

**In 20 to 40 years, most Americans won't have sex to reproduce.
Get ready.**



For 100 million years, all our ancestors reproduced basically the same way. A male reproductive organ deposited sperm into a female reproduction organ, where it could fertilize eggs — leading to baby ancestral tetrapods, mammals, primates, and eventually humans. The past 60 years have seen this begin to change, first with clinically available artificial insemination and then with in vitro fertilization (IVF).

In the United States today, these two techniques lead to about 100,000 births each year, roughly 2.5 percent of the 4 million children born annually. Within the next few decades, that percentage will skyrocket. Developments in bioscience, galloping forward in most cases for reasons having nothing to with reproduction, will combine to make IVF cheaper and much easier.

These new techniques will allow safe and easy embryo selection – but they will also open doors to genetically edited babies, "their own" genetic babies for same-sex couples, babies with a single genetic parent, and maybe babies from artificial wombs.

Starting in the next few decades, these new methods of reproduction will give people new choices. They will also raise a host of vexing legal and ethical questions, questions we need to start discussing.

Closest at hand is greatly increased genetic selection of embryos. For more than 25 years, clinicians have been able to take cells from embryos growing in vitro in petri dishes, do genetic tests on those cells, and use the test results to decide which embryos to transfer to a womb for possible pregnancy. This process, known as preimplantation genetic diagnosis, or PGD, led to about 2,500 births last year in the US.

If PGD has been clinically available since 1990, why does it remain relatively uncommon? Two reasons.

First, PGD has only been able to look at one or two of a limited set of characteristics: a genetic disease known to run in the prospective parents' families, syndromes caused by the wrong number of chromosomes, and sex. Looking at more costs too much and takes too long.

Second, the in vitro part has been essential. The reason is simple: otherwise the embryos are somewhere in one of the woman's two fallopian tubes. Good luck finding them. With IVF, the embryos are in the dish you put them in.

And IVF is neither cheap nor fun. In California, it costs about \$15,000 – typically not covered by insurance – for the most basic version. IVF is always uncomfortable and sometimes risky. Most of the cost, and all of the discomfort and risks, lies in harvesting eggs. Egg harvest requires weeks of injections with powerful hormones, the side effects of which lead to several hundred hospitalizations a year in the US. Until IVF becomes less burdensome, PGD will not be easy.

Both problems, however, are being solved, for reasons having nothing to do with reproduction.

Stem cells could set off a reproductive revolution

Today, we can sequence an entire human genome — think of it as 6.4 billion letters, or a thousand copies of *The Lord of the Rings* — in a day or two for about \$1,500, a price that continues to plummet. It's harder and more expensive using a few cells from an embryo, but that will change, too. Cheap sequencing will allow parents to learn all the things about their prospective children that genetics can reveal.

So the genetic testing is improving, and its price is coming down. Meanwhile, stem cell research holds the promise of eliminating egg harvest. In 2007, Shinya Yamanaka, a professor at Kyoto University (and now a Nobelist), discovered how to make skin cells become like embryonic stem cells. These "induced pluripotent stem cells," or iPSCs, are among today's hottest areas of biomedical research. Scientists hope to turn them into brain, heart, pancreas, and other cells that a patient's immune system will

recognize as his own.

Such a development would open up a world of therapeutic possibilities, but it also will transform reproduction. Eggs and sperm (collectively, "gametes") are also human cell types. Scientists should be able to turn iPSCs into gametes that carry a prospective parent's own genetic variations. Gametes derived from iPSCs have already been used for successful births in mice; research is now beginning in humans.

When you add cheap whole-genome sequencing to stem cell-derived gametes, you get what I call "Easy PGD." In, let's say, 30 years (following extensive safety testing and FDA approval), a couple who want to have a baby will go to a clinic. She will provide a small skin sample; he will provide sperm. The clinic will turn her skin cells into mature eggs and then fertilize them with his sperm to make embryos.

Choosing from not 12 but 100 embryos

PGD today is constrained by the number of ripe eggs harvested — usually around a dozen. Easy PGD has no such limit, because the eggs are being created from tissue samples. Assume the clinic makes 100 embryos. Each embryo will then have its whole genome sequenced, and the parents will be asked what they want to know from what those genomes can tell them.

Parents will be able to learn a lot from these whole genomes. First, genetic variations can confidently predict thousands of nasty early childhood diseases, each individually rare but collectively accounting for 1 or 2 percent of all births. Second, genomic sequencing can predict the risk of developing many later-life diseases, such as certain cancers and Alzheimer's disease. Third, parents will be able to learn something about how their future child would look: hair color, eye color, skin color, height, and more.

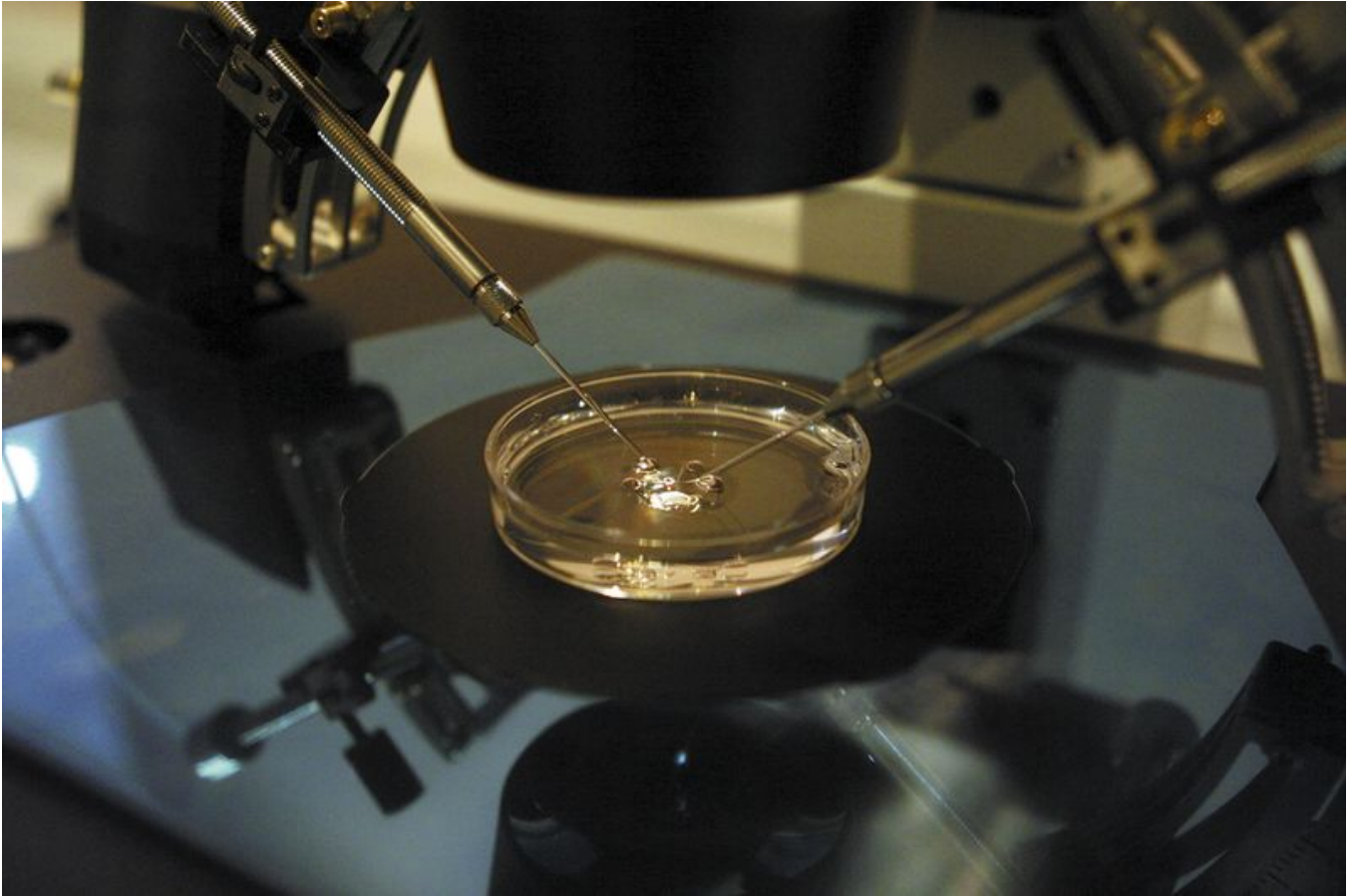
"We would be able to make children of children too young to have useful gametes, or of people who have died but left behind carefully preserved tissue samples"

Fourth, genetic variations provide hints about behavioral traits, like personality type or intellectual ability. Since genetic associations with non-disease behaviors are both complex and weak, this could probably only tell prospective parents whether, for example, an embryo has a 60 percent chance of being in the top half for some trait; still, that's something. Finally, the tests can easily tell parents "boy or girl."

After learning what they want to know, parents will then have to choose which embryos to transfer to a womb — the final step in Easy PGD.

Cross-gender gametes and "unibabies"

But the possibilities that come from creating gametes out of skin cells go far beyond Easy PGD. If we can turn skin cells into gametes, we create opportunities for people who cannot now reproduce because they do not make useful eggs or sperm, whether from disease, accident, or age. Many examples that come to mind are benign, but others seem worrisome. For example, we might make children of children too young to have useful gametes, or of people who have died but left behind carefully preserved tissue samples.



Fertilizing an egg, under a microscope.
Tina Stallard/Hulton Archive/Getty

This could also lead to unwitting parenthood. It is not easy to steal a man's sperm and nearly impossible to steal a woman's eggs. But we constantly leave cells on water bottles, eating utensils, and a thousand other places, cells that might be made into gametes.

Take yet another step. What if we could we turn a man's cells into eggs and a woman's into sperm? Who would want such "cross-gender" gametes? Ask gay and lesbian couples who would love to have children without turning to an outside gamete donor; today they can't. Stem cell-derived gametes do not make the ability to do this certain, but they certainly make that next step quite plausible.

What would happen if a woman had a clinic make both eggs and sperm from her skin cells, create embryos from them, and then transfer one of the embryos into her womb

for birth? This method risks creating lots of diseased embryos as a result of this inbreeding, but whole-genome screening could weed out the unhealthy ones. What *is* the resulting child? I call it a "unibaby," produced by a "uniparent," not a clone but a new human very similar to its one parent

At the step beyond unibabies are actual clones, the ultimate in genomic selection – from "I want *that* one!" to "I want me" – and inbreeding. Dolly the sheep's birth caused a panic (and much rushed legislation) about possible human cloning, but as the years went on and scientists could not manage to clone even a human embryo, let alone a baby, fears subsided.

Finally, in 2013, Oregon researchers discovered how to clone human embryos successfully, making cloned babies at least plausible but, based on what we see with other cloned species, way too risky for humans.

Even if cloning became safe enough to try, I doubt making a genetic replica would ever be terribly popular, particularly when people realize they will not get "themselves" but an infant, subject to all the variations different environments can produce. But it is a big world; someone, somewhere will eventually try it.

CRISPR and the world of designer babies

Everything we have talked about so far takes parents' existing genetic variation as given. But thanks to other bioscience advances — again, pursued for reasons having nothing to do with reproduction — it has become much easier to change these sequences through gene editing.

We have been able to change the genes of living organisms for more than 40 years, but only slowly, expensively, and imprecisely. A new invention called clustered regularly interspaced short palindromic repeats ("CRISPR") makes these changes cheap, easy, and accurate. Researchers are feverishly trying to use CRISPR to cure genetic diseases in living persons, but it might also be used to change the genes of persons not yet born.

While Easy PGD only offers "embryo selection," a choice among the genetic variants the parents have to offer, embryo editing using CRISPR offers parents the possibility of a true "designer" baby. Prospective parents would not be limited to giving their children their own genetic variations. They could use variations found anywhere among the 7.3 billion living humans. Or, indeed, beyond humans — to genetic variations from other species or "new and improved" synthetic variations.

Eventually, people might even be able to build an entire human genome from scratch, DNA "letter" by "letter." One prominent geneticist recently, and controversially,

proposed a project to do just this.

Non-human or artificial genetic variations, as well as completely synthesized human genomes, are a long, long way off. But more mundane gene-edited babies — those who have had one well-known human genetic variation changed into another one — could be here soon. If its safety can be demonstrated, gene editing could follow quite quickly after Easy PGD, in, say, 30 to 50 years.

Finally, consider one more possible change to baby making, one that would not alter the embryos but rather change where they grow – the artificial womb. We know very little about what happens inside the uterus in the early stages of human pregnancy, and it is hard to see how we could safely learn much more. But there may be a path forward: a uterus grown from induced pluripotent stem cells.

It would be hooked to a machine providing it with human blood with just the right amounts of oxygen, sugar, and hormones, quantities that should be discoverable from monitoring old-fashioned pregnancies. This would make reproduction a process that took place entirely outside human bodies – although we are now pushing to the edge of speculative science, or, at least, of my imagination.

Confronting the ethical challenges

Which of these new techniques will we be comfortable using ourselves, or letting others use? Even my most banal future, straightforward Easy PGD, might seem politically and practically impossible—a brave new world that people and their governments will reject. Voters and politicians may balk at the idea of couples creating hundreds of embryos and selecting the finest examples, based on possibly idiosyncratic genetic preferences, and discarding the others. But let's walk through it.

"Standard" PGD has been legal in the United States for more than 25 years with no real attempts, at the federal or state level, to restrict it. It already involves selection according to genetic criteria, and the destruction of embryos. When it comes to abortion, attempts to stop fetal selection have been and continue to be made. But most people do not see in vitro embryos as equivalent to fetuses, let alone to children. No legal barriers stand in the way of PGD with whole-genome sequencing; the burden would be on those who want to stop it.

Using stem cells to make gametes is new and could be controversial, but it will first be introduced, and approved by the Food and Drug Administration, for people who want to have their own genetic babies but lack either eggs or sperm. These couples will have a politically compelling argument – they just want the same kind of children their neighbors have, children that accidents, diseases, or age has denied to them.

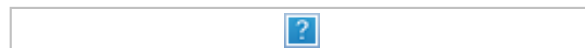
Under existing law, once the FDA approves stem cell–derived gametes for that purpose, doctors could use it for any purpose, including Easy PGD. That law could be changed, but, again, the burden of changing the law will fall on those who want to restrict the use of these gametes.

I predict that eventually, Easy PGD will be free of cost for prospective parents. Avoiding the 1 or 2 percent of births with predictable severe genetic diseases would not only improve public health but also save money. If Easy PGD costs \$10,000 for each birth, 100 babies would cost \$1 million. Avoiding one or two cases of genetic disease in those 100 would save much more. Health financing systems, private or public, will want to encourage its use.

These factors, plus a robust, profit-seeking fertility industry, constitutionally protected advertising, and the libertarian streak in American culture (especially around parents and children), lead me to believe that sometime in the next 20 to 40 years, Easy PGD will be the most common way Americans conceive their children.

But there are good reasons to be concerned about Easy PGD and the host of other new reproductive technologies lurking at the horizon. Safety, coercion, equality, and family relationships raise real and tricky questions. Many people, though not me, will also consider questions of "naturalness" or "playing God" to be real and serious.

Some laws would clearly need to be changed. (Personally, I would put laws against unconsenting parenthood through cell theft or youth high on the list.) Other changes will be widely debated. Should these methods be limited only to avoiding serious diseases? All diseases?



A couple consults a doctor about IVF. The questions in such sessions are soon going to get much tougher.

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Should Easy PGD to select for cosmetic or behavioral traits be allowed? What about enhancement? Or parents selecting for certain disabilities, like deafness? Or picking boy or girl? Should unibabies be banned, or clones?

Will legislatures try, for the first time in America, to regulate assisted reproduction choices? If they do, will the Constitution, which has offered some protection for reproductive and parental rights in areas ranging from contraception and abortion to limiting state control over children's education, allow them to? And if one state bans it, how will it stop its citizens from visiting more permissive states? Governments everywhere will have to answer these questions, and many will answer at least some of

them differently, based on their different cultures.

Families will also have to answer these questions. How much safety from genetic risks will they want for their children in a universe where perfect safety can never be obtained? How much choice will they want in their child's non-health traits?

What would *you* want? Would you use embryo selection or gene editing, and, if so, to what ends?

We need to start thinking about these questions. The future is coming. It may not be exactly the future I foresee, but, like it or not, it will certainly feature far more choices, for families and for societies, about making babies.

You now know more about that future than 99.9 percent of humanity. Learn more, pay attention to the relevant news, and talk with your family and friends. The more we consider, debate, and plan for plausible futures, the more likely we are not to create any kind of perfect future, but, at least, to avoid some catastrophes. And that is not a bad goal.

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