CRISPR and The Ethics of Genetic Engineering
What Happens Next - 11.25.22

Larry Bernstein:
Welcome to What Happens Next. My name is Larry Bernstein. What Happens Next is a podcast which covers economics, finance, politics, and science.

Today's topic is CRISPR and the ethics of genetic engineering.

Our first speaker is Stanford Law Professor Hank Greely who is the author of the book CRISPR People: The Science and Ethics of Editing Humans. A Chinese scientist recently edited the genes in a human embryo with the purpose of improving that child's defense to the HIV virus. Three children were born with these genetic enhancements and their progeny will carry those genetic changes in their germline. Hank will discuss whether the science is sufficiently advanced and that the risk/reward makes sense for babies and can the scientific community police itself to adopt appropriate safety procedures before doing this genetic manipulation again.

Our second speaker is Jacob Appel who is making his third appearance on What Happens Next. Jacob teaches medical ethics at Mt. Sinai Medical School, and he will provide us with an ethical framework to evaluate human genetic testing. Genetic engineering on babies is coming soon, now what?
Buckle up.

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Ok, let's start with Hank's opening remarks.

Hank Greely:
Almost four years ago now, on Sunday, November 25th, an email from a friend caught my eye. It had the subject line CRISPR Babies. And I thought, "Oh my, this is going to be interesting." And it turned into this book, CRISPR People: The Science and Ethics of Editing Humans.

I want to talk about the particular genetic manipulation involved in this case, called human germline genome editing.

What was that email about? Word had just broken that a Chinese scientist, who was trained as a Biophysicist in the US and got his PhD at Rice.

Larry Bernstein:
I know this is unbelievably confusing, but the Chinese scientist's name is "He". It reminds me of that Abbott and Costello routine about Who's on first.

Hank Greely:
He did a postdoc here at Stanford. He went back to China and became interested in becoming famous and immortal by being the first person to CRISPR babies. And that's what He did. CRISPR is a verb derived from an acronym. Clustered Regularly Interspaced Short Palindromic Repeats. We're all so happy that the acronym is CRISPR.

CRISPR is a way of editing DNA. It is not the only way, but CRISPR is faster, cheaper, easier and more accurate than the ways we had before.

What He did was get some people who desperately wanted to have children. The men were all HIV positive; the women were not. They were married couples. They wanted to have kids and they were very worried about the kids' getting HIV. He said, "I will change the genes of your children, so they will not be able to get HIV." They went through IVF, breaking Chinese law, by the way, which forbids HIV positive people from using assisted reproduction. They went through IVF, He changed one gene. Now we've got roughly 22,000 genes that code for making proteins. You change one of them called CCR5, which makes a protein happily also called CCR5, which sits on the outside of some of the cells of your immune system, including importantly T cells. An important part of the immune system, the most common type of HIV locks on to the T-cell and infects them by finding two proteins on the outsides of those T cells. He was going to break the CCR5 proteins. He had 16 embryos that he tried to modify this way. He put about eight of them into the uterus of the volunteer women who wanted to be the mothers. Three of them took, two of them led to births sometime in October 2018, He had five videos professionally produced and translated into English ready to go as soon as the news broke.

And two days later, a large global international human genome editing summit took place in Hong Kong, very close to his home in Shenzhen. He spoke at the summit. He expected, I think, to be received as a hero. He was received as an anti-hero. He didn't become famous. Well, He became famous except there were the letters "in" in front of the famous. He eventually stormed off the stage and has not been seen in public since. He ultimately was sentenced to three years in prison by the Chinese authorities.

But the first news report in China talked Chinese scientists has amazing breakthrough, leads world. Then 122 Chinese academics used WeChat to put out a public letter saying this is a terrible thing. This shames our country in front of the world. And a few hours later, Beijing announced that the guy had been suspended from his work. Two babies were born. Who are

they? We don't know. China says they're monitoring them closely, but for reasons of their privacy, they're not releasing any information. We only learned a year later after his trial that a third baby had been born the following summer.

I think it was an awful experiment, mainly because one of the first rules in human experimentation dating back to the Nuremberg trials of Nazi doctors, was the risks and the benefits have to be in some sort of reasonable balance.

The risks to these babies to be the very first humans created using this with very little evidence from non-human primate models, with very little evidence from ex vivo embryos. The benefits were that they would be somewhat more HIV resistant. Small potential benefit, huge potential risk. The informed consent was terrible. The parents were told they were getting a genetic vaccine against HIV. They were not told these were the first humans in the world who were going to have this done to them.

What should science do about this? This topic had the closest thing I've ever seen in 30 some years of following bioscience to a scientific consensus. This should not be done now. Maybe when we know more about safety and efficacy, maybe it makes sense, but not now. And yet science didn't stop it from happening. There were at least eight academics, including three of my colleagues here at Stanford, who knew about this before it happened. And they didn't say a word. Maybe they should have.

Bigger question, what should we think about it? There are two camps. One says because this changes not just one person, but potentially changes every descendant of that person, we should never do it. If you want to fix sickle cell disease in people, you change the genes in their blood forming stem cells from their bone marrow, but you don't change their eggs and sperm. The next generation is not affected with this because you're changing it at a very early embryonic stage.

Larry Bernstein:
How different or more radical is it to change the genes in embryo and the risk that the gene is passed onto the next generation?

Hank Greely:
Every cell on the body, including eggs and sperm is affected. The implications could go on forever, although they may not. These babies may not have babies. If they do, they may not get the edited gene. Part of the opposition is this sense that there is an almost sacred "THE human germline genome". There's no such thing. There are 7.8 billion human germline genomes. Every one of you has a human germline genome that is somewhat different. And every one of your human germline genomes is somewhat different from the human germline genome that your

parents had. Because in the time it took your parents to go from a fertilized egg to somebody who makes eggs and sperm, there were mutations that changed their DNA.

And your kids have different DNA slightly than you do. And what humans do influences that. Agriculture has changed our genes by making us able to digest starch more easily. We all have four or five copies of a gene that helps us digest starch. 50,000 years ago, our hunter-gather ancestors had one. Humans have changed their genome.

I don't think there should be this hard line banning human germline genome changes that affect future generations. On the other hand, I don't see much good in it even if it is proven safe and effective. Because instead of modifying the embryo to avoid sickle cell, treat the baby and cure the sickle cell.

Larry Bernstein:
Scientists only have a limited understanding of the nature of things. Stanford Professor Fei Fei Li spoke to us recently about Tylenol. She highlighted that the scientific community does not really know how Tylenol works in the human body. We know it reduces pain in most patients and that based on studies it does not harm patients who take it in small doses. Since there will always be limited knowledge about the effects of CRISPR, how are we to get from the lab to using it in human trials?

Hank Greely:
I know how CRISPR works in terms of the chemistry, what we don't know are what the effects are. My basic instincts are pretty libertarian in the sense that people should be able to do what they want unless there's a good reason for them not to. In health, we tend to be much more paternalistic in part because people typically don't understand very much about health and medicine. When they have to make decisions, it's usually because they're sick, which may not be the best time for rational decision making. And it's really complicated. It usually involves probabilities and statistics, which we know people are bad at or the lottery wouldn't exist.

I'm a health paternalist, although I'm not a paternalist elsewhere. What I really am offended by here isn't the idea of germline editing. It is this experiment on these people. Try it with a hundred monkeys. Try it for some awful terrible disease like Tay-Sachs. Don't try it for somewhat improved immunity to HIV, which these girls will probably never be exposed to anyway. And which by the time they're adults and sexually active may well be treatable or curable. Now the bigger issue, at some point you have to say, yeah, this is ready to go, and you will never be certain whether it’s safe.

Safety is a relative thing and an illusion. My favorite example of this is a law school case, involving a morning sickness drug from the fifties and sixties.

Larry Bernstein:
This was the drug called DES.

Hank Greely:
Turns out women liked it. It was safe except when they had taken it at a certain stage of pregnancy. 20 years later, women whose mothers had taken the drug during the wrong time of the pregnancy got reproductive tract cancers at a high rate. There's no way we could have known that when that drug was approved. It wasn't a mistake to approve the drug. It would've been a mistake to keep it on the market. We have to live with uncertainty, but it doesn't mean we have to be reckless in the face of uncertainty. And He was reckless. Some adults who could say, "I've got metastatic pancreatic cancer. I recognize this may be a really bad treatment, but what else do I have? I'll go for it." This was with two embryos who really didn't have a say in the matter.

Larry Bernstein:
Just to clarify your medical ethics decision tree. Are you saying that if the disease is particularly deadly, and the risk/reward is very skewed to the patient's benefit, then you would favor CRISPR experiments?

Hank Greely:
Not at the time that He did it. Because He hadn't done the research that you can do. Do a hundred Rhesus monkey babies and see what happens. Make a bunch of CRISPRed human embryos and follow them for the 14 days that's currently allowed and see if they're developing normally or not. Do the homework before you try something that might end up really devastating a couple of babies who never volunteered for this.

I figure 5 to 10 years of pre-clinical trials, 5 to 10 years of ex vivo work, 5 to 10 years of work with non-humans, then you start clinical trials with carefully selected people where the risk benefit ratio is most favorable. And you see what happens. We got lucky with IVF. And it's still the case that every IVF baby could drop dead at age of 45, because I think Louise Brown, the first IVF baby, is now 44. I'm not of the camp that says, no, we can't cross this line. I'm in the camp that says, if it's safe and effective, we should be able to think about it. But there aren't very many cases where I think it would be important and necessary.

I will give you an example, cystic fibrosis disease, life expectancy used to be like under 10. It's now forties or fifties. But if two people with cystic fibrosis meet, they're now often pretty healthy, healthy enough in their twenties and thirties to want to have kids. All of their children genetically would have to have cystic fibrosis because of the nature of the genetic inheritance. It's what we call in the trade autosomal recessive. In that case, I would say if it's proven safe and effective, they've got a good reason to use it. How many couples like that are there in the world?

Not zero, but not probably tens or hundreds of thousands. Not just with CF, but with all the similar diseases.

Here's the problem. We don't know squat about genes. What we do know about genes makes it a little more problematic because it appears that most genes do many different things. I said CCR5 is a gateway for HIV to infect T cells, it probably didn't evolve for that purpose.

It's found in all non-fish vertebrates. It does something good. We don't know what it is. One thing you have to worry about in the long-term project that may well turn out to be a good idea, but we'd have to know a lot more than we do.

Larry Bernstein:
This is a big world. In the future, there may not be a global scientific consensus on what is acceptable behavior for embryo gene editing using CRISPR. Parents will want to make choices. They may prefer a specific gender, athletic talent, intelligence, creativity, physical attractiveness, whatever. Scientists will try to meet customer demands. Maybe it gets done in the US, maybe it happens on a Caribbean Island. If it works, it is coming.

Hank Greely:
The thing people care most about often is intelligence. We know that genetics is involved in intelligence.

We know several hundred genes powerfully affect intelligence. If the genes broken, your intelligence is extremely low. We know next to nothing about genetic variations that increase intelligence. Other than there appear to be thousands of them. And there's a simplistic algorithm being used by what I think is a quasi-quack company to sell parents about intelligence of their embryos. It assumes that all these different pluses and minuses, all of which are in the area of 0.0, 0.5 to 2.0 IQ points, that they're all additive. But we don't know that.

I don't see a permanent and complete ethical wall against germline genome editing. Not for me. It is for some people. 150 countries in the world don't have any law on this. But of the countries that do regulate it, they all currently ban it. I think that's kind of unwise.

The US bans it. Congress has passed appropriations riders that say FDA cannot spend any money or view as received any application to do research on anything that changes human heredity. It's been passed now five years in a row. Politically it's an uphill climb.

Larry Bernstein:
You mention in your opening remarks that Stanford scientists were aware of the Chinese scientist HE's experiment, but they did nothing about it. What happened?

Hank Greely
Part of it is a strong cultural reaction in many places including mainstream American culture against snitching.

I use snitch on purpose rather than a whistleblower because there is the negative connotation. There's a lot of confidentiality in science and in medicine. Most patients have no idea how limited that confidentiality is legally. And how in some cases their doctor not only can't keep things secret but required to tell the police on you.

You walk into your doctor with a bullet wound in your shoulder and she's got to tell the cops. I propose there should be at least an aspirational ethical view in science that if you see science that is too unethical, however you define that, you should tell somebody. One of the three Stanford people who was involved said in a forum that I moderated that in retrospect he wishes he had talked. But who would he talk to? He didn't know the hospital in Shenzhen that approved this. Chinese authorities who he doesn't know? Does he talk to US authorities? He said, "Well, you could talk to the press that probably would've worked." But part of it is having structures that make that kind of information gathering information distribution easier.

Larry Bernstein:
What is the current state and the progress with CRISPR research?

Hank Greely:
CRISPR is being used enormously. It's often used for pure research. Cells in Petri dishes. It's also often being used in live animals and plants and bacteria and other organisms. It's being used in humans, including here at Stanford to try to treat genetic diseases.

What has been roundly condemned is humans modifying embryos with the intention of having them give rise to babies who would then be able to pass that trait on. That's the small, tiny subset of CRISPR research that has been condemned.

And I'm opposed to doing human germline genome editing at this point when it hasn't been shown to be reasonably safe and effective. And to tie it into the severity of the condition. Safe and effective is a relative thing.

If I had a drug that if given to people with metastatic pancreatic cancer, one of the worst prognoses you can get, and it instantly painlessly killed half of them and instantly and painlessly cured half of them, that's a miracle drug. FDA approves that in an instant as it's incredibly safe and effective in that context. Once it's approved for one thing, under what's called the off-label use doctrine, a physician can prescribe it for anything else. If you think for some reason that it's

good at treating teenage acne and it painlessly kills half the teenagers and cures the acne of the other half instantly, it’s not safe and effective. So, the safety and efficacy are intertwined with the danger of the original condition.

Larry Bernstein:
I end each episode on a note of optimism, Hank what are you optimistic about?

Hank Greely:
I think CRISPR is going to change our world, our children's world, our grandchildren's world. It gives us control over the biosphere. We'll be able to really engineer biology from the bottom up. We will do great and wonderful things with that. We will also do stupid and terrible things with it because we are people and that's what we do. We're really terrible about getting things perfect, but we're really pretty good at muddling through.

We need to plan for the problems, and we need to monitor what happens and make midcourse corrections as necessary. And we're not wonderful at that, but I do think it's going to be, on balance, a great benefit. And I only wish that I'd be around in a hundred years to see how it ends up.

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Larry Bernstein:
Jacob, tell us about genetic engineering and CRISPR and how medical ethics applies to this emerging technology.

Jacob Appel:
CRISPR is a technology that involves changing the genetic makeup of human beings in a way that will affect not just them but their progeny by making genetic changes to the germline. There are two different sets of ethical issues that arise. How much risk should any individual, whether a parent or a scientist, take in creating a child. Then the societal risk the implications of making such changes for the world.

Larry Bernstein:
Let's start with societal oversight and decision making. In 1927 in the Supreme Court Case Buck vs. Bell, Supreme Court Justice Holmes famously concluded that three generations of imbeciles were enough, and that the state was justified in sexual sterilization for the mentally disabled. That decision is now viewed as abhorrent; I suspect because the state should not be involved in interfering with private decisions like having a child.

In the future, the public policy issue will be the opposite. It will be regulating designer babies that are smarter, more attractive, faster, more creative, simply better. Does the state have a stake, a valid interest, in preventing parents from engaging in genetic engineering?

Jacob Appel:
So that's a very complex question. Ask yourself: were the individuals involved in the eugenics movement wrong because their science was wrong? Based on racial theories of eugenics, but simply inaccurate and disturbing because of their inaccuracy? Or were they also wrong, even independent of the science? Even if they could have improved the species by reducing the risk to disability and increasing life expectancy and the like, would they still have been wrong?

And the second question is, were they wrong because they imposed this upon people? It was involuntary, which many find deeply objectionable.

The state clearly has some interest in the reproductive welfare of human beings. It wants to make sure that there are relative gender balances in the population like India or China, where you see a tendency to either abort or euthanize infant females.

Society may have interest in preventing birth defects or disorders that cause severe suffering for infants. Beyond that, we tend to step back and allow parents to make decisions. But as those decisions affect other people that might give us pause. I will offer two very different thoughts on the issue of genetically enhanced children.

They might prove the great equalizer, because right now, if you are well off, you get into good colleges or excel intellectually or athletically. You get an SAT tutor, a tennis coach. You use all sorts of economic means to make your kids better. CRISPR offers similar opportunities at a very cheap rate to other individuals who can't afford a tennis coach or an SAT tutor but might be able to afford genetic engineering to make their kids brighter or more talented.

By changing these polymorphisms in society, you may have unintended consequences. For example, there is good data to suggest that individuals who have bipolar disorder have close relatives who are more creative. Now, if you removed the gene that causes bipolar disorder from the population, you would have one fewer debilitating illness, but you also might have less creativity. We would notice the visible victims we saved. We'd never notice the invisible loss. And that's the challenge of tinkering with the genome.

Larry Bernstein:
Eugenics is now discredited. Science is uncertain and can often be wrong.

Jacob Appel:
I think the most important thing is we want to be very humble in our approach to any matter of scientific policy. I always like to say that half of what we teach you in medical school is wrong, and we don't know which half. In the 1920s in New York City, there were two treatments for heart disease. In the great Mount Sinai Hospital where I work, they prescribed six months of bedrest and a pioneering cardiologist across town prescribed beer. Now, which patients did better? The answer is those who got beer, not because beer cures heart disease, but because bedrest after heart attack leads to clotting and strokes and killed thousands of people. There were repeated episodes of this all throughout history.

We gave people anti-arrhythmic drugs in 1970s because we thought they would prevent benign arrhythmias, but they led to increased fatality rates. Medicine is far from foolproof.

With that in mind, when I get on the elevator, I'm confident it's going to stop. And when I get on the airplane, I'm confident it's not going to fall out of the sky. So, to some degree, we do rely on science. I think the challenge today is that we have far more experts than we have expertise. We have the demonization of expertise where everybody sitting in their living room thinks they understand nuclear physics. So, we want to be humble but understand that some people know more about these questions than others and to at least a limited degree defer to their wisdom.

Larry Bernstein:
I want to bring it back to CRISPR. Professor He, either on his own or in collaboration with members of the Chinese government, decided to make CRISPR embryos. They are now young children. Members of the global scientific community were outraged by these births, and Professor He was later arrested and has not been seen publicly since.

Our previous guest Stanford Professor Hank Greely thinks that before we use CRISPR technology, there should be a scientific consensus on the matter. Do you believe in that framework, and if so, who should be the decision makers, and what does it mean for the scientific community to have consensus?

Jacob Appel:
I mean those are great questions. There's been this portrayal of Dr. He is a rogue scientist. I find that highly unconvincing the notion that any leading scientist in China could engage in a project of this size without the knowledge if not outright condonement of the Chinese authority seems highly implausible. He was given a large research institute funded heavily. The day after his announcement was made it was championed in the Chinese state media. Only later when there was an international backlash did they retreat from that claim. People in the Chinese authority thought this was going to be viewed as a great breakthrough and were surprised it wasn't.

With that caveat, scientific consensus is a way of making sure that nobody does something that has large negative implications that they haven't thought through. It could be in an area like CRISPR. It could be an area like genetic engineering of crops. It could be an area like nuclear technology. There are some things that are dangerous, and you want to make sure that there's a scientific body or a consensus of scientists looking at the parameters of the extremes to make sure somebody's not getting so far out of the tent that they do something that damages the rest of us.

Larry Bernstein:
At the outset of COVID, President Trump called it the China virus, and he said there was a significant possibility that the virus originated from a lab in Wuhan. Immediately thereafter, there was a letter signed by several scientists that made it seem like there was a scientific consensus on the issue that the virus originated in a wet market and the scientists condemned Trump's Wuhan lab leak hypothesis, effectively shutting off debate. In the last month, there was an article from a prestigious scientific journal that suggested that the COVID DNA included clips of genetic information that likely came from a lab. I am not suggesting it is definite one way or the other, just that the scientific consensus seemed dogmatic before the facts were in, probably because Trump said it.

We all make mistakes like the scientists who promoted the eugenics movement. What do you make of this Wuhan experience specifically and the interaction between the scientific community and the public during COVID more broadly?

Jacob Appel:
Well, I think science often gets things wrong, and we should not lose sight of that. I always like to say, we should not mistake incompetence from malice. Looking forward, it doesn't really matter whether COVID was developed in a lab or whether it developed from natural evolution in a wet market, because both are threats to us going forward. The more we focus on the danger going forward, and less on rehashing scientific mistakes or potential mistakes, the better off we're going to be. Because there are still wet markets in China engaging in the exact same kinds of agricultural processes and economic processes that if they didn't give us COVID, are going to give us another pandemic sooner rather than later.

On the other hand, there are still people engaged in function research around the world that are going to likely give us some pathogen. Rather than squabbling over where we put the deck chairs in the Titanic, we really need to build a better boat.

I am sensitive to the concern that scientists may be too quick to make pronouncements, sometimes without the humility that they should have. I think the verdict is still out on the

origins of COVID as it is on many other scientific mysteries. We may not know for 50 years exactly what the origins of COVID were.

Larry Bernstein:
Back to CRISPR. This is a readily available technology and there's lots of experimentation and learning going on right now. There is a consumer desire to do genetic engineering for their kids. How should we use this technology in a responsible way?

Jacob Appel:
The first step is to make sure the technology works. Science has a very careful, generally agreed upon process for doing that, where we begin by testing in a lab and then test in animal models and then test in a very controlled setting on human beings. I would've suggested to Dr. He that even once this reaches a level for trial in humans, when it's ready for the marketplace that we would begin addressing a disorder that was a hundred percent fatal for which parents had no other recourse, rather than a disease like HIV. You really want to follow the chain of command from most safe to least safe when going through this process rather than skipping steps.

Larry Bernstein:
Dr. He skipped some steps. We know that there are three children that were born with a permanent change to a genome that might reduce the likelihood of HIV transmission. You've mentioned that there is a societal risk associated with these three children because they will pass on these new genes. What do you think society should do about it? Should these three kids be allowed to reproduce? What rights do these children have simply because they are now living human beings?

Jacob Appel:
That's a great question, and I should begin by saying there's clearly an individual risk to these children. These children are susceptible to a range of genetic disorders that might suggest they won't live full healthy lives. It's also not even clear that they're going to have a reduced risk of HIV based on the scientific techniques used. The community risk is that CRISPR babies will become reproductively or evolutionarily more efficacious than their peers. They will reproduce more, and their traits will spread through the population at the expense of others.

The odds of that occurring from three babies in China are low enough that we really don't need to think about at the communal level, and we want to be very cautious in denying rights to these individuals who are human beings and presumably have the same inalienable rights as the rest of us. On the other hand, letting this technology spread further, where you create thousands or millions of children with similar traits could lead to rapid change in the species.

1% of the people in Mongolia are descended from Genghis Khan, a handful of families in Central Europe in the ninth century mothered all the Ashkenazi Jews, and all the people in Ireland traced back to a small set of ancestors. The odds of these three young people in China producing a similar effect are one in 8 billion more or less. So, I would not worry too much about it.

Larry Bernstein:
Do I own my genetic code? Who has the right to clone me? Can someone steal some of my skin cells and clone me? Who has the ethical and property rights to my genome?

Jacob Appel:
Well, you raised two very distinct phenomena. First, there's the theft of genetic material and some states criminalize the theft of genetic material, but others don't. There was a longstanding lawsuit between two billionaires over a piece of dental floss that one of them stole from the other one's garbage to prove paternity in a well-known suit. The question of whether stealing someone's cells was theft or not was litigated in the courts.

But the second question you're asking is, once I take that DNA and create a human being who is a clone, will you have any proprietary right in that clone? I would suggest that clone would probably be an independent human being with its own set of rights.

What's more interesting from a legal and ethical point of view, is what your relationship with that clone. Would that clone be your sibling? Would it be your child? Where would it fall on continuations of next of kin and inheritance in the medical decision making? How would that fit in with the other members of your family? I will add that there is in the New York Family Healthcare Decisions Act, where it says that first your spouse makes decisions, and then your children, and then your parents. There's no place for a clone.

Larry Bernstein:
Dr. He did his experimentation in China and the Chinese government arrested him. But it's a big world and given that this technology is relatively easy to use, a scientist could set up a lab in a Caribbean Island or some third-world country. In this unregulated place, the scientists could create embryos that reflect the parent's preferences. What are the implications for enforcement of these laws, norms and scientific consensus when there are limits to global enforcement? Could the parents bring their enhanced child back to the US in utero or after birth?

Jacob Appel:
That's an excellent point because in the past we've often thought of scientific consensus in areas where there was such a gap between the average person's knowledge and the scientific community, that it was easy for the scientific community to regulate. It would be very difficult,

for example, for you to build a plutonium bomb in your backyard. CRISPR is easily portable. You can look up online how to do it. The barriers to entry are much lower. So, unfortunately, there is high risk of a rogue scientist somewhere. I would add that if I were Dr. He, in hindsight, I would've chosen someplace like Cayman Islands where there's far less regulation and far less state pressure than an authoritarian regime like China. Somebody else will follow that path. There are people going to small islands, doing science they could never do in the United States or in China.

Larry Bernstein:
Medical ethics evolve. In 1796 Dr, Edward Jenner scraped some cowpox and inoculated it into the arm of his gardener's 8-year-old son. What do you think about that behavior? He was highly honored at the time and is known as the father of immunology and recently he was listed as one of the top 1800 Britons by the BBC. What do you make of Jenner's action in the context of a lack of scientific consensus or responsible behavior for his medical experimentation?

Jacob Appel:
I will add, Jenner was not the first person to try to inoculate someone against smallpox. He was just the best publicist of the technique. Other people before him, both in Germany and in Britain, had done this to reasonable effect. He just presented his paper before the Royal Society and got credit.

You could argue that the stakes for smallpox were so high that taking some risk was worthwhile. But then you have to ask, who should that risk be imposed upon? Should it be imposed upon a random member of society chosen by lot? Should it be imposed on Jenner himself?

It's hard to come up with a moral regime where it should be imposed upon the gardener's son, some random person who has no knowledge to take this risk.

Which is why IRBs today make sure that we don't choose some vulnerable population and test our treatments on them. Now, we do view Jenner as heroic, even though we would never be able to do his experiment today. Science is full of stories of people thinking they were doing something useful and causing a great deal of danger. In my own field, things we were doing in the last century include frontal lobotomies, insulin comas, and implanting the testicles of animals under the forearms of children to prevent mental illness.

Larry Bernstein:
Jacob, you were on the What Happens Next podcast in the Spring 2020. At the time the Moderna mRNA vaccine was developed and was ready for testing. I suggested that we seek volunteers to take the vaccine and then be exposed to heavy doses of the virus to test its efficacy. I want to apply this risk/reward tradeoff to disease like smallpox. At the time, you said that

medical ethics did not allow for this voluntary choice even though millions of lives hung in the balance. What do you think now?

Jacob Appel:
There could have been an alternative scenario where the vaccine killed everybody in the trial and then I would have the better half of the argument.

Larry Bernstein:
If you expose the vaccine trial participants directly to the virus, you can use a much smaller trial size. Every day counts. We will know immediately whether the vaccine prevents hospitalization, and then we can increase the trial size to evaluate if the vaccine harms the individual over time.

Jacob Appel:
If you believe in classical economics that is a very convincing approach. The problem is that ignores human irrationality and optics. If you give the vaccine and 10 of them die, then the damage you do has implications to deter people from getting care even when they need it. And where there's already a lot of suspicion, the risk of that is a major factor in your calculus.

Larry Bernstein:
In Operation Warp Speed, the Health Department decided to have a trial population that matched US race demographics. They had trouble finding African Americans and Hispanics willing to participate and that delayed the trials by a few weeks. There was no scientific evidence that matching US race demographics improved the efficacy of the vaccine trial. Other countries like Brazil or Canada decided to use the Pfizer and Moderna vaccines even though their racial demographics differ from the US. Why apply racial optics that have no scientific basis where the cost of delay is thousands of lives?

Jacob Appel:
It's a calculus. In an ideal world, we wouldn't have to do that. There is no plausible reason to believe that people who have different races or different ethnic groups or backgrounds are going to respond differently to a vaccine like this. It borders on racial pseudoscience. On the other hand, particularly in communities that have been victims of things like Tuskegee, they're already doubtful. If you tell the African American community, we have this vaccine we've tested in white people, many of them are going to be very suspicious of taking the vaccine. So, the reason they did this was not just biological, it was also optical.

Larry Bernstein:
The Tuskegee experiment affected the decision making for operation warp speed policy makers. But I'm not sure what the African American population knows about Tuskegee and therefore its relationship with vaccine hesitancy might be tenuous. As a public policy matter aren’t these fears

better dealt with education. Should we do things that cost lives, millions of dollars that have no scientific basis for purported optic reasons?

Jacob Appel:
In the long run, obviously education is the way to solve this challenge. In the short run, you can't really educate the population in a manner that guarantees trust in the health system or the government. I think we underestimate the level of distrust that people have, not just in the African American community, but in many communities, particularly today with lots of misleading information out there about vaccination.

Whether or not people can tell you specifically about the Tuskegee experiment, many African Americans, they've had experiences that make them think, do I really trust the white-run healthcare system? I've seen experiences in my own career that make me understand why they might think that way.

Larry Bernstein:
If you want to deal with African American vaccine hesitancy, why not deal with it directly instead of doing non-scientific studies. Why not ask Michelle Obama or another leader in the African American community to do advertising to persuade them?

With COVID, the scientific community seems unwilling to be transparent about the risk/reward and have thus lost the trust of some of the American public.

Remember that incident when Fauci said that masks have no benefit and then a week later said, “Actually, masks are really helpful.” And then when asked about the abrupt change, he said, “I was worried that there would be a run-on masks and I wanted to keep the masks available for the medical community.” That upset people because it showed that he was willing to mislead the public to achieve other objectives.

Jacob Appel:
I think transparency is important. The crisis we face right now is if there were another pandemic or another public health threat, we will be able to get nobody to do anything to prevent it. Because everybody has their own doubts. If I were the average person and the government announcement about the next pandemic, I would be very suspicious.

That's a problem because the odds are, there's going to be a next pandemic and we need people to act accordingly.

Larry Bernstein:
What do you think about the interaction between local public health officials' proclamations and individual behavior? There was a COVID study done in the Quad cities where half the population lived in Illinois and the other half in Iowa, and when the relevant states changed its COVID policies, there was no difference in individuals' behavior across the state lines. The study concluded that individuals evaluated COVID risks and decided to protect themselves based on their own heuristics and did not rely on state guidelines.

Jacob Appel:
I'd like to draw an analogy to surgery. In surgery, if you have different values as a patient, whether you want to take a certain risk of dying on the table versus a certain risk to watchful waiting, we let you make that decision. But if you have different opinions about the surgery itself, you want to use a size seven Alexander clamp rather than a size nine Alexander clamp during the procedure, we don't let you make that decision. One is an empirical question of science, and the other is a question of values. I think the same logic to some degree applies to the public role in decision making. The actual risk is something that should be scientifically determined by the experts. How that risk should affect decisions about policy is something the public should have a say in because they live with the consequences and that is a moral or value judgment.

Larry Bernstein:
One bizarre aspect of today's medical care is that when you need to make a major health decision you consult with medical experts in the field, often with a loved one because the issues are too complicated to decide on your own. You meet three doctors, and they recommend three different medical procedures. Oftentimes, the doctors say that the other doctors are wrong. And then this uninformed patient needs to make a major life decision. What do you think about these patient interactions with physicians?

Jacob Appel:
A good doctor would not be highly dismissive of other approaches but would be open-minded that other people may do it differently. But I realize that's not often the reality in the community. I hear that story all the time, the assumption that one of these doctors is correct and the other two doctors wrong. But I think a better analogy is to marriage. You married your spouse. You don't think there could have been two other women I could have married and lived happily ever after with although there very well might have been.

Therefore, with a lot of these medical interventions, all of them have some significant potential for success. All of them have some potential for failure, and the differential between them is actually very low. It doesn't behoove any doctor to say the differential between me and my colleagues is very low. But from the inside, I can tell you that's often the case. You might make a

system where you could be responsible for malpractice if you didn't acknowledge other people's success rates is better than yours. But for a whole bunch of social reasons, we have chosen not to do that.

Larry Bernstein:
Back to CRISPR. This technology is coming, and it will be used. If the US bans it, Americans will go to a country that allows its use. Now what?

Jacob Appel:
I think you're asking both what I would do on the individual level, what I would do on the collective level. If I were a scientist, I'd be very interested in the technology.

If I were a businessperson, I'd be very interested in the potential. If I were a parent, the last thing on earth I would do right now would be to line up for CRISPR, because we have not worked out the potential damage.

I don't think there is very much that an individual government or even the world can do to prevent CRISPR from happening. I don't think we can build walls between countries to keep it from happening. We need to keep a very careful eye on what is going on and adjust our policies accordingly. We're going to have to have very clear laws for how to deal with babies born of CRISPR, but specific laws are going to be something we can work out with time. Knowing that we have to be proactive to create those laws is really important. And I hate to say this, but I don't think the government is doing a very good job preparing for that eventuality and setting up the bodies of experts to inform the government when that time comes.

Larry Bernstein:
Stanford Law Professor Hank Greely, who just spoke on this podcast suggests that we should have sound and reasonable guidelines for CRISPR. What does sound and reasonable guidelines mean to you?

Jacob Appel:
I'm sure that that Professor Greely and I have a strong commitment to very different ideas of sound and reasonable. I think the first goal would be to make sure that CRISPR is not done until we're fairly confident that the downside for the individual is outweighed by the potential benefit. We want to be pretty sure, by a wide margin, we don't want to have the 51% to 49% chance your kid will be better off. Secondly, we want to do it in a controlled way, not just in the short term, but in the medium term, so that we have a generation of children, a small number, who grow up because of CRISPR, to see their impact on each other and on society before we have widespread CRISPR. Finally, we need complete transparency with the public. We should not announce to the public 20 years from now that there have been CRISPR children living in their midst, and they

don't know about it. We should make sure that the average person can find out what the state of CRISPR technology is and make their own choices accordingly.

Larry Bernstein:
My two favorite foods are tomatoes and chicken. And CRISPR technology is used to improve plant and animal production. How do sound and reasonableness apply differently with plants and animals versus humans?

Jacob Appel:
I think plant models are a really good example to show what the impact on human models can be. If you allow Monsanto to grow genetically engineered corn, which can certainly increase the corn output and feed lots of people. If you are a corn grower who doesn't use Monsanto crops, you end up with thinner, less healthy, degenerate corn. A rising tide raises all ships and the same is going to apply to human beings. But once we allow some people to be faster, be smarter, be stronger, other people are going to feel the pressure to do so, even if they don't want to buy into genetic selection or CRISPR. I also should emphasize that we really do want to have some centralized control mechanism for any of these biological changes in plants or animals.

Because there's a lot of risk involved as well as a lot of reward. If the government and the central authorities know the variations that are being put into place, it'll be easier to take action to stop them or protect us if something goes wrong. If we don't know what some small company is doing in some Caribbean Island, they could do something catastrophic, and we won't know until it's too late. Someday you could discover that your tomatoes taste like chicken.

As a doctor, I have to tell you an all tomato and chicken diet is probably not a good choice.

Larry Bernstein:
Why is that?

Jacob Appel:
Tomatoes are good for you. Chicken in small numbers is good for you but you're missing a lot of other material in the process.

Larry Bernstein:
I had some sauteed spinach with my chicken yesterday.

Jacob Appel:
That's a good step.

Larry Bernstein:
Will CRISPR be widely available in the future? And if so, should equality be considered, or should we try to maximize the number of creative geniuses or some other objective like increasing average intelligence. Another Shakespeare or Einstein can benefit all of humanity.

Jacob Appel:
I think the potential for CRISPR to be very cheap and easily available is very high in the long run. You will go to your doctor get CRISPR the same way you get blood testing or an EKG.

Larry Bernstein:
Aren't you referencing non-embryo situations?

Jacob Appel:
Or in embryo situations. There's going to be the potential simply because it'll be large scale economies of scale, and this will be something that could be readily available to most people when they choose to produce children. That may be 20-30 years from now, but there's going to be a lot more equality involved than people think, although possibly not in the developing world. I'm not saying that if you live on a subsistence farm in India, you're going to have CRISPR available. But if you're a middle-class family in the suburbs, you may have CRISPR available to you. I do think you make an excellent point, which is another key advantage of CRISPR, is you shift the entire population in a direction. Meaning, if you add five IQ points to everybody that means you get five more geniuses per generation at the top of the bell curve, or 10 more geniuses that is in Einstein or a Newton every five years, that can improve the quality of life for everybody.

Why do I really care about increasing equality? If you equalize resources over a certain threshold, data shows, society ends up more stable and people who have more resources end up with higher quality of life as a result. So, we all are in essence in the same boat.

Larry Bernstein:
I have two kids made the old-fashioned way. They look like me and are clearly related. As a society we want more Einstein's, but I want my kids to be like me. How should we think about genetics as it benefits society relative to the preferences of the individual or the family?

Jacob Appel:
You did not choose a random partner. You chose someone. I have not met Mrs. Bernstein, but I assume she's intelligent and attractive and talented and-

Larry Bernstein:
She's also very excited to meet you, Jacob.

Jacob Appel:
I am looking forward to it, and I have no doubt she will meet my expectations because you clearly chose her because you thought that she was a preferable mate. Intelligent, handsome, successful people tend to find similar attributes in their mates. It isn't random and there's some balance between wanting to better your children and wanting your children to be like you. But you make a great point. I give thousands of lectures around the country, and I ask people how many of them would like to be cloned, and I ask them what they're looking for. And most people, when I talk about choosing children, say they want someone who looks like them or acts like them or reflects them.

It's a natural, healthy, egocentric view of child raising. On the other hand, people also want their children to do better than them in some ways. There are going to be some people who want their kids to be a little more intelligent than they are, and some people who want their kids to be just as intelligent than they are. That'll balance out in a way that slowly improves the lot of humanity. It's very rare that I meet someone who says they want their kids to be less successful than they are. They probably shouldn't be having children at all.

Larry Bernstein:
I know that with some diseases we can do genetic testing for example with breast cancer or Parkinson's. Will CRISPR allow doctors to excise those genes that promote disease?

Jacob Appel:
Yes. I think that is a realistic goal in the future, maybe not next year, but we're already doing gene therapies for certain disorders. There have been ophthalmologic diseases which we have treated with gene therapies that work. We are in our lifetimes going to be able to use gene therapies to prevent a wide range of disorders. That will involve CRISPR doing it in the human being rather than in the germline.

Larry Bernstein:
Just to clarify that, what you're saying is that what you find problematic is genetic engineering done at the embryo level because that change in the genetic material will be passed onto future generations. But if you manipulate the individual's genetic code after birth then it will not be passed on through your eggs or sperm in the germline.

Jacob Appel:
Yes. That is the goal and most likely the scientific outcome. My personal view is if you're not affecting the germline, if you're not affecting future individuals, you should be able to do anything you want to your own genes, certainly in an enhancing way. I don't see the societal risk to that as long as there's informed consent and you're competent, I don't see the individual

concern. It's when you start doing it in a way that affects your offspring that there are ethical issues involved.

Larry Bernstein:
Jacob, I like to end each episode on a note of optimism. What are you optimistic about?

Jacob Appel:
Scientific technologies having enormous potential to change the way we live to eradicate disease and help the world. It's important that we not get focused on the details of the ethics or the details of the science, instead to focus on a larger potential. If we lived in a perfect world, I would be an arch conservative because I would want no change. But since we don't live in a perfect world, it's very important as a scientist and a thinker that we should be disruptors, because the more disruption we engage in, the more likely we are of achieving a better world in the future.

Larry Bernstein:
Thanks to Hank Greely and Jacob Appel for joining us today.

If you missed last week's show on Food Porn, check it out. Our speaker was Rebecca Halpern who wrote and directed the new documentary film Love Charlie that is currently in theaters and is available for streaming on Apple and Amazon. The film is about the life of Top Chef Charlie Trotter who revolutionized American cuisine. Charlie was a creative genius who used a different 10-course menu each day for 25 years. He introduced us to farm to table, placed a table in the restaurant's kitchen, and eliminated hard liquor and foie gras from the menu.

Charlie Trotter influenced many of the great top chefs of his generation and demanded excellence from everyone around him.

Next week the topic is, are you white?

Our speakers will be Dan Bouk who has a new book called Democracy's Data: The Hidden Stories in the US Census and How to Read Them. Dan will speak about our ongoing governmental data collection to determine race, gender, and other personal information. The search for these answers and ethnic classification divides us.

Our second speaker is George Mason Law Professor David Bernstein who is the author of the book Classified: The Untold Story of Racial Classification in America. The answer of who is White, Black, Hispanic, Asian, or other has consequences in getting government contracts, jobs, and college admissions. The question is should the government be ascertaining race and is that undermining our objective of having a post or multi-racial society?

You can find our previous episodes and transcripts on our website whathappensnextin6minutes.com.

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I would like to thank our audience for your continued engagement with these important issues, good-bye.