zyme's test, which screens the nine chromosomes that are most often abnormal, increases the likelihood that an embryo with a normal set of chromosomes will be placed in the woman's womb.

Ethicists have been discussing the proper uses of PGD for about a decade, but no medical organization in the United States has issued comprehensive guidelines. The American Medical Association Code of Medical Ethics approves of PGD "to prevent, cure or treat genetic disease," and opposes it to select for "non-disease related characteristics or traits." In the United States, the practice of medicine is regulated at the state level; no state has a law or set of regulations that comprehensively govern PGD. England and Australia have set up agencies that have authority over PGD, but they have not yet resolved some of the more ethically controversial policies. As preimplantation genetic diagnosis is likely to grow rapidly in Europe, Australia, and the United States, the need to resolve issues is pressing.

What are the key issues? The threshold moral question is: Should PGD ever be used at all? In choosing PGD, a couple knowingly creates embryos, some of which will not be transferred to the womb. Consider the typical case of a family at risk for a severe autosomal recessive (single gene) disorder. To maximize the chance of having a pregnancy that results in the birth of a child free from the disease, the physicians will harvest about ten eggs, create as many embryos, test all of them, and transfer two unaffected embryos (if there are two) into the woman. Healthy embryos may be saved, but all affected embryos will be destroyed.

Is it ethically permissible to conceive embryos under such technological constraints? Certainly, the goal sought by the couple—to conceive and bear a healthy child—is good. But what of the means to achieve it? Catholic doctrine teaches that it is immoral to isolate procreation from conjugal love, and thus forbids the use of in vitro fertilization as a treatment of infertility. Although no papal encyclical directly discusses PGD, there is no doubt that the Roman Catholic church would condemn a procedure that destroys human embryos. Orthodox Jews and many conservative Protestant sects would almost certainly take a similar position. Most liberal Protestant groups would condone PGD.

The contrasting views turn on two questions: (1) When does life begin and (2) under what circumstances, if any, is it permissible to end a human life? Theological discourse on the beginning of a human life has an

ancient history and, not surprisingly, the great world religions do not hold uniform views. The Catholic teaching is that ensoulment (equivalent to the beginning of humanhood) occurs at the moment of conception, whereas Islam teaches that ensoulment occurs 40 days after conception. Neither of these religions countenances abortion. Many liberal Protestant groups sidestep the question of when human life begins, as they must if their theology accommodates abortion.

Until recently, theologians had no reason to ponder the distinction between fertilization and implantation. However, because extrauterine fertilization creates a conceptus that cannot attain full humanhood unless it is placed in the womb, it is possible to argue that its destruction is not tantamount to abortion. Indeed, to argue that an unimplanted human blastocyst has the moral worth of an infant risks defining a human as nothing more than a diploid set of genes, for a frozen conceptus is little more than this. Such a position flirts with biological determinism.

If one can accept the premise that a morally valued human life begins only at the moment of *implantation*, then theological and ethical objections to in vitro fertilization, PGD, and the use of certain contraceptive agents (the "morning-after pill") vanish. However, the decision to define humanhood as beginning at the moment of implantation does not clear the ethical path for approval of PGD, coupled so tightly as it is with making choices about the value of one conceptus over another. As soon as one has granted the point that there are circumstances in which one embryo is more valuable than another (such as in choosing to begin a pregnancy with an embryo not destined to have a fatal disease rather than with one with such a genetic burden), one has agreed that not all human lives are equal. Does anyone have the right to define the criteria upon which to choose the most valuable among embryos? In our constitutional democracy, it is the woman who provided the eggs and who wants the pregnancy—for only she can consent to the placement of the embryo in her body.

Whatever one's theological position on the question of ensoulment or the morality of abortion, one can sympathize with the urgent desire of an at-risk couple to avoid the birth of a child destined to die slowly and horribly or to live a life burdened with severe disability. But where is the boundary that defines the severity of the burden that makes the act of choosing ethically tolerable? No two genetic diseases are alike. Tay-Sachs disease (TSD) is a horrible degenerative disease of which

young children die slowly over several years. Virtually every woman who learns that the fetus she is carrying has TSD chooses to terminate the pregnancy. Thirty years ago, most children with cystic fibrosis died before adolescence; today many affected children will live into their 30s, some longer. PGD is now being used to avoid implanting embryos that would be born with cystic fibrosis. Given the progress in caring for individuals with CF, some would question the morality of using PGD to avoid births of children with this disorder. PGD is now also available to older women who wish to avoid parenting a child with Down syndrome. Yet, many couples are willing—even eager—to adopt children with Down syndrome.

For decades, clinical geneticists and obstetricians have steadfastly refused to use amniocentesis and fetal chromosome analysis to sex a fetus in response to similar requests. Social sexing has been condemned as devaluing fetuses of one sex in favor of another, an inappropriate use of scarce technology, and a step toward eugenics. But what is the moral difference between seeking to implant an embryo unaffected with cystic fibrosis and seeking to implant one of a particular gender? Is using PGD to avoid the birth of a child with CF morally acceptable because of the severity of the disorder, its early age of onset, or its limited prospects for cure? Significant gains in treating children with CF suggest that many of the affected children born today have good prospects for living into their middle years, and there is every reason to hope for further therapeutic advances over the next decade.

The first use of PGD was to sex embryos so that a couple at risk for having a child with a serious sex-linked disorder could avoid that fate. As such disorders only affect boys, the selection of female embryos for transfer ensured the birth of a child without the particular disease. Today, a few couples who can afford it are seeking to use PGD simply because they want to have a baby of a particular sex. Imagine the well-heeled couple with three daughters who, nevertheless, yearn for a son. Although the British and Australian regulatory agencies will not permit this use of PGD, a growing number of clinics in the United States will choose and transfer an embryo of the desired sex. This is a sharp break with established tradition, but is it wrong? Many people clearly view such decisions as within a zone of privacy that should not be regulated by government. Many other people view PGD for selecting the sex of a baby as morally reprehensible. One

could even imagine that some state legislatures would enact laws (probably unconstitutional) to forbid this practice.

The European Society for Human Reproduction and Embryology views social sexing as unethical, but it does not explain its reasons. The scarce availability of the service, an argument often made in the early days of a new technology, is no longer a credible objection to limiting its application. Indeed, in the United States, social sexing is emerging as just another expensive option for the wealthy, one that is not likely to be any more objectionable than buying expensive automobiles while Africa starves.

One of the most rapidly growing applications of PGD is to identify and avoid embryos that have chromosomal abnormalities, a condition called aneuploidy. The best-known example of this is Down syndrome, in which affected persons have an extra chromosome 21. Abnormalities involving the number of sex chromosomes (which cause comparatively less severe, but still significant, clinical problems) are fairly common (affecting about 1 in 200 live-born children). Aneuploidy is quite common and is a major cause of spontaneous abortion. It is an important possible problem for older (>35) women, infertile women, and couples in which one partner has a type of unusual chromosome called a balanced translocation. For these reasons, there is a growing interest in routinely testing all IVF embryos for aneuploidy. In the near future, it is likely that screening with a panel of 24 probes (one for each human autosome plus the X and Y) will be offered to every IVF couple. This is a standard that in the United States might well be driven by fear of litigation. Given its prevalence among embryos, the severity of the disabilities associated with most forms of aneuploidy, and the existence of a screening test, it would be difficult to defend a clinician's decision not to urge that it be performed.

Some discern especially troublesome ethical issues when a couple chooses IVF and PGD to bear a child for the primary purpose of using him or her as a tissue donor to attempt to save the life of an existing child affected with a fatal disorder. Such babies have been nicknamed "savior children." Between 1985 and 1995, several of these poignant cases, which involved efforts to save the lives of children with Fanconi anemia (FA), an autosomal recessive disorder characterized by bone marrow failure, leukemia, and high risk for other cancers, became national news. Until ad-

vances involving PGD, the only effective treatment was bone marrow transplant, a therapy that was far more likely to provide a cure if the cells were donated by a sibling who had exactly the same HLA gene pattern. Unfortunately, for a couple with an affected child, each new pregnancy carries a one-in-four risk that the fetus, too, will have the disease, and the odds of an HLA match are comparatively low. Once it became possible to use PGD to identify the particular HLA genes carried by an embryo, hope for curing children with FA soared. Instead of proceeding pregnancy by pregnancy while time ran out on a dying child, couples could use IVF to screen many embryos for a potential donor sibling.

In 2000, a clinical research team at the University of Minnesota School of Medicine, working with a team at the Illinois Masonic Medical Center, became the first to successfully treat a child with FA with tissue obtained from a younger sibling conceived by using IVF combined with PGD. The Nash family (the couple has permitted public use of their name) had a daughter who was dying of FA. They used IVF to create several embryos, one of which was both an HLA match to the little girl and free from FA. The resulting pregnancy led to the birth of a healthy boy in August of 2000. Several weeks later the team infused blood collected from the placenta and umbilical cord (which contain bone marrow stem cells) into his older sister. Four years later, her blood and immune systems are normal, and she appears to be cured.

The jubilant publicity surrounding the Nash case engendered hundreds of requests from couples around the world with an ill child (the list of disorders which might be cured includes leukemias, lymphomas, autoimmune diseases, severe anemias, and some biochemical disorders) who might also be saved by this new approach. This led some bioethicists to warn about the dangers of what they call the commodification of human embryos. Recalling that in earlier days some couples had aborted fetuses that were not HLA-matched so that they could quickly try again to conceive a donor sibling, the bioethicists asked whether it was proper to use IVF and PGD to create a child for therapeutic purposes. Some also worried that when they eventually learn the reason for which they were conceived, "savior siblings" will be deeply troubled by the behavior of their parents.

I find the first concern ridiculous and the second unlikely. In this age of small families, I often hear parents say that they are having a second child so that the first will not be an only child—as though an only child

somehow has been denied something of fundamental importance in the human experience. Parents who decide to add a child to the family in part for that reason do not love the younger sibling any less. Similarly, parents who bring forth savior siblings do not love them any less. They do not offer them for adoption after their bone marrow has been harvested. I think it far more likely that such children become part of a nuclear family that is bound by extraordinary ties.

In the United States, years of ethical debate over the proper use of a new procedure in medicine are often resolved by decisions taken by insurance companies and HMOs about what services they will rule are medically necessary. In 2004, some third-party payers reached rough consensus that PGD may be medically necessary (read "covered") in the circumstances where both partners are carriers of an allele for a recessive disorder, one partner carries a gene for a dominant disorder, or one partner carries a gene for an X-linked disorder. In addition, the disorders in question must be potentially lethal or disabling and have poor treatment options, there must be a reliable test, and the woman must affirm that she does not wish to undergo prenatal diagnosis and selective abortion. Some third-party payers have decided that they will not pay for PGD to screen out embryos destined for late-onset adult disorders such as colon cancer, but most have not issued guidelines. None have agreed to pay for what is called "social sexing."

In addition to covering couples burdened with single-gene disorders, some insurers that cover infertility services have agreed to cover PGD in three circumstances: inability to become pregnant after three IVF cycles, advanced maternal age (the eggs of women over 35 are more likely to have one or more abnormal chromosomes), and when one partner carries a balanced translocation (a normal complement of chromosomes in which two are joined in a way that can often lead to an abnormality in the chromosome complement of the egg).

Insurers do not lightly agree to cover new services. They carefully scrutinize the reports and opinions of relevant professional organizations. Each year, the European Society of Human Reproduction and Embryology, one of the most influential organizations in the PGD field, collects data from the voluntary report of about 25 European clinics. The most recent available report (2002) brought the number of PGD cases up to 1,561. The data show that 370 cases were to screen for single-gene

disorders, 334 were for recurrent pregnancy loss, and 78 were for social sexing to balance children by gender. Two encouraging findings were that embryo biopsy was successful 97% of the time and that diagnostic efforts succeeded about 86% of the time. Successful pregnancies were established in about 20% of embryo transfers, not much different from the monthly rate from sexual intercourse.

The European clinics reported 13 patient requests that they had rejected on ethical grounds. These included requests for an embryo that would become an HLA-matched (savior) sibling, requests when the risk of affected offspring was low, a request to identify a male embryo that would have been infertile, and a request to identify and transfer an embryo destined to have achondroplasia (a dominant disorder that is the most common cause of short-limbed dwarfism). The last request is of particular interest because, in making it, the parents inverted the standard notion of "normalcy." A couple in which one parent has achondroplasia was seeking PGD to avoid the birth of a normal child in favor of one who would also have achondroplasia.

In 2007, the Preimplantation Genetic Diagnosis International Society (PGDIS) published voluntary guidelines for PGD clinics. It noted that PGD has been provided to more than 30,000 patients at risk for bearing children with more than 170 different genetic disorders. The PGDIS recognized an expanded list of indications. In addition to couples at risk for bearing children with single gene disorders, it approves PGD to select for embryos that will be tissue matches with existing siblings who are ill and need a bone marrow transplant, and for adults with unusual chromosomal conditions called balanced translocations (that can become unbalanced as the egg or sperm is formed, causing serious birth defects). More controversial was the decision by the organization to recognize that recurrent pregnancy loss and infertility of unknown cause were proper indications for the technology. A recent paper in the *New England Journal of Medicine* reports no benefit of PGD to such couples, a finding that drew a sharp retort from some PGD practitioners that the authors were just not as practiced in the art as they should have been. The rationale to offer PGD to infertile couples is that many may be burdened with recurrent pregnancy loss at a very early stage due to chromosomal abnormalities in the embryo and that PGD can guarantee that an embryo without major chromosomal defects will be placed for implantation.

The most troublesome ethical issue raised by rapid developments in PGD (but which still lies in the future) is whether there should be limits placed on the use of diagnostic techniques to select for positive (as opposed to avoiding negative) traits in children. For half a century, novelists, futurologists, geneticists, and ethicists have worried that our ability to decode the human genome ordains a future in which we can first pick, and ultimately, shape important traits in offspring. No one has raised this concern more effectively than Aldous Huxley in his prescient novel, *Brave New World* (1932). In the chilling opening chapter, the Director of the Hatchery in London explains Bokanovsky's process, an extrauterine technology that combines cloning with embryo manipulation to create up to 96 identical individuals, each fit for a particular station in socioeconomic life. In Huxley's world, many human embryos have substantial cognitive limits which will make them comfortable in performing sets of repetitive, uninteresting, but essential tasks (please substitute here your own least favorite job) in the society.

I do not fear that we will soon be using a technology reminiscent of Bokanovsky's process to create drones. But it would not surprise me if by mid-century, wealthy couples routinely use PGD to accomplish much more than avoiding the birth of a child with a severe, untreatable disorder. PGD is already being used to identify embryos at risk for late-onset adult diseases such as Huntington's disease, polycystic kidney disease, and colon cancer. If one is taking the trouble to avoid giving birth to a child with one severe disorder, does it not make sense to avail oneself of tests to screen out scores more? Currently, there are not enough available cells to obtain the DNA needed for such mass screening. However, Alan Handyside, the first to successfully perform PGD, has managed to grow hundreds of cells from a single cell plucked from an eight-cell mouse embryo. If that could be done routinely with human cells, it would be possible to develop a much broader approach to screening human embryos. Such a service would be offered to the tens of thousands of couples who each year use IVF to circumvent infertility. The rationale: You have worked so hard to have a child, should we not use tests to rule out unanticipated risks and select the embryo that appears to have the best chance of being the healthiest child?

The use of PGD to screen for gene variations that appear to enhance socially valued traits (intelligence, musical talent, physical prowess) is a