

Barren Promise: The Hope and Heartache in Treating Infertility

by

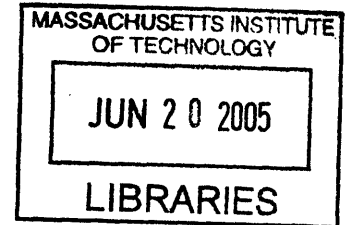
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ABSTRACT

Preimplantation Genetic Diagnosis (PGD) is a reproductive medicine technology that allows the genetic characteristics of embryos to be examined. Created through in vitro fertilization, embryos are grown in a Petri dish for three days, at which point they have eight cells. One cell is then removed from each embryo and tested for certain genetic characteristics. Based on the results, selected embryos are transferred into a woman's uterus.

Originally developed as a way to screen embryos for genetic disorders, PGD was used among a limited number of patients. More recently, however, some physicians and researchers have deemed PGD a useful infertility treatment. As a result, the number of people using PGD has increased every year since the technology was first developed in 1989.

The role of PGD as an emerging infertility treatment was examined from research, clinical, and personal perspectives. This was done through literature searches, interviews, laboratory observations, and attendance at infertility support meetings.

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Finally, I'd like to thank all of the people that shared their thoughts, their stories, and their tears with me. This piece is in part about how technology can affect our identities, our relationships, and our goals. And it is for everyone whose life has been touched by the field of reproductive medicine.

At 7:05 a.m. the phone rings, and Kevin DeLegge lets out a sigh.

“That’s someone calling to apologize for running late,” he says.

The embryologists at the Fertility Centers of New England must get to work early. Before a day of embryo transfers and egg retrievals begins, a delicate test called PGD has to be started.

At the center, Patient 98523 had recently been taking drugs at the clinic to stimulate her ovaries into producing extra eggs. Then later, three days ago, this patient and her husband came back into the clinic, where she was anesthetized and her eggs siphoned out; he spent some time down the hall in a tiny room full of magazines not sold to children under the age of eighteen. Today, Kevin will carefully manipulate the nine embryos that resulted in the union of his sperm and her egg.

In the infertility world, time is not measured in days, months, or years, but cycles: that twenty-eight day window of opportunity between ovulations, when a woman will either become pregnant or won’t. Patient 98523’s chart clearly documents seven unsuccessful cycles.

Doctors tried to get her pregnant four times by intrauterine insemination (IUI). Four times, a long thin tube was snaked up her vagina and into her uterus, delivering sperm more directly to her egg. Next they tried three cycles of in vitro fertilization (IVF). Three times, her eggs were sucked from her ovaries, fertilized in the lab, and then the artificially conceived embryos were inserted back into her uterus. Again, she failed to become pregnant. Her chart notes that all seven assisted reproductive cycles were negative—negative for pregnancy. This time, following her doctor’s recommendation,

they are trying the newest acronym in the medical staff's artillery: PGD or preimplantation genetic diagnosis.

PGD is essentially one extra step in the in vitro fertilization procedure. Embryos are still created in a Petri dish from a couple's sperm and egg and then transferred back to the woman's uterus. But with PGD, before the embryos are transferred, each tiny eight-cell embryo is tested for genetic diseases and abnormalities. Based on the results, only the best-fit embryo is selected. It's presumed that infertility patients will be more likely to get pregnant if the best embryo is chosen.

This wasn't the original purpose of PGD. The test was initially designed to help couples at high risk for specific inheritable diseases. By testing the embryos and then selecting the ones that don't carry the family's genetic mutation the tragedy of conceiving what would become a sick child is avoided. In 1989, the first successful PGD was performed to select a female embryo for a couple, because a boy would have had a 50 percent chance of inheriting a severe disease. Then in 1992, the first PGD baby to be screened for a single gene mutation, cystic fibrosis, rather than for a sex linked disease was born. PGD is also used for selecting a genetic match. Parents, who have a sick child in need of a stem cell transplant, can try to have another child who may be a compatible donor. For many children with leukemia, for example, their only hope is a bone marrow transplant from a genetic match. Without PGD, there is a one in four chance that the blood from a new sibling's umbilical cord, which contains stem cells, will be a match for the sick child. But with PGD, these parents can now select the embryo that will grow into the infant that has the specific genetic characteristics that can save the sibling's life.

But over the last decade, the use of PGD has changed dramatically. Currently, the vast majority of people doing PGD come from infertility clinics and, unlike avoiding a genetic disease or selecting a stem-cell match, the benefits, if any, are less obvious. For parents who are both carriers for cystic fibrosis, a successful cycle of PGD helps them have a child without the disease. For a couple struggling with infertility, the goal is to get pregnant. Whether PGD is actually helping is still in question. Some doctors involved with the development of PGD believe that it won't help most infertility patients at all. Yet others, who have been in the game almost as long, believe that PGD should be done on every IVF cycle.

There is money to be made and lost by clinics and the health industry. And for couples, there is hope to build up and tear down. Springing from every issue surrounding this technique is the question, is PGD worth it? Should this new technology be applied to one and all? At what cost to couples seeking infertility treatment? At what cost to society? The only certain thing about this emerging technology is that disagreement lies at every turn.

The logic for providing infertility patients with PGD testing is based on a few known facts. First, as a woman ages, she produces a higher percentage of abnormal eggs. When she is over 35 years old, 50% of her eggs will be abnormal, and when she is over 40 year old 80% will be abnormal. Embryos generated from abnormal eggs will typically fail, resulting in either miscarriage or no pregnancy at all. When a woman undergoes IVF, she creates more embryos than can be transferred back into her. This leaves room for the selection of the best embryo. If embryos made from normal eggs are selected over the abnormal ones than the chance of a woman getting pregnant increases.

Unlike IVF though, which resulted in more than 45,000 births in 2002 alone and accounts for slightly more than 1% of annual US births, PGD has helped make only around 1,000 babies since it was first successfully used in 1989. This is due to its relative newness and limited use. Yet each year the number of patients trying PGD has doubled, and most medical professionals expect this trend to continue. And the number of physicians that recommend it climbs. Like it or not, few deny that PGD represents the future of reproductive medicine.

Before the embryos are taken out of the incubator, Kevin prepares for the test. Better to take the time now than later. Besides, embryos can't be moved from one dish into another until someone else arrives.

"We have a witnessing program. If I want to move an embryo out of a drop into another dish, I want someone here to make sure that I have the right dishes. Just take a peek at the names, make sure they match. It protects everybody," Kevin says.

As a woman ages, what gets scrambled in her eggs are the chromosomes. Wound up into 46 separate structures within a cell's nucleus, the chromosomes contain all the instructions for the life of an embryo, an infant, and an adult. When an egg and a sperm meet, each parent is delivering half of their own genetic material to the embryo. When 23 chromosomes from mom and 23 from dad merge, a genetically unique single cell is created that can then grow into a normal embryo. What is lost with age is a woman's ability to produce eggs with the correct number of chromosomes. Some eggs get 22 or 24, others get all 46 or none at all. If these eggs are fertilized they will usually become an

embryo that will not implant into the uterus or if they do, will often result in a miscarriage.

That's what's been happening to patient 98523. She's 35 years old, and the phrase "advanced maternal age" is noted on in her chart. Her increased risk for producing abnormal eggs might be the reason why she isn't getting pregnant. Her doctor explained that if they could select the normal embryos by using PGD she might finally carry to term. This test, now in the hands of Kevin, will cost her an additional \$2,500.

Thomas O'Leary, another embryologist strolls into the lab. "How do they look?" he asks about the embryos.

"I don't know," says Kevin. "I haven't seen them yet. It's going to be a surprise."

Tom checks the names quickly, and Kevin moves the embryos from the Petri dishes where embryos are grown, into the bench-top dish.

PGD has several steps. It's Kevin's job to tackle the first and most crucial procedure: the cell biopsy. He will carefully take one cell out of each of patient 98523's nine embryos. To do that he must first break through the membrane that surrounds the embryo to gain access to the individual cells. Then he carefully sucks out one cell without disturbing the rest of the embryo.

He works with three embryos at a time and grades each based on the number of cells it has and the quality of the embryo's morphology. In the best-case scenario, a three-day-old embryo will have eight cells, but many don't. The quality of the embryo is scaled from one to five: one being the "prettiest" embryo and five being the "ugliest." The traits that determine its loveliness are the graininess of the nuclei, the relative size of the cells,

the presence of cell fragments, and the shape and thickness of the membrane that surrounds the embryo.

In the first group of three, one embryo is of very poor quality with only five cells, the next is a fairly nice eight-celled embryo, and the last has only three cells. Kevin won't even bother to biopsy that one because it is in such poor shape.

He carefully adjusts his weight in the chair and focuses the microscope on the five-celled embryo.

"You gotta get in a zone for PGD," he smiles before slipping a red tipped tube into his mouth.

Very delicately, he moves the needle over to the embryo and blows out a small amount of acid. This creates a hole in the zona, which is a membrane that temporarily surrounds an embryo in its early stages and holds the cells close together. Kevin is doing artificially what would happen naturally in the uterus: a stage that is called hatching.

After hatching the embryo, he changes needles and places a green tipped tube carefully between his lips. Very slowly, he breathes in, pulling one cell away from the embryo. When the cell is finally extracted, he quickly moves it to the other side of the dish. His shoulders relax and the mouthpiece falls away from his lips. He gives the lone cell a good looking over to make sure that the nucleus can be seen.

The next embryo to be biopsied is the nicest. It's an eight cell, and Kevin gives it a quality score of two. If the lab were not doing PGD, today, this would be the embryo transferred back into Patient 98523's uterus on looks alone. So if the results come back saying that this embryo is genetically normal, then there was no point in doing PGD.

By 8:15 a.m., after an hour of work, Kevin finishes biopsing the last set of three embryos. With a sigh of relief he hands the three single cells off to Alison Finn for the next step in the procedure: the fixation.

In order to examine a cell's chromosomes, its nucleus must be firmly fixed onto a microscope slide. This is done by swelling the cell until it bursts onto the glass, leaving the nucleus stuck. First developed in the 1960s, fixation is a common procedure in thousands of laboratories. But most of the samples worked on are blood or amniotic fluid, which contain hundreds or thousands of cells. When Alison fixes the biopsied cells, she has only a single chance with each one. She will line up the nuclei on a glass slide, marking each microscopic spec with a diamond point pen, and ship them off for analysis.

"It's very simple, it's just nerve wracking," she says.

To begin, Alison adds the solution, swelling the first cell in the line up. Standing at the microscope, ready to pounce, she adds the fix at just the right moment.

"Shit. There it is. That one jumped, but I was able to find it," she says.

If you drop a little too much fix on the bloated and bursting cell, it can fly right off the slide or into one of the other cells. When this happens, the embryo must have a second cell removed. Embryos that have two cells sucked out are half as likely to lead to pregnancy as those that are only biopsied once. When PGD is used to prevent a disease, the need for accurate genetic information outweighs the additional harm to the embryo from a second biopsy. But for infertile couples, the goal is to get pregnant, not examine chromosomes. The decreased rate of pregnancy caused by a second biopsy can make PGD for infertility pointless.

Because laboratories only have one cell to test, PGD for chromosomes has a 10 percent misdiagnosis rate. PGD is crude compared to genetic testing done on blood samples, which are always well over 99 percent accurate. This is because thousands of cells are examined with blood samples, where as PGD tests only one. Embryologists who opt for two-cell biopsy may achieve a more accurate genetic picture of the embryos, but the chance of the patient getting pregnant is slashed in half. Out of fear of misdiagnosis, many European laboratories routinely take two cells from each embryo. While this caution may be necessary for couples trying to avoid a genetic disease, infertility patients do not benefit. For PGD to be useful, the laboratory must get it right the first time. And as Alison performs the fixation, this thought is never far from her mind.

The LCD screen on the humidifier reads 40%—exactly where it should be. The moist air keeps the solution that bloats the cell from evaporating. Alison breathes heavy onto the microscope slide. After adding the fix she explains, “Huffing, even though you look like an idiot, adds humidity to the slide so that it doesn’t dry up.”

The last cell fixes easily and Alison exclaims, “Ah, here it is, and it’s so pretty.” The nucleus isn’t grainy, it’s spread wide, and it’s the proper distance from the other nuclei on the slide. The slides are then packed in a large box and driven by a courier service to their next destination. They will arrive half-a-day later in West Orange, New Jersey, at the Reprogenetics laboratory. After each cell’s chromosomes are tagged with florescent markers and carefully examined for abnormalities. The results are phoned back to FCNE. This highly coordinated effort ends less than 36 hours from the time Kevin first took Patient 98523’s embryos out of the incubator.

Dr. Lynette Scott is in charge of the advanced reproductive technology laboratory at FCNE. She has been a laboratory director for more than 16 years and before that worked in reproductive medicine research for five. No stranger to the intrinsic drama of the field, when asked what she does for a living she casually replies, “I make babies.”

“Someone’s hopes and dreams are relying on the embryos that you’re biopsying and fixing,” says Scott. “You’re working with one nucleus. And one nucleus comes from one embryo that can potentially make one baby. It’s intense.”

She has a small office, but that doesn’t stop her from turning it into the unofficial embryologist break room. After the first embryo transfer and egg retrieval of the morning Kevin, Allison, and Tom buzz in and out to grab gulps of coffee. Proud of her team, she is more than happy to reward them with half of her office and lots of caffeine.

“You need a highly skilled, dedicated person to do the biopsy and the fixation,” says Scott. “Not any old ninny can go and do it.”

The need for competent technicians is often the limiting factor in how many PGD procedures a clinic can perform per year. In the past, FCNE conducted only 50 PGDs per year, its maximum capacity. Starting in 2004, however, Scott reorganized and cross-trained her staff so that every patient who wanted to do PGD could get it. By the end of that year, 180 PGDs had been performed. Scott wants this number to climb even higher.

“I came into this whole process sitting on the fence,” she says. “I almost want to do PGD on everybody now.”

As a scientist, Scott wants to gather as much information as possible about a patient and her embryos. She examines the clinical history, the eggs and sperm, and the embryos’ morphology, all in search for the cause of a couple’s infertility. PGD provides

her with a new lens for examining a case—a look at each embryo’s chromosomes. Scott embraces PGD not as a treatment, but as a way to identify and better understand the causes of infertility.

For example, take the case of a 34-year-old woman who has gone through three cycles of IVF and is still not pregnant. In each cycle she produces very pretty embryos, and the doctors can’t figure out what’s going wrong. PGD is added on her fourth try, and the laboratory reports that only five percent of her embryos are normal. Her inability to become pregnant is explained, even if the reason why she has so few normal embryos is not.

The exact opposite results are also useful. Another 34-year-old, for whom IVF has also repeatedly failed, does PGD and learns that 70 percent of her embryos are normal. The doctors now know that for this patient, the chromosomes are not the problem. Maybe it’s the endometrium, the lining of her uterus. Maybe the hormonal support from the ovary is off. Maybe it’s some other physiological cause. PGD has ruled out one potential obstruction, but the cause of her infertility is still unknown.

As a tool for gaining insight into a patient’s infertility problems, PGD works. And in Scott’s opinion, that makes it a very valuable technique. But when a patient agrees to pay the additional \$2,500 out of pocket for PGD, her goal is to get pregnant. PGD is caught in a twilight zone: it’s a treatment but also a valuable research tool. The difference can get lost. The test is pitched to patients as a technique that will increase the chance of pregnancy, because only normal embryos will be transferred. That PGD is sometimes called a “treatment” and other times a “test” leaves some professionals uneasy.

When doctors offer patients a new technology that will report their embryos' chromosomal status and may provide answers to their infertility, few people decline the test. These couples are desperate to have a baby and will gladly find hope in the latest technique. But there is a big difference between getting answers and getting a baby.

“There are definitely some cases where PGD will never, ever, give them a baby, but it may give them closure,” says Alison. “And if they are financially secure and they want to do that, that’s fine. Because these people will always ask, what if? What if I drank more orange juice?”

PGD results that explicitly show that a woman is not making normal embryos can help a couple move on to either adoption or a donor egg procedure. The case of Patient 98523 will likely end this way. Her doctors probably recommended PGD because they didn't know what else to do.

It's not the scientists that are leaving patients confused about the true benefits of PGD; people who hold PhDs, like Scott, rarely come in contact with patients. They do not hand out pamphlets claiming, “PGD offers new hope for enhancing the probability of a healthy baby.” Confusion arises in the way that PGD is marketed.

Doctors establish their fertility clinics by advertising that they can get people pregnant. This leads to competition between clinics that is both real and often fierce. In the United States, more than a billion dollars was spent on IVF treatments in 2002 alone. But PGD is a technology that not every fertility center can perform, and so for a clinic that does offer the testing this can be a selling point—a way to increase the bottom line.

While the doctors promote their clinic and advertise PGD as the next big thing, the folks back in the lab are more ambivalent. PGD can certainly help some couples gets

pregnant and provide others with answers or closure. But scientists, like Scott, add a note of reservation to their enthusiasm. She firmly states that checking chromosomes is only one piece in the much bigger puzzle of infertility. PGD is a tool, not a cure. But that's not what doctors who own and operate the clinics want to hear. So they call PGD a "new hope," while the scientists call it a "new test."

"In this field everybody's looking for the golden bullet. I've seen the golden bullet a number of times," she says.

New culture medias, assisted hatching, ICSI (Intracytoplasmic Sperm Injection), and "embryo glue" were all labeled golden bullets when they were first developed. Some of these advances led to higher success rates, but others fell by the wayside. Self-promotion and the search for the next big thing are ever-present features in this field. Knowing this history, Scott never joined the camp that claimed PGD would solve everyone's fertility problems. In 1993, when doctors first stood up at conferences proclaiming the good news of PGD, she was skeptical.

Eventually PGD's biology, rather than its clinical success rates, convinced her it was worth it. Before PGD was developed, the only way to assess an embryo was to watch it grow. What does the egg look like? What does the sperm look like? How is the embryo maturing? Today, Scott can use PGD to look deeper into an embryo's biology and ask, what do the chromosomes look like? Even if it isn't a golden bullet, at least it's a step toward understanding the root causes of infertility.

But the fertility industry doesn't step slowly and carefully in pursuit of success. Instead, it runs frantically in all directions, trying to stay ahead in a race where no one knows the location of the start and finish. Doctors advertise the latest technological

developments before the scientific community has empirical data supporting any true benefit.

Take the case of EmbryoGlue, a culture medium that includes special nutrients absorbed by embryos. These nutrients supposedly help an embryo attach more firmly to the uterus once they have been transferred. Doctors everywhere began using it as soon as it hit the shelves. Websites of fertility clinics started advertising that they used EmbryoGlue, calling it a superior medium that increased chances of pregnancy. After studies confirmed that an embryo grown in this new medium was no more likely to implant in the uterus, many clinics switched back to their old media. But some clinics continue to use and advertise EmbryoGlue, in spite of the evidence that it doesn't work. Scott becomes frustrated when doctors ignore the scientific facts in order to meet patients' demands.

"I think a lot of the problems we have in this industry is that it moves too fast," Scott says. "There is a very, very demanding consumer. The consumer is driving it. And the consumer is a desperate person," who longs for a baby.

These patients beg their doctors for hope. When everything that is standard procedure has failed, doctors start looking to the most recent developments for something else to try. All it takes is one scientific paper for an idea to be noticed by the entire industry. All it takes is one study saying that Medium A works better than Medium B for every reproductive medicine clinic in the country to switch their brand of media.

The jury is still out for PGD. There is continued support for its use as a clinical tool, but its disappointing success rates for infertile couples (given the fanfare) has caused some doctors to conclude that the test doesn't greatly help patients, leading them to reject

the technology altogether. For that matter, many medical professionals are unsure what statistics to believe about PGD at all. The only statistics available are generated by the laboratories that do PGD testing, and these facilities appear to face conflicts of interest. The same doctors that pioneered the use of PGD in infertility also established profitable businesses that promote it. They report that PGD increases an embryo's chance of implantation by two-fold—from 10 to 20 percent—and in the same breath advertise their service. Even if these entrepreneurs are able to keep their scientific and monetary interests separate, the apparent conflict leaves a number of members of the community concerned.

Another reason some people hesitate to support widespread access to PGD is that it may open the floodgates for selection of embryos based on either sex—often called family balancing—or such non-medical traits as intelligence or appearance. When PGD is used to analyze chromosomes, the results include identification of the sex chromosomes. The doctor then knows that embryos 1, 4, 5, and 7 will be girls and embryos 2, 3, 6, and 8 will be boys. Most clinics, including FCNE, don't allow the patient to choose the sex of the embryo to be transferred, but some facilities will.

It's impossible to know what percentage of PGD babies have had their sex selected by their parents because clinics are not required to report the number and type of cases they perform. In Europe, where infertility treatments are paid for by socialized health care, restrictions on family balancing have become increasingly tighter. In the United States, however, sex selection appears inevitable as long as infertility treatments are market-driven. If a consumer wants to determine the sex of her baby, she can go to the clinic that allows her to do so. If she is already paying for IVF and PGD for fertility

reasons, there is no barrier, other than perhaps her own ethical stance, holding her back from selecting her baby's gender. If the pro-PGD doctors get their way and every IVF case is accompanied by PGD, more than 40,000 women will have their embryos tested. The greater the number of people getting PGD the more room there is for niche markets, such as family balancing. If every IVF patient does PGD, the total number of women who both want to and can choose their baby's gender will increase.

But what if people who aren't infertile want to use PGD for family balancing? What if it becomes possible to select embryos for non-medical traits? In Dr. Scott's opinion, these ethical issues will not be faced on a significant scale, because the IVF process is so difficult on a woman's body.

"You take these nasty shots twice a day. Every day," Scott says. "You come in for blood sticks. You end up looking like a pincushion. You go through surgery. You have your ovaries stuck. You've got vaginal probes in you every day. There's nothing private about this. Everyone is in there all the time. Your husband is in and out giving sperm samples to all sorts of people. He has to ejaculate in a little room into a little cup. There's nothing romantic about this."

If someone wants to use PGD for superficial purposes, they are going to have to go through the same painful and physiologically difficult procedure that an infertile couple experiences.

"If you're that egotistical and you're that arrogant that you're going to design a perfect little baby, you aren't going to be the person who's going to go through [IVF and PGD]," Scott says.

The people who go through IVF and PGD are like Devina and Barry.

After eleven years, five states, five miscarriages, and two IVF cycles, Devina and Barry are still not pregnant. Yet, they have hope.

Their journey with infertility began shortly after they were married, when Devina was diagnosed with endometriosis and her doctor told her that if she wanted children, she should try to get pregnant as soon as possible.

“Do it while you can,” Devina recalls with a smile. “So basically we’ve been trying for eleven years.”

But while Devina and Barry became pregnant on their own approximately once every two years, those pregnancies always ended in miscarriage. When they first started seeking treatment they were living in Arizona, which doesn’t require insurance companies to cover IVF. They did the treatments they could afford, which included intrauterine insemination and drugs that would stimulate ovulation. While waiting month after month to see if Devina would become pregnant, the couple also began to slowly save up the \$9,000 to \$17,000 it would cost to try a single cycle of IVF. That’s one egg retrieval, one batch of fertilizations, and one embryo transfer. Their journey continued in the same vein from Washington to Iowa to Texas. Where no IVF insurance coverage is mandated, none is provided. They continued to save.

When Devina and Barry moved to Massachusetts they were thrilled to discover that the state requires insurance companies to cover IVF. Devina braved the shots, the blood draws, the exams, and the surgery to finally try IVF. She got pregnant, and then miscarried.

Following her doctor's recommendation, they tried IVF again, but this time with PGD. Before the embryos were transferred back into Devina, PGD was used to look for chromosomal abnormalities in the biopsied cells.

Four embryos were produced from that round of IVF, and one cell from each was sent to West Orange, New Jersey. The results came back. One had no genetic material at all, but that might have been because it was lost in the biopsy process. The second had only one X chromosome and no Y chromosome and would have led to miscarriage if it had been transferred. The third would have also failed because it had two X chromosomes and one Y chromosome. The last one was normal and had the sex chromosomes of XY. They had one normal embryo.

“When they said [our only normal embryo] was XY, I looked at my husband and said that means it's a boy. The smile that came over his face I will never forget,” recalled Devina. I'm sure that he would have had that same smile if it was a girl, but he just kept repeating over and over for a couple of minutes ‘so it's a boy, so it's a boy.’”

When Devina became pregnant, the couple thought, “This is it.” Finally they were going to become parents.

“We felt very hopeful because the way that it was described was that if there was a genetically normal embryo that there would only be a ten percent chance of miscarriage,” says Devina. In reality, according to Dr. Scott, patients like Devina have a much higher chance of miscarriage than ten percent, even with PGD. This shows the danger in giving patients a new technology into which they can invest all of their hope. When patients are in such a precarious position, it's very easy for them to latch onto wrong information.

“I know in my mind that it’s not a baby,” Devina says. “I know this. But when you see that embryo being transferred into your uterus, it’s like, oh my god, there’s my child. I know that it’s not logical, but it’s just an over whelming feeling. Maybe it’s just the well of hope—it’s just so full.”

But, yet again, the pregnancy ended in miscarriage.

In reviewing her medical history, her doctors realized that a routine test had not been done. There is a correlation between recurrent miscarriage and a blood-clotting factor caused by a genetic trait called the Prothrombin gene mutation. A simple and routine genetic test, which had been overlooked, was then conducted. Devina carried the mutation. If she had been taking a drug called heparin, which prevents blood from over-clotting before and during her pregnancy, she may not have miscarried. Barry was furious. Devina was distraught.

They had tried everything, and nothing worked. But Devina and Barry believe that PGD did work. Even though she miscarried, she became pregnant with the embryo that was deemed genetically normal by PGD. This gives her hope that if they had known about the blood-clotting factor she would have had a baby boy nine months later.

Devina knows that there is limited data showing that PGD really helps women get pregnant. But, she also says that not everyone has the luxury of time to sit around and wait for scientists to establish some kind of proof. Logically, PGD should help a woman get pregnant, and Devina doesn’t have time to waste. It’s the needs of people like Devina that reach for the latest technologies as a new source of hope.

Perhaps the most difficult thing for Barry and Devina is the waiting. They waited nine years to be able to do IVF, and even now they are facing delays.

“When you build up that strength to say okay, we’re going to do another cycle and then little things seem to get in the way, whether it’s finances or you’re required to do one more test, it’s very, very stressful, says Devina.

In the face of so much personal tragedy, Devina and Barry manage to stay remarkably positive, with perhaps one exception.

“I think one of the things that we are mad about is that we have to choose between building a family and having a home of our own,” says Devina. “Even now, PGD isn’t covered by insurance, which is still \$2000 that we are paying and then you have all of the deductibles, which easily add up. Our first IVF here in Massachusetts wasn’t covered 100% and we had to pay thousands of dollars.”

The desire to become parents can support even the heaviest burden. Devina and Barry have not lost hope.

Infertility affects 6.1 million people in the United States. One in six couples who try to get pregnant will have problems. In recent years, infertility has been called an epidemic and a national health crisis. But whether this problem is actually on the rise is still in dispute.

Until recently, infertility was a hushed topic. The number of people before 1980 who found themselves unable to have a baby will probably never be known, as there were few major medical or social efforts tracking infertility. In comparison to the American Medical Association, which was founded in 1847, the 60-year-old American Society of Reproductive Medicine is in its youth. Without a documented history, it is difficult to

know whether the number of people facing infertility has been climbing or if it is just being diagnosed more often.

One factor that could possibly contribute to an increase in couples seeking infertility treatment is the older age at which women are deciding to have children. A couple, with normal functioning reproductive systems, has a 25 percent chance of getting pregnant in any given month. That same couple will have only a 10 percent chance each month after the woman turns 35. Therefore, women who take time to establish careers before settling down to start a family are more likely to face fertility problems.

For 80 percent of infertility cases, the cause can be determined. A third of the diagnoses are attributed to the female, a third are attributed to the male, and a third are related to both partners. For women, infertility can be caused by an obstructed fallopian tube, low ovarian reserve, excess or very low body fat, or a hormonal imbalance. A man may face infertility if he has a low sperm count, low sperm motility, or has been exposed to harmful chemical or environmental conditions. For the diagnoses that are linked to both partners, the problem is the result of compounding complications. For example, a woman may have a slightly low ovarian reserve, meaning that her ovaries don't have many eggs left, and her partner may have slightly low sperm motility. The combined effect of each partner's reduced fertility keeps the couple from getting pregnant.

Even though diagnoses are split evenly between the sexes, it is women, particularly women of advanced maternal age, who are most active in the infertility community. Many of these women are intelligent, educated, and driven. Whether or not the number of cases has reached the level of a national health crisis, many women are determined to educate the public and remove the stigma of infertility.

Thirty years ago, a time when women were gaining political and social power and infertility was not spoken about openly, the national infertility association RESOLVE was established. RESOLVE's primary goal is to bring infertility out of the closet so that people can have access to accurate information about available treatment options. While the organization only has 15,000 active members, there are typically more than a million information requests made through RESOLVE's hotline and website. Much has changed in thirty years. Since its founding RESOLVE has fought for state legislation requiring insurance companies to cover infertility treatments, and has won in fifteen states, including Massachusetts. The 2003 Miss International's service platform was, "Infertility: A National Health Crisis," radio stations play advertisements for fertility clinics, and Lee Rubin Collins, a member of the national board for RESOLVE, can sit and talk openly about her struggle with infertility in Starbucks.

Collins exemplifies the case of a successful woman who put her baby-making years on hold. She graduated summa cum laude from Harvard University and received her J.D. from Harvard Law School. She went on to work as a trial attorney and become a partner at Ropes & Gray, one of Boston's oldest and largest law firms. When she turned 36, Collins had her first daughter. She wanted to have more children, but after six months of trying to get pregnant again without results, she decided to see a specialist. Her doctors discovered that due to an infection she developed while giving childbirth, one of her fallopian tubes had closed. This cut her chances of getting pregnant in half. She was also now 38-years-old, and a few years can make a huge difference in a woman's fertility. Secondary infertility—when a woman can't get pregnant after she has already had

children—appears to have become more common as women choose to start their families later.

Collins proceeded with the normal series of treatments, first taking drugs to stimulate egg production, then trying intrauterine insemination, and finally doing IVF. To bring her second child into the world, she went through the IVF procedure five times. Today Collins might have been offered PGD, but five years ago examining an embryo's chromosomes wasn't done. After the birth of her second daughter, her family finally complete, Collins became more active in the infertility community. She became a member of the board for the local Massachusetts RESOLVE chapter, and a few months later, was elected to the national board.

Collins never had to make a decision about whether or not to use PGD. However, she has witnessed the ever-increasing clamor for the test among members of RESOLVE who are currently seeking treatment. It is a new technology—a new hope.

“I have definitely encountered couples who have had failures with infertility treatments who are really looking for answers, information, and any treatment that will help them have that baby,” says Collins. “PGD happens to be one of the newest developments, so certainly it is of interest to people who are having difficulty with infertility treatment.”

She stresses, however, that PGD is not for everyone. Even if every IVF patient were to do PGD as well, the total number of babies born would only make up one percent of the births in the United States. Here is where RESOLVE gets caught in an awkward position. Technologies such as IVF and PGD are controversial in themselves because they involve the creation and destruction of embryos. Given people's ethical concerns,

RESOLVE stresses that only five percent of couples who seek infertility treatment end up using IVF. At the same time, RESOLVE advocates state-mandated insurance coverage for infertility treatments because many people are unable to afford to pay for the more expensive technologies. A delicate balance must be struck between saying that infertility deserves more attention and stating that the controversial technologies that can help patients aren't used widely enough to warrant ethical concerns.

Collins is acutely aware that negative reports about the use of PGD for purposes other than infertility can have a harmful effect on the public's perception of the infertility community. She was saddened when the *Washington Post* ran a front-page story about how PGD can be used for sex selection. The article told the story of how a woman with three daughters decided to use PGD to have a boy. She traveled from her home in Massachusetts to a clinic in California, and while her daughters visited Disney Land, artificially conceived twin boys. Collins worries that when the media or social scientists call attention to these rare cases it makes the rest of the PGD world look bad.

"I think theorists spend so much time worrying about marginal cases that it's ridiculous: What is it going to be like if we have a society where every person selects sex of their embryo? I don't know but contact me in 500 years when it has a possibility of being true," says Collins.

Deaf people have also used PGD to choose embryos that will grow into deaf children, and dwarfed people have selected embryos in order to have children like themselves. For someone like Collins, who is worried about the perception of advanced reproductive technologies, the fact that these kinds of cases create headlines is very

frustrating. These controversial goals are not shared by the majority of patients seeking PGD. Most people are like Devina and Barry.

“We are every day women and men who want to have babies. We want to be good parents. We want to help bring up the next generation of American children. We are as American as apple pie,” says Collins.

After her last, most devastating miscarriage, Devina joined RESOLVE. Offering support in the form of informational meetings, personal testimonies, and online chats, she fell in love with the organization and its sense of community. When an advertisement was posted that the national helpline was looking for part time peer counselors, Devina jumped on it. In less than a year she became director of the helpline service.

Devina is a PGD believer. She speaks about her work on the hot line with the enthusiasm of an evangelical. When people who are struggling from infertility call, she makes sure that they have information about PGD. To her, the technology just makes sense. If a couple is going to put themselves through the difficult process of IVF, why not spend a few thousand dollars more to make sure that the embryos being implanted are normal? As a peer counselor, she tells callers about her personal experience. She explains to people every day about how PGD helped select her only normal embryo, how she became pregnant, how she miscarried due to an unrelated blood-clotting factor, and how she has faith that next time she will be taking a baby home in her arms.

But Devina’s faith is based on a personal experience and not on studies published in scientific journals. When tells people about PGD on the hotline, she speaks from her heart. There is a grave risk of passing on misinformation.

A five-minute drive from Manhattan, just on the other side of the Lincoln Tunnel, lives Dr. Santiago Munné, his wife, and his six-month-old daughter. While being a laboratory director rarely denotes celebrity status, to people like Devina, Munné is practically a rock-star. He signed off on the chromosome results from her last PGD test, and he will likely autograph the next as well.

Munné is the director of Reprogenetics in New Jersey. Fertility clinics all over the world, including FCNE, send slides with fixed cells to be examined by Munné's staff. Since its founding in 2000, the company has become the largest PGD laboratory in the world. More than 1,500 cases were completed last year, and 85 percent were for infertility patients.

His lab labels chromosomes numbered 13, 15, 16, 17, 18, 21, 22, and the sex chromosomes with fluorescent probes. Looking under a microscope, a technician checks each cell to see if it received one copy of each chromosome from mom and one from dad. We receive 23 chromosomes from each of our parents, but the current technology limits the total number of chromosomes that can be more closely examined to eight. These specific chromosomes were chosen for PGD testing because they are often found to be abnormal in miscarried fetuses. The total bill paid to Reprogenetics is \$2,200.

Munné shrugs when asked about the price of PGD. "It's expensive in what you compare it to," he says.

In places like Massachusetts, where IVF is covered by insurance, patients are often surprised and upset when they are informed that PGD is not covered and they must pay out of pocket for the testing. But for patients that are already financing \$14,000 to

cover the cost of IVF, the additional \$2,200 doesn't seem like much of an additional cost. In fact, if doing PGD means that a couple is more likely to get pregnant and less likely to have to pay another \$14,000 for a second IVF treatment, the cost of PGD pays for itself.

Examining the currently available statistics does little to clear up the issue of whether PGD is worth the price. This is because the scientific papers that report success rates of PGD are produced by individual clinics, which work with small and isolated groups of patients. Many doctors, including Munné, are calling for a national effort to gather information about PGD and the clinics that offer it. This kind of data collection and clinic monitoring is already in place for IVF. The CDC keeps a registry that includes information about most fertility clinics in the country, including the number of patients seen per year, the kinds of procedures performed, and clinics' success rates. It's a voluntary registry, but fertility clinics that do not submit their statistics are listed as not participating. Based on the gathered data, the CDC reported that the chance of a woman having a baby after one IVF procedure was 33.4 percent.

Citing a paper that was published in 1999 by one of his colleagues, Munné claims that PGD doubles the chance that an embryo will implant in the uterus. The study reported that the chance of implantation for a woman in the control group was 10.2 percent. The PGD patients on the other hand, had a 20.5 percent chance of getting pregnant. Munné himself published a similar paper in 2003 that looked at slightly older patients. Again he reported a two-fold increase, this time from a 10 percent to 20 percent chance of implantation. In both studies, the control groups and PGD patients groups had a lower than average chance of getting pregnant. This inconsistency could exist because the people who seek out labs like Munné's are the toughest cases. It could also be because

Munné advises transferring no more than three embryos back into the patient's uterus. He does this in order to reduce the likelihood of twins or triplets, which are high-risk pregnancies, but it may reduce the overall success rate. Whatever the cause, the discrepancy casts some doubt on the effectiveness of PGD for infertility.

While 85 percent of the embryos that Reprogenetics tests are from patients struggling with infertility, a small subset of these patients are definitely being helped by PGD. Ten percent of the patients that the lab tests have infertility caused by translocations. These special kinds of abnormalities are not caused by a woman's aging eggs but by a genetic problem in one partner's own chromosomes. A person with a translocation has a piece of one chromosome switched with another chromosome. For example, a piece of chromosome number one could be attached to number three and a piece of number three hooked onto number one. A translocation is "balanced" when the same amount of genetic material is swapped between chromosomes. While people with balanced translocations appear completely normal, many eventually find themselves facing infertility.

When a cell with a balanced translocation divides up its genetic material to make eggs or sperm, the chromosomes can break. These broken chromosomes often generate a translocation that is "unbalanced," where the exchange of material between chromosomes is uneven. An unbalanced translocation typically prevents an embryo from implanting in the uterus or results in miscarriage the same way that an embryo with a chromosomal abnormality does.

For patients struggling with this specific kind of infertility, PGD is very useful. Selecting the embryos that do not have a translocation improves the chances of getting

pregnant dramatically. The same type of cell biopsy, cell fixation, and fluorescent probing techniques are used to distinguish the normal embryos from the abnormal ones. Reprogenetics charges \$2,500 for its portion of the testing.

As Munné sits back comfortably into his couch and talks about PGD, he radiates confidence. He explains, again, the logic of PGD: it just makes sense to check the embryos' chromosomes before transferring them back to the patient. He admits, however, that the success rates are not as high as the scientific community had hoped. The reasons he gives as to why more people are not benefiting from PGD are almost entirely based on things beyond his control. His step in the procedure is to look that the cells already fixed to the slides. The first problem he cites is that success rates vary depending on who is performing the PGD.

“There is a learning curve with these technologies,” Munné says.

PGD is a delicate procedure and expertise is needed to produce consistent results. Though Reprogenetics was only established in 2000, its team of scientists has been involved in the field for over a decade. Munné himself wrote a seminal paper in 1993 that first suggested that PGD could be used to treat infertility patients. While experience is not an issue for Reprogenetics, Munné worries that other labs are offering PGD testing without proper training and so are lowering overall success rates.

In order to protect patients from laboratories new to PGD testing, New York State requires a specific laboratory license for the testing.

“For us [the law] is great,” Munné laughs. His facility is currently the only lab with certification and therefore all of New York's business is sent to Reprogenetics. But

more importantly, he says, is that these kinds of laws help protect both the patients and the reputation of experienced PGD laboratories from the unqualified facilities.

“There are some groups that shouldn’t be doing PGD. People will say it’s not working because in their hands it’s not working,” Munné says.

Another reason Munné gives for the lower success rates is that “damage must be compensated by the selection.” The cell biopsy procedure causes some trauma to an embryo and there is a higher percent chance that a biopsied embryo will stop growing and never grow into a baby. Therefore, PGD’s selection process must be more helpful than the cell biopsy procedure is harmful. But this is not always the case.

For example, a couple might produce five embryos but only one is pretty. PGD is done, and the test shows that the only normal embryo is the pretty one. So this embryo, which would have been selected without PGD, has been traumatized by the cell biopsy procedure and is now less likely to result in a pregnancy. This kind of case actually pulls down PGD’s success rate, and is the reason that Munné recommends doing PGD only for patients who have produced at least six embryos. However, if a doctor sends him a slide with cells from less than six cells fixed to it, he does not turn down the case.

Munné suggests that the take-home-baby rate could increase dramatically if more research were done to improve the cell biopsy process. But his laboratory doesn’t do that part of the test. Like the advancement of the cell biopsy technique, Munné leaves the pondering of ethical questions to others.

Despite some public worry about the potential abuse of PGD, Dr. Munné has no reservations about the technology at all. He believes that the desire to practice better medicine will require PGD to be done with almost all IVF, and that will be a good thing.

Even when confronted by the controversial topic of family balancing Munné does not see a problem. In the U.S. couples request girls as often as they do boys, he says.

Regardless of his personal feeling, the New York State regulations provide Reprogenetics with an easy way out of a sex selection controversy. The law requires that all information deemed from testing results be passed on to referring physician. This includes the sex of each embryo.

“How this information is used, I don’t know,” says Munné.

If Munné is the name and face that infertility patients recognize, Mark Hughes is the hero to people like Kevin DeLegge, Alison Finn, and Lynette Scott. They refer to him as “the saint.” Like Munné, Hughes is the director of a PGD laboratory, but unlike Munné, he doesn’t run tests for infertility patients and he doesn’t have a luxury apartment minutes from downtown Manhattan. The Genesis Genetics Institute makes up no more than a thousand square feet of the Samaritan Hospital in downtown Detroit, and there is nothing lavish about it.

Hughes calls himself a geneticist and a scientist. He is neither an entrepreneur, nor a reproductive medicine physician, though he has started his own laboratory and has a medical degree. It was because he was a geneticist that he entered the burgeoning world of PGD back in 1989.

In that year, a team of researchers at Hammersmith Hospital in London reported the first PGD pregnancy. In order to avoid a disease that would be inherited only by sons, female embryos were selected and transferred back into the patient. The results were reported in *Nature*, and the story rocked the reproductive medicine community. The team

tried the procedure again, but this time had a misdiagnosis and a male embryo was mistakenly transferred.

“And then they realized that they were embryologists and reproductive doctors. They weren’t molecular biologists and geneticists,” says Hughes. “If they were going to make this work, [they] had to bring together these different groups with different experiences.”

So they called Hughes, and he joined the research team. They did the next twelve PGD cases together, all of which were for screening out embryos that would have become children with cystic fibrosis. This was the beginning of PGD—grounded in collaborative science and intense research. Hughes recalls with genuine nostalgia the time before egos were at stake and financial interests were in play.

One of his happy memories includes sitting around at the hospital with his colleagues, waiting for an experiment to finish up, and trying to come up with a name for their procedure.

“We had a list: blastomere, embryo, reproduction, genetic, in vitro,” says Hughes. “Then we thought, ‘preimplantation diagnosis.’ But that would be PID, which in the medical community stands for ‘Pelvic Inflammatory Disease’ which wouldn’t be good. So we came up with the term BABI : blastomere analysis before implantation. That was the term. But it never took off. PGD became the term.”

Today, Hughes does similar work with PGD as he did more than thirteen years ago. He tests embryos for specific genetic diseases that the parents carry. He believes that this is where PGD can help people the most: making sure that a baby is born without a

genetic disease. It is a process that is more difficult and requires more precision than chromosome testing for infertility patients.

The testing procedure at Reprogenetics resembles an assembly line. First, the slides with cell nuclei fixed and clearly labeled are received. Next the technicians add the fluorescent markers, examine the chromosomes, and the results are then sent back to the patient's fertility clinic. The testing that goes on at Mark Hughes' lab, on the other hand, is custom in nature. He first spends an hour on the phone consulting with each patient. Next he receives the couples' blood and confirms the family's mutation. The testing is then fine-tuned for the specific mutation. Finally, the biopsied cells are tested and the results reported back to the patient's physician. More than a thousand cases per year are sent to Mark Hughes' lab.

"We do all of that for \$2,500," says Hughes. "That's why we're basic. That's why we don't have anything on the walls. We're not trying to be glitzy. We're not trying to impress people. We're just trying to do good science."

No one speculates whether Mark Hughes runs a PGD lab to make money. If anything, people wonder how he manages to stay open. The persistent hum of the sequencing machine and the large stack of patient files on his desk are signs that even if good science hasn't made him rich, it sure has kept him busy.

It's not that Hughes doesn't want to see PGD used to treat infertility patients. Rather, he just doesn't believe that the science is strong enough to warrant all of the hype.

"I'm not convinced that it helps most patients," says Hughes. "A few years ago, we all stood up at genetics meetings and reproductive meetings and we said, 'now this is

going to be the best thing since sliced bread!’ But the bottom line is that it isn’t improving the take-home baby rate at all.”

This, however, is not what Devina and Barry were told, and it’s not what they believe. They have put their lives on hold to pursue the dream of having a baby and pin their hope on prayers and PGD. But Hughes, a respected scientist and neutral party—who has nothing to gain or lose by the success of an infertility treatment—doesn’t see evidence for the procedure in which the couple entrust so much hope.

“Geneticists, we tend to be pretty cautious folks,” says Hughes. “The reproductive people tend to be exactly the opposite. They adopt every new technology that comes along, because if they don’t, the people down the street will advertise it as being an important add-on, or adjunct test to help you.”

It may be too easy to fault the people collecting the checks for the acceptance of misinformation, because the patients themselves are partially to blame. The desire for hope is a powerful part of the human condition, and people suffering from infertility find hope in both prayers and science. What doctors offer are not just tests, pills, and surgeries. Their potential treatments are the very embodiment of hope.

Yet when the coldness of scientific accuracy collides with the burning desire for a family the result is either relief or more heartache. A small fraction of couples assuredly come away pleased. They successfully complete their family. Other couples find relief in simply concluding treatment. After years of moving from one procedure to the next, being physically, financially, and emotionally beaten, the journey ends. Currently, PGD marks the end of infertility treatment. It means they have tried everything, which makes the most comforting technology a couple can buy. But there are those whose desire to

achieve parenthood are all consuming. They never rest, and continue to wait for the next new thing.

After having spent thousands of dollars and years of their lives trying to have a baby, Devina and Barry are not done yet. Devina will take medication for her blood clotting factor and try PGD again. She is unsure what options she will pursue if she fails to get pregnant. But right now, all that matters is that there is another month of treatment in which to find hope.

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