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Appendix B – The Synthetic Human Growth Hormone (hGH)

Medical Indications

Since their introduction in 1985, the list of FDA-approved indications for synthetic human growth hormone has been expanded from classical human growth hormone deficiency in children to include, among other things, renal failure and Turner Syndrome. Pediatric endocrinologists have used synthetic hGH for several other off-label indications such as intrauterine growth restriction (IUGR) and Prader-Willi Syndrome.¹ Chronic renal insufficiency causes kidneys to fail, leading to an accumulation in the child's blood of toxins that hamper the normal growth process. As such, chronic renal insufficiency does not affect the production of hGH, yet treatments with this hormone have proven effective. Approximately 3,000 children yearly are affected by chronic renal insufficiency.² IUGR is also a clear case of a physiological dysfunction. IUGR is associated with abnormal growth in the uterus. (Affected children are said to be small for gestational age.) Just like chronic renal insufficiency, IUGR does not impair the production of the hGH; nevertheless, administering this hormone has been shown to help. Turner Syndrome is caused by a genetic defect that affects only girls. Symptoms include shortness and a failure to fully develop ovaries. Girls are on average only 4'8" tall, versus 5'5" for the average female.³ Girls with Turner Syndrome do not have an hGH deficiency, yet when treated with hGH, they too display a faster growth rate. Prader-Willi Syndrome is another genetic defect that stunts growth. It is rare, affecting only 1 in 10,000 to 12,000 newborn babies. Children with the Prader-Willi Syndrome tend to be obese and of short stature, and have small hands, small feet, a small mouth, and small genitals. In these children, hGH treatment can add several inches to their stature, reduce their body fat, and even improve their physical activity.

The FDA decision to approve the use of synthetic hGH for idiopathic shortness represents a significant departure from earlier practice in that this condition may be described as a cosmetic use of hGH. Idiopathic short stature (ISS) has no clear or obvious physiological cause. The pharmaceutical industry has been trying to identify the causes of idiopathic shortness for many years, without success. Many ISS children have levels of hGH well above what is considered normal. On the other end, some children of normal stature have been shown to have growth hormone levels at or below the norm. This shows that the relationship between levels of hGH

¹ Hormone Foundation, "Get the Facts: Growth Hormone Issues in Children and Adults," (Chevy Chase, MD: The Hormone Foundation, 2003); Mary Lee Vance and Nelly Mauras, "Growth Hormone Therapy in Adults and Children," *New England Journal of Medicine* 341, no. 16 (1999).

² Dieter Haffner et al., "Effect of Growth Hormone Treatment on the Adult Height of Children with Chronic Renal Failure," *New England Journal of Medicine* 343, no. 13 (2004).

³ Paul Saenger, "Turner's Syndrome," *New England Journal of Medicine* 335, no. 23 (1996).

secretion and height is far more complex than normally assumed. To complicate matters further, there is no agreed-upon definition of short stature. In some studies, children in the third percentile for their age and sex are considered short; in others, the threshold is the fifth or tenth percentile; in still others, all children below two standard deviations from the mean are characterize as short.

That one should be careful in diagnosing idiopathic shortness was demonstrated by a recently conducted study in which approximately one-third of both idiopathic short boys and girls eventually reached a normal stature.⁴ This result indicates that growth velocity may vary considerably over time: In other words, a significant fraction of ISS children are simply growing at a speed slower than average for their age at the time of the measure, but their developmental velocity could accelerate significantly at a later point in time. These so-called ISS children not only are healthy, they are also not short. In sum, it is quite possible that ISS children are perfectly healthy, and often their shortness is only temporary.

Safety and Efficacy

Two key aspects of the debate over the use of synthetic hGH are safety and efficacy. The hormone may be effective, could critics argue, but should it be used to treat healthy children if there are any doubts about its safety? Alternatively, one may argue that it is not sufficient for this treatment to be safe. In order to justify the exorbitant costs of an hGH treatment, a treatment that usually lasts several years, the pharmaceutical company must be able to show clear and unambiguous evidence of effectiveness.

With regard to safety, there is very little evidence of risks or adverse effects associated with hGH treatments; very few adverse effects have been documented. Recently, the Growth Hormone Research Society reviewed approximately 200 peer-reviewed articles on this subject and concluded that the use of HGH for approved indications is safe.⁵ The safety of synthetic hGH is not a concern for the FDA, which – at its June 10, 2003, meeting convened to review the pharmaceutical manufacturer’s application for the non-medical uses of synthetic hGH – concluded with few reservations that hGH in general and Humatrope in particular are safe.⁶

Assessing the efficacy of synthetic hGH to treat ISS children is considerably more difficult. hGH treatments for children with a discernible physiological condition generally are considered very effective and can add several inches to these individuals’ adult height, though these treatments usually do not entirely compensate for their shortness. Nevertheless, there is agreement in the medical community that hGH treatments are quite effective, if not in

⁴ Luigi Greco, Chris Power, and Catherine Peckham, "Adult Outcome of Normal Children Who Are Short or Underweight at Age 7 Years," *British Medical Journal* 310 (1995).

⁵ Michael O. Thorner, "Critical Evaluation of the Safety of Recombinant Human Growth Hormone Administration: Statement from the Growth Hormone Research Society," *The Journal of Clinical Endocrinology & Metabolism* 86, no. 5 (2001).

⁶ Briefings materials are available at <http://www.fda.gov/ohrms/dockets/ac/03/briefing/3957b1.htm>.

completely treating then at least in significantly mitigating the negative consequences of severe hGH deficiency. We were surprised to discover that the same treatment is far less effective in treating ISS children. In this case, the evidence is mixed. Opponents of the use of hGH for non-medical reasons have claimed that the efficacy of this treatment has not been demonstrated. Several recent studies seem to support this view.⁷ Not surprisingly, supporters of legalizing hGH⁸ for treating ISS children point to other studies that seem to demonstrate precisely the opposite. The literature on this issue is simply too large and too technical for us to offer an independent assessment, but it should be mentioned that researchers funded by the leading manufacturers of synthetic hGH tend to produce supportive studies, while the FDA, in reviewing the extant literature, including the studies conducted by pharmaceutical companies, is much less sanguine about the effectiveness of the treatment.

There are several reasons for these conflicting results. First, and perhaps most importantly, the non-therapeutic use of hGH remains controversial among medical practitioners. Medical doctors and scientists may read the available empirical evidence differently depending on their personal inclinations. Second, it is much easier to evaluate the efficacy of hGH treatments for traditional, medical indications, as these indications have been treated for a much longer period of time and the available empirical evidence is sizeable. Third, it is also important to recognize that a thorough evaluation of the efficacy of hGH treatments on final height requires conducting lengthy and costly longitudinal studies. Many studies on the efficacy of hGH for ISS children started in the mid-1990s and have not yet been concluded.

In sum, while the safety and efficacy of hGH treatments for traditional medical indications is not in dispute, the efficacy of these treatments for ISS children is debatable at best and inadequate at worst.

Social-Psychological Pathologies

In this section, we examine the possible negative psychological and social effects of shortness. We start by offering an obvious but important observation: The ethical questions raised by individuals of normal stature trying to gain a few inches are quite different from the concerns associated with parents trying to help their short children grow taller. Much of the debate surrounding the use of synthetic growth hormone is centered on treating short stature, but the abuse of synthetic hGH in individuals of normal stature is just as relevant to our discussion.

⁷ C.G.D. Brooks, "Growth Hormone: Panacea or Punishment for Short Stature?," *British Medical Journal* 315 (1997); Sharon E. Oberfield, "Growth Hormone Use in Normal, Short Children – a Plea for Reason," *New England Journal of Medicine* 340, no. 7 (1999).

⁸ John G. Buchlis et al., "Comparison of Final Heights of Growth Hormone-Treated Vs. Untreated Children with Idiopathic Growth Failure," *Journal of Clinical Endocrinology and Metabolism* 83, no. 4 (1998); Beth S. Finkelstein et al., "Effect of Growth Hormone Therapy on Height in Children with Idiopathic Short Stature," *Archives of Pediatric & Adolescent Medicine* 156 (2002); Raymond L. Hintz et al., "Effect of Growth Hormone Treatment on Adult Height of Children with Idiopathic Short Stature," *New England Journal of Medicine* 340, no. 7 (1999).

Accordingly, one should distinguish between the (mostly positive) effects of above-average stature on individuals (mostly men), and the (largely) negative effects of shortness on children and adults well below normal height.

Tallness – a Requisite for Success?

Popular wisdom holds that taller-than-average individuals – especially men – are more successful than the average population. Surprisingly perhaps, in this case popular wisdom seems indeed to be correct. A recent study of the relationship between stature and socioeconomic status in the former West Germany – defined as a composite of educational level, occupational types and of occupation and income – has shown that men of average social status are 1.7 cm (0.67 inches) taller, and men enjoying a higher status are 3.9 cm (1.54 inches) taller than men of a lower social status. A similar pattern emerges for citizens of the former East Germany and for women.⁹ Two factors that could explain these results – limited access to health care and poor nutritional habits – are most likely not responsible for the study results, as Germany has an excellent health care system and high standards of living.

Height is not only associated with status and income. It also affects the reproductive chances of males. According to a recently conducted survey, taller men are much more likely to have children, even after controlling for residence (compared to the urban population, the rural population is shorter), health (hGH deficiency and other conditions can have a dramatic impact on final height), and education – all factors that have been shown to affect stature.¹⁰ The size of the sample – 3,000 individuals – does not leave any doubts about the robustness of this conclusion. Height has also been shown to account for the differences between males and females in status and income.¹¹ According to another study, career chances seem to be considerably higher for taller-than-average individuals.¹² The study analyzed homogenous groups of professionals (nurses, individuals in clerical positions, and craftsmen) and found that height correlates with seniority – even after controlling for education level and socioeconomic background.

It doesn't stop here. It is a well-documented empirical fact that there is a significant – albeit weak – correlation between height and IQ. One may have serious doubts about the adequacy of IQ tests as indicators of cognitive performance, but it would be hard to ignore available empirical evidence. In one study, the authors assembled a very large, representative sample of the entire U.S. population.¹³ These children were examined twice, between 1963 and 1965, and again

⁹ J. Komlos and P. Kriwy, "Social Status and Adult Height in the Two Germanies," *Annals of Human Biology* 29, no. 6 (2002).

¹⁰ B. Pawlowski, R.I.M. Dunbar, and A. Lipowicz, "Tall Men Have More Reproductive Success," *Nature* 403 (2000).

¹¹ Paul V. Crosbie, "The Effects of Sex and Size on Status Ranking," *Social Psychology Quarterly* 42, no. 4 (1979).

¹² A. Schumacher, "On the Significance of Stature in Human Society," *Journal of Human Evolution* 11 (1982).

¹³ Darrell M. Wilson et al., "Growth and Intellectual Development," *Pediatrics* 78, no. 4 (1986).

between 1966 and 1970. The longitudinal sample consisted of more than 2,000 children ages 8 to 11. Each sample included approximately 14,000 children. The study found a small but significant correlation between height and IQ in both cases. The correlation persisted even after controlling for socioeconomic status (i.e., family income), and race (black versus white).

These findings have been repeatedly replicated, suggesting that the relationship between stature and IQ, while not strong, is indeed real. For example, a recently completed study of physical, psychological, and cognitive aptitudes of a nearly complete cohort of more than 38,000 18-year-old Swedish young men showed that taller men perform significantly better than average on a variety of cognitive tests and are psychologically more stable.¹⁴ A Danish study of 76,000 young men confirmed these results.¹⁵ However one decides to account for this evidence, it is hard to ignore the fact that on the whole, taller and good-looking men (for women tallness is often a handicap) seem to be considerably more successful than their average peers.

Shortness as a Psychological and Social Impairment?

The question of whether short individuals are at a disadvantage compared to individuals of normal height is analytically distinct from the question we have discussed in the preceding section, i.e., whether individuals taller than average enjoy (undeserved) benefits. One can easily imagine passing a ban on the use of synthetic hGH for individuals of normal height on the ground that the ubiquitous use of hGH in this case could trigger a costly arms race with no discernible benefits for the participants. The rationale for administering synthetic hGH to extremely short children is rather different. In this case, it is presumed – and parents have argued to the FDA – that children of idiopathic short stature suffer from low self-esteem and are at a significant disadvantage compared to their peers. Determining whether these claims are justified is therefore of some import to this discussion.

The prevailing wisdom until the late 1980s was that short children are indeed at a disadvantage. According to some studies, they frequently experience teasing and bullying, they have poor social skills, they are isolated, they are plagued by low self-esteem, and their academic performance is poor.¹⁶ Similar conclusions were reached for adult short individuals. Among the most frequently cited concerns are education,¹⁷ employment, romantic relationships, and friendships.¹⁸ In more recent times, however, the prevailing view has begun to shift. New,

¹⁴ Torsten Tuvemo, Björn Jonsson, and Ingemar Persson, "Intellectual and Physical Performance and Morbidity in Relation to Height in a Cohort of 18-Year-Old Swedish Conscripts," *Hormone Research* 52 (1999).

¹⁵ T.W. Teasdale, David R. Owen, and T.I.A. Sørensen, "Intelligence and Educational Level in Adult Males at the Extremes of Stature," *Human Biology* 63, no. 1 (1991).

¹⁶ David E. Sandberg, Amy E. Brook, and Susana P. Campos, "Short Stature: A Psychosocial Burden Requiring Growth Hormone Therapy?," *Pediatrics* 94, no. 6 (1994), p.832.

¹⁷ Teasdale, Owen, and Sørensen, "Intelligence and Educational Level in Adult Males at the Extremes of Stature."; Melissa Wake, David Coghlan, and Kyle Hesketh, "Does Height Influence Progression through Primary School Grades?," *Archives of Disease in Childhood* 82 (2000).

¹⁸ F. Ulph et al., "Personality Functioning: The Influence of Stature," *Archives of Disease in Childhood* 89 (2004), p.17.

methodologically more rigorous studies and larger samples suggest that short children do indeed experience stress as a result of teasing and bullying, but that these experiences have very little impact on their psychological well-being and on their ability to cope with these problems. Studies conducted in the UK¹⁹ and in the United States²⁰ found that boys of idiopathic short stature differed only moderately from peers in the control groups on a variety of psychological tests such as self-esteem, self-perception, and behavior. Girls of idiopathic short stature, for their part, were nearly indistinguishable from their normal counterparts.

These results have been corroborated by other studies. A Dutch group analyzed the impact of short stature on the quality of life of five different groups of short individuals: individuals affected by classic hGH deficiency, individuals suffering from renal failure, women with Turner Syndrome, individuals of idiopathic short stature, and individuals presumed to be idiopathically short. (The latter group is a reference group of short individuals who had not been referred to an endocrinologist.)²¹ According to the study, all participants experienced difficulty in finding a partner. In other respects, however, the picture is far more nuanced. Only women with Turner Syndrome reported problems with job applications, and normal short individuals did not report any reduction in their quality of life.

Surprisingly, individuals of idiopathic short stature who were referred to an endocrinologist did report reductions in their quality of life. They also reported a range of psychological and social problems.²² This result has been confirmed by other studies²³ and has been attributed to the failure of the hGH treatment to produce the expected results. It is not entirely clear whether the failure should be interpreted in physiological terms, i.e., as an ineffective treatment, or whether it should be attributed to the realization by the subjects in question that increased stature alone was unlikely to have a significant impact on their quality of life. Either way, this finding suggests that the medical treatment of what is ultimately a psychological and a social problem could exacerbate rather than mitigate the problem.

In sum, the available empirical evidence suggests that there is no basis for the claim that children of idiopathic short stature are psychologically impaired, that their chances of success in life are limited, or that their quality of life is poor. Short children do report experiencing bullying and teasing, but this does not seem to have a significant impact on their well-being.

¹⁹ Bruce A. Dowdney et al., "Are Short Normal Children at a Disadvantage? The Wessex Growth Study," *British Medical Journal* 514 (1997); A.B. Downie et al., "Psychological Response to Growth Hormone Treatment in Short Normal Children," *Archives of Disease in Childhood* 75 (1996); Ulph et al., "Personality Functioning: The Influence of Stature."

²⁰ Sandberg, Brook, and Campos, "Short Stature: A Psychosocial Burden Requiring Growth Hormone Therapy?."

²¹ J.J.V. Busschbach et al., "Quality of Life in Short Adults," *Hormone Research* 49 (1998).

²² H.-C. Steinhausen et al., "The Behavior Profile of Children and Adolescents with Short Stature," *Journal of Behavioral Pediatrics* 21 (2000); L.E. Underwood, "The Social Costs of Being Short: Societal Perceptions and Biases," *Acta Paediatrica Scandinavica*, no. 377 (1991).

²³ Sandberg, Brook, and Campos, "Short Stature: A Psychosocial Burden Requiring Growth Hormone Therapy?."

Patterns of Use

Could the medical profession contribute to discourage parental demands for treatments with synthetic hGH, or is it more likely that it will actually support and amplify questionable parental desires? Should the government trust the medical profession not to indulge demands for what may be cures of dubious effectiveness? To explore this question, in this section we examine prescription patterns for synthetic hGH among medical specialists.

A fairly recent, comprehensive survey of prescription practices among pediatric endocrinologists and their views on numerous questions pertaining to the prescription of synthetic hGH provides several important insights.²⁴ The survey was sent to the members of the Lawson Wilkins Pediatric Endocrine Society, the largest professional organization of pediatric endocrinologists. The response rate was very high: 81 percent, or 434 out of 534 physicians, returned the survey. A first important conclusion emerging from this survey is that pediatric endocrinologists do not treat ISS children very often. According to this survey, 58 percent of the patients were treated for classical hGH deficiency, 15 percent for Turner Syndrome, 11 percent for neurosecretory disorders, and 2 percent for renal insufficiency. Of the remaining 14 percent, 5 percent were treated for other, non-endocrine medical conditions and 9 percent for familial, constitutional, or unknown causes of short stature. In other words, only approximately one out of 10 treated patients were ISS children.

Based on this initial observation, one might conclude that pediatric endocrinologists are generally cautious in prescribing hGH for the treatment of idiopathic short stature. This conclusion would be premature. Asked whether short children in the third to fifth percentile for their age are likely to be psychologically impaired, 83 percent of pediatric endocrinologists answered that this is either “sometimes” or “often” the case. This percentage rises to 91.5 percent for children in the third percentile. An analogous pattern emerges for adults in the same height intervals. The survey also shows that pediatric endocrinologists are more likely to recommend a treatment the shorter the child is, the slower his or her growth rate is, and the more advanced bone age is.²⁵ These patterns of prescription again are inconsistent with the medical literature: Shortness is a poor indicator of responsiveness to treatment, and so are slow growth and bone age.²⁶ This data suggests that the decision to recommend treatment is based on two equally unwarranted perceptions – that shortness causes psychological impairment, and that shorter children are more likely to respond well to a human GH treatment.

These observations indicate that if an increasing number of ISS children were to be referred to pediatric endocrinologists, the total number of prescriptions for hGH treatment would increase significantly. We do not have recent data on this question, but the aforementioned study offers

²⁴ Leona Cuttler et al., "Short Stature and Growth Hormone Therapy: A National Study of Physician Recommendation Patterns," *Journal of the American Medical Association* 276, no. 7 (1996).

²⁵ Bone age is a measure of skeletal maturation, and its used to evaluate a child's remaining potential for growth.

²⁶ Cuttler et al., "Short Stature and Growth Hormone Therapy: A National Study of Physician Recommendation Patterns," p.535.

some clues. The survey reports that 68 percent of respondents believed that the rate of prescription for ISS children had increased either “somewhat” or “significantly” in recent years.²⁷ Anecdotal evidence indicates that parents are indeed likely to refer their short but otherwise healthy children to an endocrinologist,²⁸ so much so that insurance companies have found it necessary to clamp down on prescriptions for hGH.²⁹

Perhaps the strongest evidence that making idiopathic short stature a medical condition would lead to an unprecedented increase in the non-therapeutic use of hGH comes from Australia. In 1988, the Australian government decided to eliminate mandatory testing for hGH deficiency as a condition for the prescription of hGH. The number of children receiving hGH treatment increased by a factor of four, and the annual cost for these prescriptions went from \$1 million to \$45 million in three years. Alarmed by this trend, the Australian government decided to reverse its decision, and in 1995, the total cost was reduced to \$16 million.³⁰ The situation in the United States differs from the Australian case in that the FDA has merely included idiopathic shortness in the list of approved medical uses. A prescription by a pediatric endocrinologist is still required. Nevertheless, the Australian experience clearly suggests that regulatory agencies should be very cautious in indulging societal tendencies that may be both ethically questionable and very costly.

The admittedly limited data demonstrates that pediatric endocrinologists are likely to share with parents and children inaccurate and misleading views of the relationship between shortness and psychological impairment. These views may translate into supportive attitudes toward parents demanding costly cures for non-existent conditions. More importantly, they also facilitate the creation of a powerful coalition of medical professionals, pharmaceutical companies, and patient groups dedicated to advancing what ultimately are the narrow interests of a few societal groups.

The Market for Human Growth Hormone

Reliable figures about the size and growth of the market for synthetic hGH are very difficult to come by. Repeated inquiries with the leading pharmaceutical manufacturers such as Pfizer, Genentech, and Ely Lilly produced very limited results. The lack of reliable data notwithstanding, there is no doubt that this market is both lucrative and rapidly expanding. In 1996, a group of medical practitioners estimated the cost of an hGH treatment at \$13,000 to

²⁷ Remember that the survey was conducted in 1996, so this trend might well have accelerated since then.

²⁸ Rick Weiss, "Growth Hormone's Downside; Use on Healthy Children Raises Ethical Concerns," *The Washington Post*, May 10, 1995.

²⁹ Rick Weiss, "Are Short Kids 'Sick'? Doctors and Drug Makers May Be Overpromoting a Profitable Hormone That Makes Children Taller," *The Washington Post*, March 15, 1994.

³⁰ G.A. Werther, "Growth Hormone Measurements Versus Auxology in Treatment Decisions. The Australian Experience," *Journal of Pediatrics* 128, no. 5 (1996).

\$16,000 per year, for several years.³¹ More recent figures range between \$20,000 and \$30,000 per year. The aforementioned study estimates the number of children in the United States affected by severe hGH deficiency at approximately 14,000. Based on this number, in the mid-1990s, market size was between \$182 and \$224 million – a sizeable but not a huge market.

Every new therapeutic use of synthetic hGH approved by the FDA has of course expanded the size of this market. With the recent decision by the FDA to add idiopathic short stature to the list of approved indications, the potential size of the synthetic hGH market has grown dramatically. Estimates of the number of ISS children range from 400,000 to 1.7 million.³² The lower estimate, by Eli Lilly, can be attributed to a more conservative definition of short stature, in this case below 2.5 standard deviations. Leona Cuttler, by contrast, defined ISS children as those in the third percentile for their sex and age. In the latter case, the market for hGH would expand to a very attractive \$22 billion. Another way to appreciate the economic significance of the FDA decision to declare idiopathic short stature a medical condition is to note that children with classical hGH deficiency constitute only between 0.82 and 3.5 percent of the population of ISS children, depending on how idiopathic short stature is defined.

The actual market size for synthetic hGH is even larger if one includes off-label prescriptions and illegal uses of hGH. Anecdotal evidence suggests that aging baby-boomers are beginning to rely on hGH treatments to combat age-related symptoms.³³ It appears that in modest amounts, hGH can indeed be beneficial, and the side effects are minimal. A new, more recent trend has been observed among women seeking “eternal youth.”³⁴ It is also well-known that some athletes have used hGH to boost their performance.³⁵ Finally, there is some evidence that adolescents are abusing hGH.³⁶ In sum, the synthetic hGH is on its way to becoming a major source of revenue for several large pharmaceutical companies – a point that federal regulators and most bioethicists have failed to adequately acknowledge.

³¹ Cuttler et al., "Short Stature and Growth Hormone Therapy: A National Study of Physician Recommendation Patterns."

³² Ibid.

³³ Sabin Russell, "Aging Baby Boomers Turn to Hormone: Some Doctors Concerned About Growing 'Off-Label' Use of Drug," *The San Francisco Chronicle*, November 17, 2003.

³⁴ Katrina Beikoff, "New Body-Drugs Shock Seeking Beauty in Bottle," *Hobart Mercury*, February 12, 2000.

³⁵ Sabin Russell, "Growth Hormone an Expensive Garnish: Drug Used to Treat Dwarfism in Young Appeals to Athletes," *The San Francisco Chronicle*, October 22, 2003.

³⁶ Jeannette M. Smith, "Human Growth Hormone: A New Substance of Abuse among Adolescents?," *Journal of the American Medical Association* 269, no. 11 (1993).

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Appendix C – IVF Health and Safety Risks: Some Illustrations

Major Birth Defects

In early 2002, a study published in the *New England Journal of Medicine* found that children conceived through IVF (in vitro fertilization) and ICSI (intracytoplasmic sperm injection) were twice as likely (9 versus 4.5 percent) to be born with at least one major congenital defect than children conceived naturally.¹

The study sets itself apart from other, similar studies in several respects. Unlike earlier studies, it used a single definition of birth defect and applied it consistently to both ART children and to the children in the general population.² It used a fairly restrictive definition of major birth defect. It documented congenital defects not only at birth but also at one year of age, by which most birth defects become apparent. The authors took steps to minimize a differential diagnosis based on the mode of conception. Finally, they compiled a reasonably large sample that enabled them to control for several confounding factors.

The study's main result – a doubling of major birth defects among children conceived through IVF and ICSI – seems quite robust. It is not affected by whether one analyzes the original samples or focuses exclusively on singletons or on-term singletons. Furthermore, the result is not affected if one controls for maternal age and parity, the sex of the infant, and correlation between siblings.³

As the correspondence in the *New England Journal of Medicine* between the study authors and their critics shows, these findings came as a major surprise to ART practitioners. The study was criticized on several grounds. In our view, nothing offered by the critics seriously undermines the study's credibility. On the other end, the rather vicious tone taken by these critics could lead one to conclude that the critics have a vested interest in undermining any suggestion that either IVF or ICSI are anything short of perfectly safe methods of assisted reproduction.⁴

The present study certainly does not exhaust the debate about the safety of ART treatments. As a recently published meta-analysis of the incidence of major congenital defects in ART

¹ Hansen et al., "The Risk of Major Birth Defects after Intracytoplasmic Sperm Injection and in Vitro Fertilization."

² Jennifer J. Kurinczuk and Carol Bower, "Birth Defects in Infants Conceived by Intracytoplasmic Sperm Injection: An Alternative Interpretation," *British Medical Journal* 315, no. 1260-1265 (1997).

³ Hansen et al., "The Risk of Major Birth Defects after Intracytoplasmic Sperm Injection and in Vitro Fertilization," p.728.

⁴ Maryse Bonduelle et al., "Developmental Outcome at 2 Years of Age for Children Born after ICSI Compared with Children Born after IVF," *Human Reproduction* 18, no. 2 (2003); Jennifer R. Bowen et al., "Medical and Developmental Outcome at 1 Year for Children Conceived by Intracytoplasmic Sperm Injection," *Lancet* 351 (1998); Jennifer J. Kurinczuk, "Safety Issues in Assisted Reproduction Technology," *Human Reproduction* 18,

children shows, many other epidemiological studies on this matter exist and should be included in the present discussion.⁵ The sheer number of these studies and their differing methodologies would make it very difficult for anyone to draw firm conclusions from this mass of evidence. It would also require a major commitment of time and resources well beyond our budgetary constraints.

Low Birth Weight

An obvious and quite familiar risk associated with an IVF treatment is a multiple pregnancy. Dramatic imagery notwithstanding, reproductive specialists consider twins and higher-order pregnancies an “adverse outcome,” and for good reasons. Multiple pregnancies suffer from a higher number of perinatal deaths, i.e., death during pregnancy or shortly thereafter, and are at a much higher risk of obstetric complications.⁶ In addition, twins are at an increased risk of short- and long-term disabilities. They may also suffer from low birth weight. Finally, multiple pregnancies often force prospective parents to perform what is politely referred to as “selective reduction” – i.e., the abortion of one of more fetuses. Selective reduction increases the chances that at least one baby will be born alive and reduces the health risks to the prospective mother.

Multiple gestations have been shown to be associated with low birth weight, but until recently it was unclear whether assisted reproduction is also associated with lower birth weight in singletons. A research group at the Centers for Disease Control (CDC) in Atlanta, Georgia, compared the incidence of low birth weight (2,500 grams, i.e., 5.5 pounds or less) among 42,000 ART children born between 1996 and 1997 and in more than 3 million children born spontaneously in 1997 in the United States. Among children born after a normal pregnancy (37 weeks or later), the risk of low birth weight in singleton ART children was 2.6 times higher than in the control group.⁷ Interestingly, the study did not find significant differences between ART twins and twins conceived naturally.

There are straightforward reasons for a much higher rate of twins and multiple pregnancies among ART patients. To increase the likelihood of a pregnancy, reproductive specialists routinely transfer several embryos to a woman’s uterus. This has especially been the case in the United States, where the decision as to how many embryos should be transferred is made by the reproductive specialist and the patient, and is partly dictated by cost considerations and by

no. 5 (2003); Alastair G. Sutcliffe, "Health Risks in Babies Born after Assisted Reproduction," *British Medical Journal* 325 (2002).

⁵ Jennifer J. Kurinczuk, Michèle Hansen, and Carol Bower, "The Risk of Birth Defects in Children Born after Assisted Reproductive Technologies," *Current Opinion in Obstetrics and Gynecology* 16 (2004).

⁶ Pierpaolo Mastroiacovo et al., "Congenital Malformations in Twins: An International Study," *American Journal of Medical Genetics* 83 (1999); François Olivennes, "Avoiding Multiple Pregnancies in ART," *Human Reproduction* 15, no. 8 (2000).

⁷ Laura A. Schieve et al., "Low and Very Low Birth Weight in Infants Conceived with Use of Assisted Reproductive Technology," *New England Journal of Medicine* 346, no. 10 (2002).

parental desires. By contrast, the British Human Fertilisation and Embryology Authority limits the maximum number of embryos that can be transferred to three.⁸

Neurological disorders

In 2002, a group of Swedish scientists published one of the most comprehensive studies on neurological disorders in IVF children.⁹ The authors conducted a retrospective analysis of 5,680 IVF children born between 1982 and 1995. The age of the children in the sample ranged from 18 months to 14 years. Every IVF child was matched with two children in the control group. To compensate for the high incidence of twins in the population of IVF children, the researchers matched each twin with two additional controls, also twins. Thus, the control group consisted of 15,397 children.

The Swedish group identified 138 distinct disorders and grouped them in 20 categories. These included mental retardation, infantile autism, behavioral disorders, speech disorders, suspected developmental delay, cerebral palsy, congenital malformations, chromosomal aberrations, neuromuscular disorders, torticollis, brachial plexus injury, disorder of the joints, disorders of the eye, hearing loss, hydrocephalus, habitual tip-toeing, accidents, seizures, other neurological disorders, and other disorders.

Among the most common diagnoses were cerebral palsy, suspected developmental delay, congenital malformation, mental retardation, chromosomal aberration, and behavioral disorders.¹⁰ IVF children face a risk of cerebral palsy that is almost four times higher and a risk of congenital malformations that is almost twice as high than children conceived naturally. These rather disturbing results can partly be explained by the large incidence of twins and higher-order pregnancies and associated problems, in particular low gestational age and low birth weight. For IVF singletons, the risk of cerebral palsy is nearly three times higher and the risk of congenital malformations remains twice that of the control population.

Ectopic Pregnancies

It has long been standard practice in the ART industry to cryopreserve embryos produced during IVF. Different reasons have been offered for cryopreserving an embryo. Some parents wish to preserve excess embryos for later use; others find it ethically unacceptable to authorize the destruction of their embryos; still others are simply unclear about what to do with their excess embryos. According to a survey conducted in 2003 by the American Society for

⁸ K. Duckitt, "Infertility and Subfertility," *Clinical Evidence* 9 (2003).

⁹ David L. Healy and Kerry Saunders, "Follow-up of Children Born after in-Vitro Fertilisation," *The Lancet* 359, no. 9305 (2002); B. Strömberg et al., "Neurological Sequelae in Children Born after in-Vitro Fertilisation: A Population-Based Study," *The Lancet* 359 (2002).

¹⁰ Strömberg et al., "Neurological Sequelae in Children Born after in-Vitro Fertilisation: A Population-Based Study," p.463.

Reproductive Medicine (ASRM), approximately 400,000 embryos are currently cryopreserved at U.S. fertility clinics.¹¹

As for most other standard treatments in the ART industry, cryopreservation has long been deemed safe, yet an actual assessment of its safety has never been conducted. It was therefore with considerable surprise that in 2003 ART practitioners learned that frozen embryos seemed to be associated with a higher risk of ectopic pregnancies. An ectopic pregnancy is a pregnancy that takes place outside the womb, typically in the fallopian tube, ovary, abdomen, or cervix rather than in the lining of the uterus. The condition is potentially life-threatening both for the prospective mother and the child, and often leads to an abortion. Ectopic pregnancies affect approximately 1 percent of pregnant women.

Researchers at Brown University analyzed 490 pregnancies achieved with fresh embryos and found that only nine (1.8 percent) were ectopic. By contrast, six out of 19 pregnancies achieved with frozen embryos resulted in ectopic pregnancies.¹² According to the leading author, this is the first time that an association between frozen embryos and safety has been shown. Given the small size of the sample, researchers have been cautious in drawing firm conclusions, yet these results are suggestive enough to be taken seriously.

Craniosynostosis

Craniosynostosis is a rare birth defect that causes the premature closure of the cranium in small children. Between three and five babies in 10,000 are affected by this condition, recognizable by the abnormal shape of the cranium. The condition is not fatal but may require surgery to reduce pressure within the cranium. While the precise causes of premature cranial closure are unknown, craniosynostosis has been associated with several risk factors, including advanced maternal age and maternal smoking.

In a recently published study, a group of researchers with the CDC studied the association between three ART treatments (ovarian stimulation, IVF, and artificial insemination) and the incidence of craniosynostosis. Data was collected from four regions – San Francisco and Santa Clara counties in California, metropolitan Atlanta in Georgia, and the entire state of Iowa. The study authors were able to identify 99 cases of craniosynostosis, a significant number given the very low incidence of this birth defect. The authors matched these cases with 777 control mothers.

The study showed that babies conceived through ovarian stimulation, IVF, and artificial insemination face a risk three to four times higher of developing craniosynostosis than children

¹¹ Hoffman et al., "Cryopreserved Embryos in the United States and Their Availability for Research."

¹² Shaoni Bhattacharya, *Frozen IVF Embryos Linked to Ectopic Pregnancy* (New Scientist, October 15, 2003 [cited April 26, 2006]); available from <http://www.newscientist.com/news/news.jsp?id=ns99994277>; "Frozen Embryos: Higher Ectopic Pregnancies," *The Washington Times*, October 15, 2003.

conceived naturally.¹³ In the discussion of their results, the study authors were careful to examine several alternative factors that may explain a four-fold increase in the incidence of this birth defect. It is possible that an unrecognized medical indication, rather than the reproductive technology itself, is associated with this birth defect, though the study authors observed a similar increase in all three types of fertility treatments. Other factors such as smoking could also be associated with both infertility and craniosynostosis. In this study, however, smoking was not associated with this condition.

Beckwith-Wiedemann Syndrome

Recent studies suggest that ART technologies might affect the epigenetics of early embryogenesis and might cause birth defects. Beckwith-Wiedemann Syndrome (BWS) is a congenital defect characterized by excessive body growth. Primary symptoms include macrosomia (the excessive growth of the body), macroglossia (enlarged tongue), predisposition to embryonal cancer, and abdominal wall defects. Beckwith-Wiedemann Syndrome apparently is caused by an imprinting disorder on gene 15. In the general population, BWS accounts for approximately 1.3 cases per 100,000 liveborn babies; in other words, it is an extremely rare congenital defect.

The association between this disorder and assisted reproduction has been documented only very recently. There have been three unrelated studies showing an association between ARTs and BWS. Michael DeBaun and associates have been tracking cases of BWS in the United States since 1994. More recently, they have begun to include in their registry information about the method of conception (natural versus IVF) and the type of IVF procedure. The data shows that children conceived through IVF are six times more likely (4.6 percent versus 0.76 percent in the general population) to be born with BWS than naturally conceived children.¹⁴ A French study based on 149 cases of BWS found that six of these children were born after IVF. According to the author, this figure is three times higher than in the French general population and is highly significant.¹⁵ Finally, a similar study conducted in Britain and based on the same number of BWS cases (149) found the exact same number of children conceived through ART.¹⁶

¹³ Jennita Reefhuis et al., "Fertility Treatments and Craniosynostosis: California, Georgia, and Iowa, 1993-1997," *Pediatrics* 111, no. 5 (2003), p.1164-65.

¹⁴ Michael R. DeBaun, Emily L. Niemitz, and Andrew P. Feinberg, "Association of in Vitro Fertilization with Beckwith-Wiedemann Syndrome and Epigenetic Alterations of *Lit1* and *H19*," *American Journal of Human Genetics* 72 (2003).

¹⁵ Christine Gicquel et al., "In Vitro Fertilization May Increase the Risk of Beckwith-Wiedemann Syndrome Related to the Abnormal Imprinting of the *Kcnq1ot* Gene," *American Journal of Human Genetics* 72 (2003).

¹⁶ E.R. Maher et al., "Beckwith-Wiedemann Syndrome and Assisted Reproduction Technology (ART)," *Journal of Medical Genetics* 40 (2003).

Angelman Syndrome

Two recent studies have reported on cases of Angelman Syndrome.¹⁷ This disorder is characterized by severe mental retardation, delayed motor development, poor balance, and absence of speech, among other things. Angelman Syndrome is rare: It affects only one in 15,000 live births. The cases of Angelman Syndrome observed in these two studies were due to sporadic imprinting defects, which are considered extremely rare (one in 300,000 live births).

Given the small size of the sample under consideration – only three cases – it would certainly be premature to draw any firm conclusions based on this evidence. However, after excluding a variety of possible alternative explanations for the onset of this condition, both authors attribute it to ICSI. The ASRM panel of experts also identified Angelman Syndrome as a risk associated with assisted reproductive treatments, but was not prepared to make a causal connection between this birth defect and reproductive treatments.

The Cloacal-Bladder Exstrophy-Epispadias Complex

The cloacal-bladder exstrophy-epispadias complex identifies a combination of birth defects that include cloacal and bladder exstrophy and epispadias. Simply put, babies with this set of conditions are born with their bladder and/or their rectum outside their bodies. Epispadias is a congenital defect resulting in the urethral opening on the dorsum of the penis.

The cloacal-bladder exstrophy-epispadias complex is extremely rare. Bladder exstrophy accounts for 3.3 cases per 100,000 live births; cloacal exstrophy and male epispadias occur in only one in 300,000 and one in 117,000 births, respectively. Since IVF accounts for only 0.7 to 0.8 percent of live births in the United States, it would normally take years and an extensive monitoring system to detect a case. It is thus surprising to learn that recently, a group of researchers at Johns Hopkins University was able to identify four IVF children with the cloacal-bladder exstrophy-epispadias complex simply by reviewing all cases of this birth defect, 78 cases in total, referred to the university hospital and born between 1998 and 2001.¹⁸

Statistical analysis shows that IVF children are seven times more likely to be born with these malformations than children conceived naturally. Admittedly, the sample size is small, but considering the extremely low probability of this condition, the fact that the study authors were able to easily identify four cases is disturbing. This is a condition that, given the extremely small odds, should remain all but undetected. The fact that IVF children might be exposed to a much

¹⁷ Gerald F. Cox et al., "Intracytoplasmic Sperm Injection May Increase the Risk of Imprinting Defects," *American Journal of Human Genetics* 71 (2002); K.H. Ørstavik et al., "Another Case of Imprinting Defect in a Girl with Angelman Syndrome Who Was Conceived by Intracytoplasmic Sperm Injection," *American Journal of Human Genetics* 72 (2003).

¹⁸ *In Vitro Fertilization May Be Linked to Bladder Defects* (ScienceDaily, 2003 [cited August 2, 2005]); available from <http://www.sciencedaily.com/releases/2003/03/030319082147.htm>; Hadley M. Wood, Bruce J. Trock, and John P. Gearhart, "In Vitro Fertilization and the Cloacal-Bladder Exstrophy-Epispadias Complex: Is There an Association?," *The Journal of Urology* 169 (2003).

greater risk of contracting what can only be described as a dreadful condition gives reason for pause.

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Appendix D – Congressional Legislative Activities 2001-2004

CONGRESS	BILL	TITLE	SPONSOR	STATUS
105th	H.R.3133	Human Cloning Research Prohibition Act	Rep. Stearns, Cliff [FL-6]	2/11/1998 Referred to House Subcommittee on Health and Environment.
Prohibits the expenditure of federal funds to conduct or support any research on reproductive cloning involving humans, but allows for the use of somatic cell nuclear transfer for therapeutic purposes not involving human embryos or tissues.				
105th	H.R.922	Human Cloning Research Prohibition Act	Rep. Ehlers, Vernon J. [MI-3]	Reported (Amended) by the Committee on Science.
Prohibits the expenditure of federal funds to conduct or support any research on reproductive cloning involving humans, but allows for the use of somatic cell nuclear transfer for therapeutic purposes not involving human embryos or tissues. Also allows its use for cloning animals.				
105th	H.R.923	Human Cloning Prohibition Act	Rep. Ehlers, Vernon J. [MI-3]	3/14/1997 Referred to House Subcommittee on Health and Environment.
Makes it unlawful for any person to use a human somatic cell for the process of producing a human clone. Sets forth a civil money penalty.				
105th	S.1574	Human Cloning Prohibition Act	Sen. Campbell, Ben Nighthorse [CO]	1/27/1998 Referred to Senate Committee on Labor and Human Resources.
Makes it unlawful for any person to clone a human being, conduct research for such purposes, or otherwise create a human embryo. Prohibits federal funds from being used for such research. Sets forth a civil money penalty.				
105th	S.1595	Bill solely intended to establish a Commission to Promote a National Dialogue on Bioethics	Sen. Frist, Bill [TN]	2/2/1998 Referred to Senate Committee on Labor and Human Resources.
The Commission would provide an independent forum for broad public participation and discourse concerning important bioethical issues including cloning, and report to the Congress its recommendations concerning federal policy and possible congressional act.				
105th	S.1599	Human Cloning Prohibition Act of 1998	Sen. Bond, Christopher S. [MO]	2/3/1998 Referred to Senate Committee on Judiciary.
Criminalizes the use of human somatic cell nuclear transfer technology, and importing an embryo produced through such technology. Sets penalties of up to 10 years in prison, a fine, or both.				
105th	S.1601	Human Cloning Prohibition Act	Sen. Lott, Trent [MS]	2/11/1998 Made it to the Senate floor, but was met by a filibuster and the cloture vote failed. Vote. 42-54. Record Vote No: 10.
Criminalizes the use of human somatic cell nuclear transfer technology, and importing an embryo produced through such technology. Sets penalties of up to 10 years in prison, a fine, or both.				

105th	S.1602	Prohibition on Cloning of Human Beings Act of 1998	Sen. Feinstein, Dianne [CA]	2/3/1998 Referred to Senate† Committee on Labor and Human Resources.
Makes reproductive cloning of humans unlawful while allowing for therapeutic cloning.				
105th	S.1611	Prohibition on Cloning of Human Beings Act of 1998	Sen. Feinstein, Dianne [CA]	2/5/1998 Senate preparation for floor. Status: Read the second time. Placed on Senate Legislative Calendar under General Orders. Calendar No. 305.
Makes reproductive cloning of humans unlawful while allowing for therapeutic cloning. Sets forth, with respect to violations of the cloning prohibition, requirements for: (1) civil penalties; (2) civil actions; and (3) the forfeiture of certain property.				
105th	S.368	†	Sen. Bond, Christopher S. [MO]	2/27/1997 Referred to Senate Committee on Labor and Human Resources.
Prohibits the use of federal funds for research regarding the cloning of a human individual.				
106th	H.R.2326	Human Cloning Research Prohibition Act	Rep. Stearns, Cliff [FL-6]	7/7/1999 Referred to House Subcommittee on Health and the Environment
Prohibits the expenditure of federal funds to conduct or support any research on reproductive cloning involving humans, but allows for the use of somatic cell nuclear transfer for therapeutic purposes not involving human embryos or tissues. Also allows its use for cloning animals.				
106th	H.R.571	Human Cloning Prevention Act of 1999	Ron Paul [TX-14]	2/16/1999 Referred to House Subcommittee on Health and the Environment
Bans federal funds from being received by any business, institution, or organization that either engages in or is associated with human cloning.				
106th	S.2015	Stem Cell Research Act of 2000	Sen. Specter, Arlen [PA]	1/31/2000 Read twice and Referred to Senate Committee on Health, Education, Labor and Pensions
Bans reproductive cloning while allowing for the derivation of embryonic stem cells under a specific set of guidelines.				
107th	H.R.1260	Ban on Human Cloning Act	Rep. Kerns, Brian D. [IN-7]	8/3/2001 Referred to the House Subcommittee on Crime.
Prohibits any person from engaging in a human cloning procedure (the transfer of a nucleus of a human somatic cell into an egg cell from which the nucleus has been removed) with the intent of implanting the resulting cellular product into a uterus. Sets forth criminal penalties.				
107th	H.R.1372	Human Cloning Research Prohibition Act	Rep. Stearns, Cliff [FL-6]	4/16/2001 Referred to House Subcommittee on Health.
Bans reproductive cloning while allowing for the use of somatic cell nuclear transfer and other cloning technologies for therapeutic purposes.				
107th	H.R.1608	Human Cloning Prohibition Act of 2001	Rep. Ehlers, Vernon J. [MI-3]	6/14/2001 Referred to House Subcommittee on Crime.
Bans the use of somatic nuclear transfer unless the nucleus of the clonal cell has been modified to prevent it from fully developing.				
107th	H.R.1644	Human Cloning Prohibition Act of 2001	Rep. Weldon, Dave [FL-15]	6/20/2001 Hearings Held by the House Subcommittee on Health.
Prohibits any person or entity, in or affecting interstate commerce, from: (1) performing or attempting to perform human cloning; (2) participating in such an attempt; (3) shipping or receiving the product of human cloning; or (4) importing such a product.				
107th	H.R.2059	Stem Cell Research Act of 2001	Rep. McDermott, Jim [WA-7]	6/18/2001 Referred to House Subcommittee on Health.
Bans reproductive cloning while allowing for the derivation of embryonic stem cells under a specific set of guidelines.				

107th	H.R.2172	Cloning Prohibition Act of 2001	Rep. Greenwood, James C. [PA-8]	6/25/2001 Referred to House Subcommittee on Health.
Amends the Federal Food, Drug, and Cosmetic Act to prohibit reproductive cloning, while allowing for further study on the potential of embryonic stem cells. Sets forth registration requirements for individuals who intend to perform human somatic cell nuclear transfer technology, including attesting that prohibitions will not be violated.				
107th	H.R.2505	Human Cloning Prohibition Act of 2001	Rep. Weldon, Dave [FL-15]	7/31/2001 Passed House by recorded vote: 265 - 162 (Roll no. 304).
Prohibits any person or entity, in or affecting interstate commerce, from: (1) performing or attempting to perform human cloning; (2) participating in such an attempt; (3) shipping or receiving the product of human cloning; or (4) importing such a product.				
107th	H.AMDT. 284 to H.R.2505	Amendment to Human Cloning Prohibition Act of 2001	Rep. Scott, Robert C. [VA-3]	7/31/2001 Agreed to by voice vote.
Requires the General Accounting Office to conduct a study within four years of enactment of H.R.2505 to assess the need (if any) for amendment of the prohibition on human cloning.				
107th	H.AMDT. 285 to H.R.2505	Amendment to Human Cloning Prohibition Act of 2001	Rep. Greenwood, James C. [PA-8]	7/31/2001 Failed by the Yeas and Nays: 178 - 249 (Roll no. 302).
Amendment in the nature of a substitute sought to ban the use of human somatic cell nuclear transfer technology to initiate a pregnancy but allow the use of somatic cell nuclear transfer technology to clone molecules, DNA, cells, or tissues.				
107th	H.R.2608	Cloning Prohibition Act of 2001	Rep. Greenwood, James C. [PA-8]	7/31/2001 Referred to House Subcommittee on Health.
Amends the Federal Food, Drug, and Cosmetic Act to prohibit reproductive cloning, while allowing for further study on the potential of embryonic stem cells. Sets forth registration requirements for individuals who intend to perform human somatic cell nuclear transfer technology, including attesting that prohibitions will not be violated.				
107th	H.R.2747	Stem Cell Research for Patient Benefit Act of 2001	Rep. DeGette, Diana [CO-1]	8/10/2001 Referred to House Subcommittee on Health.
Requires the director of NIH to conduct or support research using human embryonic and fetal tissue stem cells in accordance with the National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells.				
107th	H.R.2863	To direct the Secretary of Health and Human Services to establish and maintain a panel to provide expert scientific recommendations in the field of cell development.		9/17/2001 Referred to House subcommittee. Status: Referred to the Subcommittee on Health.
107th	H.R.3495	Human Cloning Prevention Act of 2001	Rep. Paul, Ron [TX-14]	12/28/2001 Referred to House Subcommittee on Health.
Bans federal funds from being received by any business, institution, or organization that either engages in or is associated with human cloning.				
107th	H.RES.21 4	Resolution urging the consideration of HR2505	Rep. Myrick, Sue [NC-9]	7/31/2001 Passed/agreed to in House. Status: On agreeing to the resolution Agreed to by the Yeas and Nays: 239 - 188 (Roll no. 300).
Sets forth the rule (modified closed) for the consideration of H.R. 2505 (human cloning prohibition).				

107th	S.1758	Human Cloning Prohibition Act of 2001	Sen. Feinstein, Dianne [CA]	12/3/2001 Referred to Senate Committee on the Judiciary.
Bans human cloning, but explicitly allows for therapeutic cloning and reproductive cloning of animals.				
107th	S.1893	Human Cloning Ban and Stem Cell Research Protection Act of 2001	Sen. Harkin, Tom [IA]	3/5/2002 Referred to Senate Committee on Health, Education, Labor, and Pensions. Hearings held.
Bans human reproductive cloning, but allows cloning for the purposes of biomedical research – therapeutic cloning.				
107th	S.1899	Human Cloning Prohibition Act of 2001	Sen. Brownback, Sam [KS]	1/28/2002 Referred to Senate Committee on the Judiciary.
Prohibits any person or entity, in or affecting interstate commerce, from: (1) performing or attempting to perform human cloning; (2) participating in such an attempt; (3) shipping or receiving the product of human cloning; or (4) importing such a product.				
107th	S.2076	Human Cloning Prohibition Act	Sen. Dorgan, Byron L. [ND]	4/9/2002 Referred to Senate Committee on the Judiciary.
Prohibits any person from conducting or attempting to conduct human cloning (defined as implanting the product of somatic cell nuclear transfer or any other cloning technique into a uterus or the functional equivalent of a uterus).				
107th	S.2439	Human Cloning Prohibition Act of 2002	Sen. Specter, Arlen [PA]	5/1/2002 Referred to Senate Committee on the Judiciary.
Amends the federal criminal code to prohibit human cloning, while amending the Public Health Service Act to require research involving nuclear transplantation to be conducted in accordance with certain federal standards for the protection of human subjects.				
107th	S.704	Human Cloning Prohibition Act	Sen. Campbell, Ben Nighthorse [CO]	4/5/2001 Referred to Senate Committee on Health, Education, Labor, and Pensions.
Makes it unlawful for any person to engage in a human cloning procedure. Prohibits the expenditure of any federal funds related to human cloning research. Sets civil and criminal penalties for violators.				
107th	S.723	Stem Cell Research Act of 2001	Sen. Specter, Arlen [PA]	4/5/2001 Referred to Committee on Health, Education, Labor, and Pensions.
Would amend the Public Health Service Act to allow the Secretary of Health and Human Services to conduct, support, or fund research on human embryos for the purpose of generating embryonic stem cells under stipulated guidelines.				
107th	S.790	Human Cloning Prohibition Act of 2001	Sen. Brownback, Sam [KS]	4/26/2001 Referred to Senate Committee on the Judiciary.
Prohibits any person or entity, in or affecting interstate commerce, from: (1) performing or attempting to perform human cloning; (2) participating in such an attempt; (3) shipping or receiving the product of human cloning; or (4) importing such a product.				
108th	H.R.234	Human Cloning Prohibition Act of 2003	Rep. Weldon, Dave [FL-15]	3/6/2003 Referred to House Subcommittee on Crime, Terrorism, and Homeland Security.
Prohibits any person or entity, in or affecting interstate commerce, from: (1) performing or attempting to perform human cloning; (2) participating in such an attempt; (3) shipping or receiving the product of human cloning; or (4) importing such a product. Sets forth criminal penalties.				
108th	H.R.534	Human Cloning Prohibition Act of 2003	Rep. Weldon, Dave [FL-15]	2/27/2003 Passed House by the Yeas and Nays: 241 - 155 (Roll no. 39).
Bans the use of somatic nuclear transfer for both reproductive and therapeutic purposes, while allowing the techniques use in animal research and human cells other than human embryo cells or tissues.				
108th	H.AMDT.	Amendment to Human Cloning Prohibition	Rep. Scott, Robert C. [VA-3]	2/27/2003 3:25pm:On agreeing to the Scott (VA) amendment

	4 to HR534	Act of 2003		(A001) as modified Agreed to by voice vote.
Requires the General Accounting Office, after consultation with the National Academy of Sciences, to conduct a study to assess the need (if any) for amendment of the prohibition on human cloning contained in the bill.				
108th	H.RES.10 5	Providing for consideration of the Human Cloning Prohibition Act of 2003	Rep. Myrick, Sue [NC-9]	2/27/2003 Passed/agreed to in House.
Sets forth the rule for consideration of H.R. 534.				
108th	H.R.801	Cloning Prohibition Act of 2003	Rep. Greenwood, James C. [PA-8]	2/26/2003 Referred to House Subcommittee on Health.
Amends the Federal Food, Drug, and Cosmetic Act to prohibit reproductive cloning, while allowing for further study on the potential of embryonic stem cells. Sets forth registration requirements for individuals who intend to perform human somatic cell nuclear transfer technology, including attesting that prohibitions will not be violated.				
108th	H.R.916	Human Cloning Research Prohibition Act	Rep. Stearns, Cliff [FL-6]	3/10/2003 Referred to House Subcommittee on Health.
Prohibits the expenditure of federal funds to conduct or support any research on the cloning of humans, while allowing federal funding for cloning animals and human cells other than human embryo cells or tissues.				
108th	H.R.938	Human Cloning Prevention Act of 2003	Rep. Paul, Ron [TX-14]	3/10/2003 Referred to House Subcommittee on Health.
Bans federal funds from being received by any business, institution, or organization that either engages in or is associated with human cloning.				
108th	S.245	Human Cloning Prohibition Act of 2003	Sen. Brownback, Sam [KS]	1/29/2003 Referred to Senate Committee on Health, Education, Labor, and Pensions.
Amends the Public Health Service Act to prohibit any person or entity, in or affecting interstate commerce, from knowingly: (1) performing or attempting to perform human cloning; (2) participating in such an attempt; (3) shipping or receiving an embryo produced by human cloning or any product derived from such an embryo; or (4) importing such an embryo. Sets criminal and civil penalties for violators.				
108th	S.303	Human Cloning Ban and Stem Cell Research Protection Act of 2003	Sen. Hatch, Orrin G. [UT]	2/5/2003 Referred to Senate Committee on the Judiciary.
Amends the Federal criminal code to prohibit human cloning, while amending the Public Health Service Act to require research involving nuclear transplantation to be conducted in accordance with certain federal standards for the protection of human subjects.				

Source: The Center for Public Integrity (<http://www.publicintegrity.org/genetics/report.aspx?aid=193&sid=200>).

