in the vignette (who is currently just below the 1st percentile for height but whose projected height is at the lower end of the normal range for adults), we would provide reassurance and recommend observation as a reasonable management option. If intervention is elected because of psychological distress, counseling, treatment with low-dose (and relatively low-cost) oxandrolone, or both could be considered. If human growth hormone is used,

we would consider an appropriate treatment goal to be a height in the lower normal range (e.g., approximately the 5th to 10th percentile for U.S. adults rather than the maximal attainable height), and we would take into account both the costs of therapy and the potential risks of prolonged or high-dose therapy.

Supported in part by a grant (R01HD030053) from the National Institutes of Health (to Dr. Cuttler).

Dr. Allen reports receiving grant support through his institution from Novo Nordisk. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

- Zachmann M, Sobradillo B, Frank M, Frisch H, Prader A, Bayley-Pinnaeu, Roche-Wainer-Thissen, and Tanner height predictions in normal children and in patients with various pathologic conditions. *J Pediatr* 1978;93:749-55.
- Deodati A, Cianfarani S. Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review. *BMJ* 2011;342:c7157.
- Finkelstein BS, Imperiale TF, Speroff T, Marrero U, Radcliffe DJ, Cuttler L. Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. *Arch Pediatr Adolesc Med* 2002;156:230-40.
- Leschek EW, Rose SR, Yanovski JA, et al. Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2004;89:3140-8.
- Wit JM, Rekers-Mombarg LT, Cutler GB, et al. Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. *J Pediatr* 2005;146:45-53.
- ChildStats.gov. America's children in brief: key national indicators of well-being (<http://www.childstats.gov/americaschildren/tables.asp>).
- Nicol L, Allen DB, Czernichow P, Zeitler P. Normal growth and growth disorders. In: Kappy M, Allen DB, Geffner M, eds. *Pediatric practice: endocrinology*. New York: McGraw-Hill, 2010:23-76.
- Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000;85:3990-3.
- Gourmelin M, Pham-Huu-Trung MT, Girard F. Transient partial hGH deficiency in prepubertal children with delay of growth. *Pediatr Res* 1979;13:221-4.
- Marin G, Domené HM, Barnes KM, Blackwell BJ, Cassorla FG, Cutler GB Jr. The effects of estrogen priming and puberty on the growth hormone response to standardized treadmill exercise and arginine-insulin in normal girls and boys. *J Clin Endocrinol Metab* 1994;79:537-41.
- Maghnie M, Ghirardello S, Genovese E. Magnetic resonance imaging of the hypothalamus-pituitary unit in children suspected of hypopituitarism: who, how and when to investigate. *J Endocrinol Invest* 2004;27:496-509.
- Cohen P, Rogol AD, Deal CL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab* 2008;93:4210-7.
- Cuttler L, Marinova D, Mercer MB, Connors A, Meehan R, Silvers JB. Patient, physician, and consumer drivers: referrals for short stature and access to specialty drugs. *Med Care* 2009;47:858-65.
- Cuttler L, Silvers JB, Singh J, et al. Short stature and growth hormone therapy: a national study of physician recommendation patterns. *JAMA* 1996;276:531-7.
- Silvers JB, Marinova D, Mercer MB, Connors A, Cuttler L. A national study of physician recommendations to initiate and discontinue growth hormone for short stature. *Pediatrics* 2010;126:468-76.
- Cuttler L, Silvers JB. Growth hormone and health policy. *J Clin Endocrinol Metab* 2010;95:3149-53.
- Persico N, Postlewaite A, Silverman D. The effect of adolescent experience on labor market outcomes: the case of height. *J Polit Econ* 2004;112:1019-53.
- Allen DB. Growth hormone therapy for short stature: is the benefit worth the burden? *Pediatrics* 2006;118:343-8.
- Cuttler L, Silvers JB, Singh J, Tsai AC, Radcliffe D. Physician decisions to discontinue long-term medications using a two-stage framework: the case of growth hormone therapy. *Med Care* 2005;43:1185-93.
- Cuttler L, Misra M. Growth and maturation. In: Jameson JL, DeGroot LJ, eds. *Endocrinology: adult and pediatric*. 6th ed. Philadelphia: Elsevier, 2010:479-508.
- Sandberg DE, Bukowski WM, Fung CM, Noll RB. Height and social adjustment: are extremes a cause for concern and action? *Pediatrics* 2004;114:744-50.
- Geisler A, Lass N, Reinsch N, et al. Quality of life in children and adolescents with growth hormone deficiency: association with growth hormone treatment. *Horm Res Paediatr* 2012;78:94-9.
- Ulph F, Betts P, Mulligan J, Stratford RJ. Personality functioning: the influence of stature. *Arch Dis Child* 2004;89:17-21.
- Wilson DM, McCauley E, Brown DR, Dudley R. Oxandrolone therapy in constitutionally delayed growth and puberty. *Pediatrics* 1995;96:1095-100.
- Ross JL, Sandberg DE, Rose SR, et al. Psychological adaptation in children with idiopathic short stature treated with growth hormone or placebo. *J Clin Endocrinol Metab* 2004;89:4873-8.
- Lagrou K, Froidecoeur C, Verlinde F, et al. Psychosocial functioning, self-perception and body image and their auxologic correlates in growth hormone and oestrogen-treated young adult women with Turner syndrome. *Horm Res* 2006;66:277-84.
- Visser-van Balen H, Geenen R, Kamp GA, Huisman J, Wit JM, Sinnema G. Long-term psychosocial consequences of hormone treatment for short stature. *Acta Paediatr* 2007;96:715-9.
- Mauras N, Attie KM, Reiter EO, Saenger P, Baptista J. High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. *J Clin Endocrinol Metab* 2000;85:3653-60.
- Noeker M. Management of idiopathic short stature: psychological endpoints,

- assessment strategies and cognitive-behavioral intervention. *Horm Res* 2009; 71:Suppl 1:75-81.
30. Approval letter: Humatrope injection device and draft package insert. Silver Spring, MD: Food and Drug Administration (http://www.accessdata.fda.gov/drug_satfda_docs/nda/99/019640_s022_HUMATROPE.pdf).
31. Allen DB, Fost N. hGH for short stature: ethical issues raised by expanded access. *J Pediatr* 2004;144:648-52.
32. Grimberg A, Cohen P. Optimizing growth hormone therapy in children. *Horm Res* 1997;48:Suppl 5:11-5.
33. Frasier SD, Costin G, Lippe BM, Aceto T Jr, Bunger PF. A dose-response curve for human growth hormone. *J Clin Endocrinol Metab* 1981;53:1213-7.
34. Cohen P, Bright GM, Rogol AD, Kappelgaard AM, Rosenfeld RG. Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: implications for efficacy and safety. *J Clin Endocrinol Metab* 2002; 87:90-8.
35. Blethen SL, Baptista J, Kuntze J, Foley T, LaFranchi S, Johanson A. Adult height in growth hormone (GH)-deficient children treated with biosynthetic GH. *J Clin Endocrinol Metab* 1997;82:418-20.
36. Tauber M, Moulin P, Pienkowski C, Jouret B, Rochiccioli P. Growth hormone (GH) retesting and auxological data in 131 GH-deficient patients after completion of treatment. *J Clin Endocrinol Metab* 1997;82:352-6.
37. Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab* 2010;95:167-77.
38. Cuttler L. Safety and efficacy of growth hormone treatment for idiopathic short stature. *J Clin Endocrinol Metab* 2005;90:5502-4. [Erratum, *J Clin Endocrinol Metab* 2006;91:3336.]
39. Child CJ, Zimmermann AG, Scott RS, Cutler GB Jr, Battelino T, Blum WF. Prevalence and incidence of diabetes mellitus in GH-treated children and adolescents: analysis from the GeNeSIS observational research program. *J Clin Endocrinol Metab* 2011;96(6):E1025-E1034. [Erratum, *J Clin Endocrinol Metab* 2011;96:2624.]
40. Allen DB. Growth hormone post-marketing surveillance: safety, sales, and the unfinished task ahead. *J Clin Endocrinol Metab* 2010;95:52-5.
41. Carel JC, Ecosse E, Landier F, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *J Clin Endocrinol Metab* 2012;97:416-25.
42. Säwendahl L, Maes M, Albertsson-Wikland K, et al. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. *J Clin Endocrinol Metab* 2012;97(2):E213-E217.
43. Lee JM, Davis MM, Clark SJ, Hofer TP, Kemper AR. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *Arch Pediatr Adolesc Med* 2006;160:263-9.
44. Schroor EJ, van Weissenbruch MM, Knibbe P, Delemarre-van de Waal HA. The effect of prolonged administration of an anabolic steroid (oxandrolone) on growth in boys with constitutionally delayed growth and puberty. *Eur J Pediatr* 1995;154:953-7.
45. Keenan BS, Richards GE, Ponder SW, Dallas JS, Nagamani M, Smith ER. Androgen-stimulated pubertal growth: the effects of testosterone and dihydrotestosterone on growth hormone and insulin-like growth factor-I in the treatment of short stature and delayed puberty. *J Clin Endocrinol Metab* 1993;76:996-1001.
46. Wit JM, Hero M, Nunez SB. Aromatase inhibitors in pediatrics. *Nat Rev Endocrinol* 2012;8:135-47.
47. Salehpoura S, Alipour P, Razzaghy-Azarc M, et al. A double-blind, placebo-controlled comparison of letrozole to oxandrolone effects upon growth and puberty of children with constitutional delay of puberty and idiopathic short stature. *Horm Res Paediatr* 2010;74:428-35.
48. Rosenfeld RG, Cohen P, Robison LL, et al. Long-term surveillance of growth hormone therapy. *J Clin Endocrinol Metab* 2012;97:68-72.
49. Wilson TA, Rose SR, Cohen P, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr* 2003; 143:415-21.
50. Allen DB. Clinical review: Lessons learned from the hGH era. *J Clin Endocrinol Metab* 2011;96:3042-7.

Copyright © 2013 Massachusetts Medical Society.

JOURNAL ARCHIVE AT NEJM.ORG

Every article published by the *Journal* is now available at NEJM.org, beginning with the first article published in January 1812. The entire archive is fully searchable, and browsing of titles and tables of contents is easy and available to all. Individual subscribers are entitled to free 24-hour access to 50 archive articles per year. Access to content in the archive is available on a per-article basis and is also being provided through many institutional subscriptions.