

Couples Cull Embryos to Halt Heritage of Cancer

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As Chad Kingsbury watches his daughter playing in the sandbox behind their suburban Chicago house, the thought that has flashed through his mind a million times in her two years of life comes again: Chloe will never be sick.

Not, at least, with the inherited form of colon cancer that has devastated his family, killing his mother, her father and her two brothers, and that he too may face because of a genetic mutation that makes him unusually susceptible.

By subjecting Chloe to a genetic test when she was an eight-cell embryo in a petri dish, Mr. Kingsbury and his wife, Colby, were able to determine that she did not harbor the defective gene. That was the reason they selected her, from among the other embryos they had conceived through elective in vitro fertilization, to implant in her mother's uterus.

Prospective parents have been using the procedure, known as preimplantation genetic diagnosis, or P.G.D., for more than a decade to screen for genes certain to cause childhood diseases that are severe and largely untreatable.

Now a growing number of couples like the Kingsburys are crossing a new threshold for parental intervention in the genetic makeup of their offspring: They are using P.G.D. to detect a predisposition to cancers that may or may not develop later in life, and are often treatable if they do.

For most parents who have used preimplantation diagnosis, the burden of playing God has been trumped by the near certainty that diseases like cystic fibrosis and sickle cell anemia will afflict the children who carry the genetic mutation that causes them. The procedure has also been used to avoid passing on Huntington's disease, a severe neurological disease that typically does not surface until middle age but spares no one who carries the mutation that causes it.

Couples like the Kingsburys, by contrast, face an even more complex calibration. They must weigh whether their desire to prevent suffering that is not certain to occur justifies the conscious selection of an embryo and the implicit rejection of those that carry the defective gene.

As doctors and genetic counselors at leading cancer centers like Memorial Sloan-Kettering in New York start to suggest the possibility of P.G.D., more young patients

are finding that their answer lies in trading natural conception for the degree of scientific control offered by the procedure. And if the growing interest in screening for cancer risk signals an expanded tolerance for genetic selection, geneticists and fertility experts say it may well be accompanied by the greater use of preimplantation diagnosis to select for characteristics that range from less serious diseases to purely matters of preference.

Already, it is possible to test embryos for an inherited form of deafness or a mild skin condition, or for a predisposition to arthritis or obesity. Some clinics test for gender. As scientists learn more about the genetic basis for inherited traits, and as people learn more about their genetic makeup, the embryo screening menu and its array of ethical dilemmas are only expected to grow.

“From a technology perspective we can test anything,” said Mark Hughes, director of the Genesis Genetics Institute in Detroit, who is performing P.G.D. this month for two couples who want to avoid passing on a susceptibility to breast cancer. “The issue becomes what is considered serious enough to warrant such testing and who decides that.”

The process is also difficult and expensive. P.G.D., which requires in vitro fertilization, can cost tens of thousands of dollars. While insurance companies often pay for the more traditional uses of the procedure, they have not done so for cancer-risk genes, fertility experts say. The barrier to affordability, some critics fear, could make preimplantation diagnosis for cancer risk the first significant step toward a genetic class divide in which the wealthy will become more genetically pure than the poor.

Knowing that Mr. Kingsbury had tested positive for the colon cancer mutation, the Kingsburys started with the basic laws of genetics: because children randomly inherit half of each parent’s genes, he had a 50 percent chance of passing it on. Since the mutation raises the risk of developing the cancer by about twentyfold, that means any child of theirs conceived the traditional way would have about a one in three chance of getting it, usually around age 45. Those who did develop the cancer would also have a nearly 90 percent chance of surviving it, but only if it was caught early. The jumble of odds meant little to the Kingsburys as they tried to think about starting a family while the cancer claimed Mr. Kingsbury’s second uncle. Then, from a cousin

of Mr. Kingsbury's who had also fought colon cancer, they heard about P.G.D., the technology that offered them a way to reload the genetic dice.

To do it, they had to overcome their own misgivings about meddling with nature. They had to listen to the religious concerns of Mr. Kingsbury's family and to the insistence of Ms. Kingsbury's that the expense and physical demands of in vitro fertilization were not worth it, given that the couple could probably get pregnant without it. They had to stop asking themselves the unanswerable question of whether a cure would be found by the time their child grew up.

It took them two months to make the decision. But every time Mr. Kingsbury looks at Chloe, with her blue saucer eyes and her tantrums that turn abruptly to laughter — and back — he knows it was worth it.

"I couldn't imagine them telling me my daughter has cancer," he said, "when I could have stopped it."

Shifting Medical Advice

Cancer-prone families are only just beginning to hear about P.G.D. in part because the procedure falls through the cracks in medicine. Oncologists tend not to think about family planning, and obstetricians tend not to think about cancer genetics. Doctors may also shy from raising the prospect of what some critics call "unnatural selection." For many couples, going to such lengths to ensure that a child will be born free of a predisposition to a certain kind of cancer is anathema. Breast and colon cancer, the two most common cancers for which genetic susceptibility tests are available, can be detected early and are often treatable, and even those who die of them often lead long and productive lives.

Many people without the risk-raising genes still get one of the cancers, and those who do carry the genetic mutations are just as likely as anyone else to develop other forms of the disease.

Prospective parents who want to avail themselves of P.G.D. must first undergo the same in vitro fertilization process often used to assist infertile couples, in which eggs are extracted from the mother and fertilized with the father's sperm in a petri dish. When the resulting embryos are three days old, doctors remove a single cell from each and analyze its DNA. Only embryos without the defective gene are then considered candidates to implant in the mother's uterus.

The out-of-pocket costs often exceed \$25,000, depending on how many in vitro cycles are required. Because embryos are selected for their genetic status, rather than solely by which look the healthiest, the chance that they will fail to develop after implantation is higher. And despite the birth of thousands of apparently healthy babies after P.G.D., there is still concern that the long-term effects of removing a cell from an eight-cell embryo have not been studied enough.

That has not stemmed the rising demand to screen embryos for cancer-risk genes. No one tracks the number of such procedures in the United States, but an article in next month's issue of The Journal of Clinical Oncology reports that clinics around the country have been quietly performing P.G.D. for hereditary cancers of the breast and the colon. The article, written by Dr. Kenneth Offit, chief of clinical genetics at Memorial Sloan-Kettering Cancer Center, suggests there would be even more interest in P.G.D. if oncologists were to begin informing prospective patients of the option.

About one in every 200 Americans carry a genetic mutation that makes them more susceptible to breast or colon cancer. The half-million or so who carry mutations in several genes associated with colon cancer have up to a 70 percent chance of developing the disease, compared with 6 percent for those with normal copies of the genes. One in eight American women will develop breast cancer in their lifetimes, but for those who carry mutant forms of the BRCA1 or BRCA2 genes, the risk jumps to one in two.

Until the last year or so, Dr. Offit said in an interview, he questioned the utility of P.G.D. for his patients, focusing instead on the increasingly effective prevention and treatment options for anyone born with an elevated cancer risk. Genetics, he said, is not necessarily destiny.

But learning of its existence, Dr. Offit noticed, could make many young patients less fatalistic about their genes and more optimistic about starting a family. The sense of relief it offered was especially strong among those who had seen a parent or a sibling die of cancer.

"Having seen so many children from cancer-prone families, I'm more sensitive to the sentiment that they would rather avoid the syndrome altogether," Dr. Offit said. "Our genetic counselors now try to bring up the potential of this technology in circumstances where we think it may be empowering to young couples."

Too Late for Some Carriers

If other cancer centers follow Sloan-Kettering's lead, the shift will still come too late for some cancer gene carriers. One woman, a professional in New York, said she blamed bad medical advice for her having possibly passed to her 4-year-old daughter a chance of developing breast cancer this is five times as great as that of women in the general population.

Unaware of P.G.D., she followed the counsel given to most women with a family history of breast cancer and had her children before getting tested for the gene. The logic is that women ought not worry about their genetic status until they can consider the most effective prophylactic measures, removing their breasts and ovaries.

But in postings to an online breast cancer support group, facingourrisk.org, the woman said she suspected that the prevailing unease over genetic selection and the question of when life begins also kept doctors from suggesting P.G.D.

"Those values should not be dictating recommendations by doctors," said the woman, 40, who declined to be identified by name because her words might be hurtful to her family. "That's what I resent. I feel like the choice was taken away from me."

In Europe, divergent values are quite explicitly shaping different P.G.D. policies. This spring, England approved the use of preimplantation diagnosis for the breast and colon cancer risk genes. In Italy, the procedure has been effectively banned for any condition.

In the United States, where the technology is not regulated, decisions about when it is appropriate are left largely to fertility specialists and their patients. Reflecting the growing demand for the procedure, the company that owns the tests for the breast cancer genes recently licensed the right to use them to three fertility centers.

"We decided we don't want to do it here," said William Hockett, a spokesman for the company, Myriad Genetics of Salt Lake City, citing both moral preferences and a disinclination to invest in the technique for business reasons. "But we don't want to impose our values on society, so we felt we should allow others to do it if they wished."

The interest in embryo testing is being driven largely by a greater knowledge of genetics among cancer patients and their family members. In the last five years, nearly 10 times as many Americans have been tested for the breast-cancer-risk genes as in

the previous five, according to Myriad, surpassing a total of 100,000 since the test was made available in 1996.

Familiarity with their own genetic profile makes some people more comfortable with intervening to alter their children's. For them, genetic traits can seem less like destiny and more like any other part of their lives that can be improved by technology.

Many of those exploring P.G.D. are the first generation of women to have reached reproductive age after their mothers developed cancer and tested positive for one of the breast cancer mutations. They see it as saving not just their children but generations of descendants from the same fate.

"I was very relieved to know that I would not have to pass this gene on to my children," said Michaela Walsh, 20, a junior at Susquehanna University in Selinsgrove, Pa., who found out she carries a BRCA mutation. She has already decided she wants to use P.G.D. when she has children. "My mother told me that the only worse thing than having cancer twice was having to give the gene to me."

But the same knowledge makes others who carry the mutations take particular offense at the selection procedure, which they say implies that they themselves, and many members of their family, should never have existed. It raises the specter of eugenics, they say, in the most personal terms.

"It's like children are admitted to a family only if they pass the test," said Denise Toeckes, 32, a teacher who tested positive for a BRCA mutation. "It's like, 'If you have a gene, we don't want you; if you have the potential to develop cancer, you can't be in our family.' "

Other critics oppose preimplantation diagnosis on the grounds that it could be used to select against homosexuals, women or people with disabilities. It reduces people to their genes, they say, and paves the way for the pursuit of children designed to suit parental ideals and for discrimination against those born with perceived imperfections. Proponents of the technology say that confusing the concept of "designer babies" with people trying to avoid deadly illnesses is hurtful and misleading. No one, they say, would endure the substantial physical and emotional difficulty posed by the process to make a baby with blue eyes and a wicked curveball. Still, the hostility couples have encountered from friends, family, colleagues and even medical professionals caused several of those interviewed for this article to request that their names be withheld.

One prospective father, a medical resident at Johns Hopkins Hospital in Maryland, said the Shady Grove Fertility Center, the local fertility clinic, required that he and his wife, also a resident at Hopkins, write a letter justifying their request for P.G.D. to the clinic's ethics committee.

The doctor's own father continually warned that in trying to prevent cancer, removing a cell from the embryo would create a mentally retarded child — no matter how many times his son cited studies to the contrary. Reactions from colleagues made the couple worry that if they allowed their names to be used, it might hurt their chances when applying for jobs at medical or research institutions.

"It became such a negative topic of conversation that my wife and I decided, 'We're not talking about this to anyone,' " said the doctor, 30, whose mother has had her breasts, uterus and ovaries removed to combat her cancer, in addition to undergoing dozens of chemotherapy sessions.

The couple held firm in their belief that there was no virtue in letting nature take its course when its outcome was so potentially damaging. "We hope to look back on this as really the first decision we made as parents," they wrote in a letter to the ethics committee that persuaded the clinic to let them move ahead.

Multiplying Decisions

Even for those who choose it, the burden of selection weighs heavily. Kim Surkan, who carries the BRCA1 breast cancer mutation, said her partner had initially described preimplantation diagnosis as a "pact with the devil." As Ms. Surkan prepares for her eggs to be extracted next month, she has nightmares that the child she selects will drown in a swimming pool, as opposed to a child chosen by fate, who might carry the cancer-risk gene but would have been a good swimmer.

"At least I know I've done whatever I can do with the information I have," said Ms. Surkan, an adjunct lecturer in women's studies at the Massachusetts Institute of Technology. "I can't control everything."

Like many people who want to take advantage of P.G.D. but cannot easily afford it, Ms. Surkan had to first convince her insurance company that she was infertile so that it would pay for the in vitro fertilization process. Because she is in a same-sex couple, that meant she had to undergo several cycles of insemination, hoping that she would in fact not get pregnant, so that she could proceed with preimplantation diagnosis.

Now more decisions are coming. What if, she wonders, she is unlucky, and all her embryos have disease genes? Should she implant a male one, since men rarely develop breast cancer, even if she is opposed to selection based on gender?

If she does get pregnant with an embryo found to be free of the gene, should she test the fetus at 16 weeks, since there is up to a 3 percent chance that P.G.D. will fail to detect an unwanted mutation? If she has two embryos implanted, and one has the defective gene, should she terminate it?

For many couples, preimplantation diagnosis is an appealing option precisely because it does not require terminating a pregnancy, a step that is common after an amniocentesis reveals that a fetus has a severe genetic disease but is essentially unheard of for predisposition to common cancers.

Danielle Jamond, who carries a gene for a severe form of inherited colon cancer, said she and her husband were considering that option a year ago. But she was saved from making the choice when she heard of a doctor who had developed a P.G.D. procedure for her form of the disease.

“At that point, the choice was obvious,” said Ms. Jamond, a human resources manager in a suburb of Paris, who has had her large intestines removed to avoid getting the cancer, a prophylactic measure for people with her genetic mutation.

Four embryos were created from her 12 eggs, and three did not have the genetic mutation. One died, the other two were implanted, and one survived. She is now six months pregnant with the surviving one, a girl.

But some people who believe life begins with conception think P.G.D. is as unethical as abortion and perhaps more pernicious because it is psychologically less burdensome. Unused embryos may be frozen indefinitely, skirting one moral issue, but at a cost of several hundred dollars a year. Reproductive Genetics Institute, a leading P.G.D. lab in Chicago that performed the preimplantation diagnosis for the Kingsburys, said about half the embryos containing the unwanted genetic profile were discarded and half donated to research.

‘Is This Genetic Engineering?’

Already, thousands of couples who are undergoing in vitro fertilization to overcome infertility use P.G.D. to weed out embryos that harbor common chromosomal disorders that would otherwise be screened for by amniocentesis. Fertility experts say

they may be the first to take advantage of the procedure for a range of other genetic conditions.

Dr. Ina N. Cholst, a reproductive endocrinologist at Weill Medical College of Cornell University, said a fertility patient of hers who suffers from an inherited arthritic condition called ankylosing spondylitis was planning to add genetic diagnosis to her in vitro procedure. She has a 50 percent chance of passing the gene to a child. Of those who carry it, four of five will be unaffected. The others will have arthritis, sometimes mild and sometimes quite severe, but increasingly treatable.

“We brought it up,” said Dr. Cholst, who consulted with the patient’s rheumatologist. “At the same time, I am thinking, ‘Is this a wonderful thing, or is this genetic engineering?’ ”

In the future, many specialists believe, most in vitro fertilizations will be performed for fertile couples seeking genetic diagnosis, not as a treatment for infertility. But as it becomes easier to identify the possible consequences of more kinds of genes, the decisions for parents may become harder. Having passed over 4 embryos with the defective gene and identified 10 healthy ones, the Kingsburys were asked if they wanted to pay \$2,000 extra to test them for Down syndrome. That test eliminated two more.

“You kind of feel like you shouldn’t be doing it,” Ms. Kingsbury said. “But then why would we go through all of this and not take those extra precautions?”

Soon, experts say, prospective parents may be able to choose between an embryo that could become a child with a lower risk of colon cancer who is likely to be fat, or one who is likely to be thin but has a slightly elevated risk of Alzheimer’s, or a boy likely to be short with low cholesterol but a significant risk of Parkinson’s, or a girl likely to be tall with a moderate risk of diabetes.

For the Kingsburys, the choice is still clear. Like any parents, they plan to tell Chloe the story of her birth. And if all goes well, they say, she will soon have a sibling who shares a similar tale.