From the beginning of recorded history, there is evidence of humankind’s profound desire to glean information about fertility, pregnancy, and reproduction. The ancient Egyptian text known as the Berlin Papyrus, which dates from around 1350 to 1200 B.C.E., discusses a test for determining a baby’s sex. As early as 1300 C.E., the Chinese formulated a calendar to divine the sex of the baby based on the month of conception and the age of the mother. The Mayans had a predictive model similar to the Chinese pregnancy calendar.

After Anton van Leeuwenhoek discovered sperm in 1677, using the microscope that he is recognized as inventing, men would meet to examine their sperm, whereby they predicted the appearance of their offspring, whose specific characteristics they believed could be seen in the amplified images.

Historically, the desire to determine the characteristics of the fetus was often rooted in misogynistic perceptions of the heightened value of male children. It was widely assumed that the male, via his sperm, was solely responsible for the characteristics of the resulting child, and women were valued predominantly for their ability to deliver children, specifically, male children. In contrast, an American study found that patients undergoing fertility treatment expressed a slight preference for female offspring. One must be careful, nonetheless, to realize that the pursuit of information regarding fertility and the fetus is often not benign, being entrenched in a system of female oppression and marginalization.

Over time, much more effective techniques have been developed to determine information both during and prior to pregnancy. Initial tests were invasive and included amniocentesis and chorionic villus sampling. And new technology is able to determine much more than sex. Today, technology can determine the chromosomal makeup of a fetus and identify hundreds of diseases and disease predispositions during pregnancy. Furthermore, the analyses of in vitro embryos via preimplantation genetic diagnosis has allowed for some prediction of the child’s health status, even prior to the establishment of a pregnancy. Most recently, techniques have been developed that go beyond detecting information about the embryo prior to implantation or the fetus during gestation. Such techniques, currently still in the experimental stage, would allow for the manipulation of embryos in ways that heretofore could only be imagined. These advances have the potential to fundamentally change the way in which we envision our developing offspring. They may also have unforeseen effects on the children that result or on future generations. Given the potential impact of such manipulations on children born several generations in the future, the ethical implications of current actions may not be realized for many years to come.

Medical science at its core aims to preserve health and eliminate disease. While the development of diagnostic modalities to predict the health of resulting children has been a fundamental aim underpinning research into prenatal and preimplantation diagnostic modalities, the knowledge gained has in some cases been utilized for nonmedical purposes. A common theme in scientific discovery is the application of findings in ways that were not the primary intent. As an example, amniocentesis developed to determine whether the pregnancy is chromosomally normal also provides information about the sex of the fetus, which normally does not affect health. The emerging gene-editing technologies that could be used to repair mutated disease-causing genes in an em-
bryo will presumably also be able to be used to alter traits unrelated to disease. And yet, I will argue, the desire to preserve the mystery of reproduction remains a central value in our quest to reproduce. This yearning to maintain the mysteries surrounding reproduction will likely temper the development of strategies to alter our genome and affect the genetic identities of our offspring.

From Prenatal Testing to Embryo Manipulation—Effects of Reproductive Decision-Making

Prenatal diagnosis has evolved toward earlier, more accurate, safer, and less invasive technologies. As early as the 1950s, amniotic fluid was extracted to determine the severity of fetal disease due to Rhesus-factor incompatibility between the fetus’s and the mother’s blood. By the 1960s, karyotypes could be identified from fetal cells in the amniotic fluid, and the first diagnosis of trisomy 21 via amniocentesis was made. The technique of chorionic villus sampling, in which cells from the fetal placenta are extracted and used to determine both the fetal karyotype and fetal genetic disease, was introduced in the 1980s. Noninvasive ways of examining the fetus trace back to the development in the late 1950s of ultrasound techniques for detecting structural abnormalities and markers for disease during pregnancy. In the 1970s, a second-trimester noninvasive test was developed for the detection of neural tube defects. It utilized maternal blood to look for levels of alpha fetal protein. More recently, noninvasive prenatal screening conducted earlier in the pregnancy has allowed for the detection of both the chromosomal makeup of the developing fetus as well as genetic diseases in the fetus. This testing occurs without any physical risk to the pregnancy or the fetus.

In an effort to know as much as possible as early as possible, the field of preimplantation genetic diagnosis offers an approach to screening that occurs prior to pregnancy. In PGD, embryos created through in vitro fertilization are biopsied to remove one or several cells, and the cells are analyzed to determine the genetics of the embryo. The first reported use of this technology was in 1991 and was for sex determination to avoid conception of a fetus at risk for X-linked disorders. Currently, both the chromosomal makeup and hundreds of disease mutations can be identified in the early preimplantation embryo. In principle, any disease whose genetic basis can be determined can be screened for in the early embryo.

From an ethical standpoint, the vital importance of PGD is the ability to detect nonviability or disease prior to the transfer of an embryo into the uterus. The ability to exclude affected embryos from implantation has allowed women to avoid miscarriage and the difficult decision of continuing or terminating an affected pregnancy.

While PGD has had a powerful effect on reproduction, it can determine only whether an embryo carries the disease of interest. When affected embryos are not transferred, the disease in the offspring is avoided. PGD does not allow for the “repair” of affected embryos. For some reproductive couples, no unaffected embryos exist, and therefore the decision they face is between pursuing a pregnancy, with the knowledge that their fetus and resultant child will be affected by a given disease, or seeking out other family-building options.

Mitochondrial replacement technology was a first step in actual repair of the early embryo. Using this modality, a woman carrying mitochondrial disease could give birth to a child who contains all the genetic material from her egg’s nucleus but that does not contain the diseased mitochondria from her egg’s cytoplasm. The embryo as a whole can be “repaired,” but the actual defect in the mitochondria is not repaired. Instead, the defective mitochondria are replaced with mitochondria from a healthy donor, which is then inherited by the resulting child in addition to the genetic mother’s nuclear DNA. Since mitochondria are inherited maternally, boys born from embryos created through mitochondrial replacement cannot pass along this change to their offspring, while girls will pass along the donor DNA to future generations.

The first reported use of this technique to produce a successful pregnancy was in 2016. According to the scientist involved, the embryo manipulation was undertaken in Mexico, due to the absence of laws prohibiting such tech-
niques there. The technique is now allowed in the United Kingdom but not in the United States.6

The National Academies of Sciences, Engineering, and Medicine addressed the ethical, social and policy considerations of mitochondrial replacement in a 2016 report. The NASEM committee concluded that prospective parents wish to use this technique to avoid manifesting serious mitochondrial disease is justifiable and that clinical research on the use of this technique could be permitted, within limits. The report went on to assert that the limits should be focused on protecting the health and well-being of children who would be born following mitochondrial transfer and that consideration should be given to using this technology for male offspring until adequate safety data could be collected, such that the children born after mitochondrial replacement would not pass mitochondria on to future generations.7

A further step in altering the early embryo came in 2015, with the first reported use of the CRISPR–Cas9 gene-editing system to repair a disease mutation in the DNA of a nonviable embryo.8 Earlier this year, scientists announced that they had used this technique to repair a gene in several dozen early embryos carrying a mutation known to cause hypertrophic cardiomyopathy.9 If transferred to the uterus, such an embryo would result not only in the birth of a child whose DNA does not carry the mutation leading to this disease but also to a lineage in which the repaired gene would be perpetuated in all future generations resulting from that child. There have not yet been reported attempts to transfer such embryos to the uterus, and no safety data exist regarding the health of children after this type of manipulation at the embryonic stage. This gene-editing technology allows for direct manipulation of DNA. The application of this technology to repair disease-causing mutations in the preimplantation embryo has opened up the possibility of eradicating disease by altering a portion of the genome in germ cells (egg or sperm) or at the earliest stage of embryonic development. Up to this point, embryos could be identified as affected by a disease or not. Such embryos could be transferred or not. This is the first time in the history of reproductive science that the possibility of eradicating disease by repairing the disease-causing genetic mutation shows promise of becoming a reality.

Societal, environmental, and ethical concerns are heightened in this situation, as the results of experiments in germline editing have the potential to affect unlimited future generations. An ad hoc group of scientists involved in this research have called for a moratorium on the clinical use of CRISPR–Cas 9 for germline genome modification in human embryos until a deeper understanding of the implications of this technology for the potential offspring as well as for society are better understood.10 There have also been calls for special oversight of research that has clinical implications for germline editing, both as relates to currently available technologies as well as those that are being developed.11

In response to the ability to edit genes within human cells, the National Academies of Science, Engineering, and Medicine convened a panel of experts to consider the medical, social and ethical aspects of this emerging technology. The resulting document stated that clinical trials using heritable genome editing should be permitted only within a robust and effective regulatory framework and only for serious conditions in which there are no reasonable alternatives. The document goes on to state that regulatory agencies should not at this time authorize clinical trials of germline genome editing for purposes other than treatment or prevention of disease. This permissive stance toward gene editing for the prevention of disease opens up the possibility of social and legal acceptance of genetic repair of embryos for reproductive purposes in the United States.12

Ethical Issues and Clinical Possibilities

The ability not only to detect disease but also to eradicate it altogether may well change the way in which reproduction is understood.13 Such a change raises a host of questions. If we are able to avoid having a child with a disease, should we not do so? And if we choose not to do so, then are we being irresponsible in our role as parents? Does society have a role to play in ensuring that children are born in the best possible state of health? And if there is such a responsibility, will there also be financial and emotional supports in place to help those who wish to navigate this new landscape? If science allows us to change the genetics of preimplantation embryos, are we obligated to utilize this science? What then happens to women and couples who choose not to find out if they are at risk for having children with a given disease and opt against using this technology? Will the resulting children be discriminated against, or will their parents be deemed irresponsible? If such knowledge regarding disease risk in one’s offspring is deemed intrinsic to responsible parenting, what will happen to those who do not invest as much thought and effort into avoiding disease? And will this ultimately lead to an effort to control reproduction to avoid disease? Would society allow for the restriction of reproductive freedom in order to decrease disease burden?

These are all questions that need to be answered as gene-editing technologies are being developed. Ideally, guidelines for the utilization or decision against utilization of this emerging technology should be discussed at a societal and policy level prior to its implementation. Such a preemptive discussion will pave the way for the ethical incorporation of gene editing into the medical armamentarium.
Concerns are often raised that advances in gene-editing technology will lead to a mad rush of individuals and couples wishing to benefit from this technology in order to optimize the traits and characteristics of their offspring. In my experience as an obstetrician and reproductive endocrinology and infertility subspecialist, people want to have, not the best possible baby, but rather their own baby. They want a child whose traits they continually discover and who reflects them in ways that are not predictable. Even today, couples at risk for disease can in many cases opt to reproduce with the help of donor sperm or donor eggs. They often reserve this option as a last resort, going to great lengths to undergo preimplantation genetic diagnoses to identify unaffected embryos. Opposite-sex couples generally desire to enjoy the mysteries of the unknown when mixing their genes with that of their reproductive partner. They endeavor, not to improve on their own traits in their offspring, but rather to bring into the world a child who mirrors these traits. Same-sex couples share in this desire to have their genetics mirrored in their children. They will often use the gametes of one member of the partnership for a first child and gametes from the other partner for a subsequent pregnancy. Alternatively, lesbian couples can reproduce by selecting one partner’s egg and fertilizing it with sperm from her partner’s brother, therefore introducing elements from each of their genetic lineages into the child that is created. Similarly, for male couples, one of the males may fertilize an egg from his partner’s sister with his own sperm to achieve shared reproduction. This desire is born out in opinion polls. In 2016, the Harvard School of Public Health conducted a survey that found that 83 percent of Americans would outlaw genetic engineering to improve intelligence or physical characteristics.14

Furthermore, I believe that people are reticent to have a hand in determining the traits of their offspring for fear of being responsible if things don’t turn out as they had intended. When choosing to have children, there are no guarantees of health or intelligence or talent. There is a deep sense among parents that their role is to welcome and nourish a child, however that child comes to them. That is part of the bond established between parent and child. My sense is that intended parents do not want the burden of choice, lest it lead to undesired outcomes. When choice does not exist, acceptance is the norm. If choice leads to unforeseen outcomes, parents may blame themselves. This is a heavy weight to bear, and one that most parents would not select even if given the choice. For this reason, I believe that the new gene-editing technologies will, at least for the foreseeable future, be used only to avoid significant disease and disability and not for trait enhancement.

The initial use of such technology would likely be for couples at risk of conceiving a child with a severe genetic disease. One can imagine a spectrum of diseases, from those that lead to death or severe disability in early childhood to ones that cause only minor health issues. If gene editing is found to be safe and effective, one can imagine a rapid acceptance of it to avoid the sequelae that are inherent to having a child with a severe disease. Over time, the question arises as to whether people will choose to use gene editing not only to repair the genetic mutations of their resultant embryos but also to improve on nature. Will those with access to this technology choose to augment embryos to improve upon the natural traits, health, and abilities of the resultant children?

Questions about the use of enhancement raise significant concerns regarding eugenics and the value of designer children. Will our society be able to differentiate between disease eradication and trait augmentation? I wonder whether tampering to such an extent with reproduction is even a capacity that many—or even some—members of our society will deem desirable. In my experience, we humans have an innate understanding that reproduction leads to an outcome that is inherently uncertain. We are aware that we can predict neither how our children will be at birth nor how they will develop over time. We embrace this uncertainty, and it allows us to strive to raise our children to be the best possible versions of themselves. We rear our children with hope and anticipation, but with the knowledge that their development and strengths and weaknesses are not fully knowable. Such a process would be dampened if much of the future was predetermined, and this would take away much of the joy of raising children. There is a beauty in not knowing and in the randomness of reproduction. Many couples contemplating children wonder if the child will draw from traits possessed by one or the other and look to see how the mixing of their two genomes results in a unique yet recognizable variant of themselves. This desire will not so easily become obsolete.

As exemplified in the desire to determine the sex of the developing fetus throughout the centuries and among many different cultures, people do want information about what their children will be like. The next logical question is whether this translates into a desire to affect the sex of the developing fetus. A small but growing number of couples use in vitro fertilization to select the sex of the future child. Much of the uptake of this nonmedical utilization of technology has come from societies in which males are valued over females, and this has led to significant discussion in the scientific and popular literature. However, as a proportion of the general population, the number of individuals utilizing preimplantation sex selection is miniscule, and the press this use receives is out of proportion to its impact on sex ratios. The trend is troubling for the same reasons as stated above when discussing amniocentesis, namely, fears of discrimination against women and misogynistic undertones.
Yet, as discussed earlier, we know this may not always be the case in the United States. One of the studies cited found that when women undergoing in vitro fertilization were asked whether they would wish to determine the sex of their embryo and if so which sex they would theoretically choose, 61 percent of American women in a study at a fertility center in Boston stated that they would prefer a female. In my professional experience, I find that, in the majority of cases, couples opt not to know the sex of their children prior to pregnancy. Screening of embryos for aneuploidy is becoming commonplace in an effort to determine which embryos are most likely to implant and to prevent multiple attempts at pregnancy. As part of this testing, the sex of the embryos is known. And yet, it is the minority of patients who wish to select the sex of the embryo for transfer.

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Extrapolating from this, I think that, in the context of gene editing on embryos, potential parents will be likely to choose to eradicate significant disease from their genetic lineage. It is much less clear that such choices will expand to the desire to determine traits that are not associated with disease. Possibly—and indeed probably—a limited few individuals on the fringes of society may wish to genetically engineer their children, raising concerns that the lines between diseases and traits may become blurred. And yet, there is a completely different possibility: the ability to edit the genes of early embryos may lead society to a new introspection, one in which we reject the uncontrolled ability to influence the genetics of our offspring. The slippery slope of eugenics may indeed lead us uphill, to a better understanding of our innate desire to enjoy the randomness of reproduction and the beauty of creating something completely new from two unique individuals.

While there will always be members of society who will endeavor to use technology for purposes for which it was not intended, these will likely be a very small proportion of people. If gene editing turns out to be a viable option at the level of the preimplantation embryo, many will likely welcome the intervention as a way to avoid disease. However, it will not be universally adopted, even if it is logistically and economically readily accessible. At present, analysis for carrier status of hundreds of genetic diseases is available from a single tube of blood. Despite the ease of obtaining knowledge of potential disease in offspring, many couples opt against using the technology. Similarly, many people will not choose to undergo noninvasive prenatal testing or invasive testing if they are deemed at increased risk for having a child with a disease. Gene editing of preimplantation embryos will likely follow a similar trajectory, in which some will choose to avail themselves of this technology and others will not consider it of value. As a society, we have a responsibility to safeguard the reproductive decisions of the biggest stakeholders, the intended parents, whether they decide to exercise their right to the randomness of reproduction or whether they value eradicating disease in their children. Such safeguards should extend to the ethical use of this technology for repair of disease and should prevent unfettered access for uses that society deems unacceptable.

Before gene editing of embryos moves from theory and research into clinical practice—a rapidly approaching reality—stakeholders need to discuss and develop mechanisms to allow access for those who would benefit from the avoidance of disease in their children while setting boundaries for experimental uses that the majority of society considers unethical.


15. Jain et al., “Preimplantation Sex Selection Demand and Preferences.”