2023 UEHIRO-CARNEIGE-OXFORD ETHICS CONFERENCE
PROCEEDINGS OF CONFERENCE REPORT - ETHICS OF CELL AND GENE THERAPY
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Organizers: Uehiro Foundation on Ethics and Education, Tokyo
Carneige Council for Ethics in International Affairs, New York
Oxford Uehiro Centre for Practical Ethics, Oxford University
Centre for Biomedical Ethics, National University of Singapore

Purpose
The purpose of this conference is to facilitate the exchange of ideas across the Carnegie-Uehiro-Oxford network in the US, UK, Japan and beyond. The organizers will also use the ideas generated at the conference to shape future programmes at their institutions.

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1) The Ethics of Cell and Gene Therapies in a Constantly Shifting Landscape

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Basically, what I want to talk about is the ubiquity of change and its implications for the ethical, legal and social and policy and political implications of biotechnology. I'm talking about changes beyond the "hype cycle", where every new technology immediately is heralded as revolutionary, and within a few months plummets to the bottom of everyone's attention. But then, often, it comes back up, and goes back down, making the pattern of a sine wave over time.

I also want to talk about changes beyond those occasioned by the long delays that seem to be inevitable. Although the COVID vaccines are excellent counter-examples, it usually takes several decades for even successful discoveries to move from the laboratory to the clinic. Monoclonal antibodies took 20 years to become what they are now—products that include Humira, the best-selling drug in the world. Gene therapy has taken 40 years to get to the point where it's now finally beginning to be approved. New treatments usually take a very long time to affect the world.

But those really aren't the kinds of changes I want to talk about. Instead, I want to talk about three kinds of changes. First, I want to talk about what happens when the relevant science changes and how that can upset our ethical, legal, social policy issues. Second, I want to discuss what happens when changes in other sciences have important indirect effects on the science in question. And then, third, what happens to technologies when the society goes through relevant changes while the technology itself is being developed? And I plan to do this in the next 25 minutes or so and then take questions.

WHEN THE RELEVANT SCIENCE DOES NOT DEVELOP AS EXPECTED

First, what happens when the most relevant science doesn't develop the way it's expected? Sometimes that's predictable. Sometimes it's not. In January 2015, I had the great good fortune of being invited by Jennifer Doudna to a small workshop in Napa Valley, where the discussion, at her request focused on issues of human germline genome editing. Jennifer, one of the co-discoverers of the CRISPR technique, was very concerned about the possibilities of human germline genome editing. She invited a dozen scientists to a meeting of 14 people. My bioethics colleague, Alta Charo, from the University of Wisconsin, and I were the only non-scientists there. We had a fascinating day's discussion that led surprisingly quickly to a consensus. That consensus led to a joint paper in Science. And that paper was part of what caused the American National Academies of Science, Engineering, and Medicine to create a special program to look at human genome editing.

I was powerfully struck by the fact that two of the people at the meeting were scientific giants. Paul Berg and David Baltimore had both won Nobel prizes (so a few years, later, did Jennifer Doudna), but they were also two of the five organizers of the famous February 1975 Asilomar meeting, which proclaimed a temporary moratorium on recombinant DNA research. Our meeting was held almost exactly 40 years after the Asilomar meeting. Both Berg and Baltimore, in talking about human germline genome editing, said that "we" had said definitively at Asilomar that scientists would never do germline editing and that it would stay forever. off the table. I asked them where that was written down or published—was it in the conference's conclusion statement. And they said, Well, no, but we were constantly saying it.

One of the truisms about science policy is that it is very easy for scientists to promise not to do things that they don't know how to do. At the Asilomar meeting, on recombinant DNA, there was no expectation that human germline genome editing was going to be feasible for many decades, if ever. So they promised that they wouldn't do it.

In retrospect, it was quite predictable that at some point (it turned out to be four decades later), that human germline genome editing would become feasible. And that is an example of the relevant science changing. A policy was set out by the scientists, in part, for public relations and political purposes, to forswear ever doing something that at that point, they didn't know how to do. But then it turned out, they could do it. And so the policies had to be changed and revisited, at least reconsidered.

Human cloning is a second great example. Many of us, who were more than eight years old in 1997, probably remember the announcement of the birth of Dolly the Cloned Sheep. Dolly was one sheep, one embryo out of 287 managed to become a living lamb. And yet, as soon as Dolly was born, the headlines around the world were filled with stories of armies of cloned warrior slaves. The hysteria that was triggered by the cloning of Dolly was, in my experience, unprecedented, as well as inappropriate. But it triggered lots of legislation. 27 American states introduced and about 15 passed laws relating to human cloning. Many other jurisdictions around the world hurriedly did so. The Council of Europe's Oviedo Convention was amended, immediately after it was adopted, to include a ban on human cloning.

But our British friends, taking what some might consider a typically British attitude said "Oh, not to worry, we've already banned human cloning." I was a little surprised by that, so I looked it up.

And in fact, in the 1990 Human Fertilisation and Embryology Act, a section forbade the Human Fertilisation and Embryology Authority the Act create from granting licenses for human cloning. So the British were right, they had banned human cloning seven years before Dolly. The problem was, they defined human cloning in that act as replacing the nucleus of a cell of an embryo with a nucleus taken from the cell of another person or embryo. That was not the process used to create Dolly. That process involves removing the nucleus from an egg, not an embryo, and replacing that with the nucleus from another cell and then triggering it to develop. The British legislation had tried to foresee the future in order to prohibit a scientific advance that they didn't like. But the science took a turn on them that the law didn't anticipate and their ban was ineffective.

Dolly the Sheep not only prompted a great deal of hysteria and legislation, but provided nearly full employment for bioethicists for about five years. Because debates about cloning, particularly about cloning humans went on for a long, long time. (There was a lot less concern about cloning sheep.) At the time, many people said, "I'm going to clone humans." Some of you may remember Dr. Richard Seed, a physicist who announced he was going to clone himself. He looked like a clone of a mad scientist from a movie—perhaps Doc Brown from the movie, Back to the Future. Then there was a religious cult called the Raelians, founded when a French race driver was visited by a UFO. They announced that the aliens had told them it was their religious duty to clone humans. They actually announced that they had cloned a human being, a baby was born around Christmas Day, 2002. They named her "Eve". But out of respect for her privacy, they never let anyone examine her to see if she was actually a clone. Except for card carrying Raelians no one don't believe that they actually cloned anyone.

We ended up with six or seven years of fervent debate about human reproductive cloning, cloning to make human babies. In late 2004, Hwang Woo Suk, a South Korean researcher, published papers in Science claiming that, about seven years after the birth of Dolly, he had become the first person to successfully clone human embryos. And over the space of the next year, that claim was revealed as a blatant fraud. Hwang was eventually charged with crimes by South Korea and convicted.

And so the world spent a lot of time thinking that human cloning was really close. We discussed it, lots of countries passed laws on it, but then, after Hwang's fraud was revealed, the conventional wisdom became that it was impossible. Many kinds of mammals could be cloned, but not primates, including humans. And so all that effort to guide the ethical regulation of the technology seemed, in some sense, wasted—the science had not developed the way the scientists, legislators, or ethicists had expected.

This story has an ironic footnote. In 2013 Shoukhrat Mitalipov, a researcher at the Oregon Health Sciences University, proved that one could clone human embryos. One of the major "secret ingredients" to his success, he assured me when we once chatted, was adding caffeine to the culture medium. So if you drink a lot of coffee or tea this morning, be careful—you may be setting up some of your cells to be cloned. Mitalipov's feat was replicated in numerous labs very quickly, but, interesting, no hysteria or ethical discussions have followed. I published a short piece in 2020 wondering where was Dr. Seed? Where were the Raelians? Since cloning human embryos has now been possible for over a decade, why haven't we heard of people trying to clone themselves? My guess is that cloning was just old news.

So human cloning still stands as an example of where we guessed wrong about the relevant science. We thought the science was going to make human cloning easy. We spent a lot of time in policy discussions, but then it turned out to be, we thought, impossible. Now it's turned out to be possible again, but no one's talking about it.

My last example here is one that I know is going to be talked about a lot in this meeting—embryo research. Similarly to Berg and Baltimore in 1975 forswearing any possibility of doing human germline editing, it was very easy for the Warnock commission and an earlier NIH commission to propose the so-called 14 day rule: that human embryos should not be the subjects of research past 14 days of development. It was easy because, at that point, no one knew how to keep them alive ex vivo for more than a very few days of development. It was another case of promising not to do something that they didn't know how to do—and did not know would, or would not, be possible. As with germline editing, I think it was foreseeable that, at some point, people would probably discover how to keep human embryos alive in a lab (not a uterus) for more than 14 days. would learn how to do it. But the 14-day rule bought a truce of almost 40 years. And I know that Professors Hyun and Lysaght are both going to talk about the embryo research and embryo models, but, in my view, this is another example of science announcing a policy position that, with then current knowledge, is easy to take because it forecloses no research. The policy decision, however, doesn't say "until the science changes." But the science does change. And when the science changes, the policies have to be reconsidered.

Another issue that I know both Julian and Professor Lysaght are going to talk about is embryo models. I really wish I were going to be there for that because I find that topic fascinating. In just the last few weeks, many different groups have announced that they've come up with new and different kinds of embryo models. This is another place where unexpected science raises new problems. The 14 day rule and other laws, regulations, and guidelines about human embryo research were created to govern "human embryos, presumably those made by the fusion of egg and sperm,. (Some of the more careful policies also include the possibility of cloned embryos being involved.) Nobody regulated thinking about the possibility of models that look like and act like human embryos but did not involve, directly at least, any eggs or sperm. Are embryo models governed by regulations and guidelines about embryos? We don't know. Changes in the relevant science can force us to revisit policy decisions.

WHEN OTHER SCIENCE DEVELOPS IN UNEXPECTED WAYS THAT AFFECT THE REGULATED SCIENCE

Second, other areas of science may change in ways that have effects on the science you're concerned with. An example may come from another reason why I'm sorry that I'm not in Singapore—I wanted to eat the chicken nuggets produced in a vat by chicken muscle stem cells, which I understand has been legal and sold in Singapore for some time. Two companies just had it approved in the United States; it's not yet available to eat, but it should be soon. I wanted to try it just to see what it was like. I have been interested in cell-line based meat for over a decade, although I've written only a little bit about it.

But in the last few years, I've become less optimistic that it's going to be an important part of future diets. Part of that is because the techniques have proven—as is always the case in bioscience—to be more complicated than we expected. *The* one great truth of moving research to clinical use or to the marketplace is that it's always more complicated than we expect. But, for

stem cell meat, the bigger issue is another area of technology that's gotten much better—plant-based meat substitutes. These have gotten to be quite good. I now cook "Impossible burgers" made from plants rather than beef hamburgers. I don't think I'm going to live long enough to be able to eat an excellent "Impossible ribeye steak" but most beef is used less demanding forms. And it's going to be a long time before anyone will make a nicely marbled stem cell ribeye steak either. The change hasn't been in the science of stem-cell derived meat, but changes plant-based meat substitutes now seems to me likely to preempt stem-cell meat.

Another example of this goes back to the cloning fights. I was the main author of a California commission's report on human cloning, written in the early 2000s. And at that point, there was a huge fight, both on our commission, but more importantly, between political parties, about what was called reproductive cloning—using cloning to make an identical twin to somebody—and what was then called either research cloning or therapeutic cloning. The idea behind the therapeutic cloning was to produce immune compatible cells or tissues for a patient. Let's say Julian has had a heart attack. The good news is he survives. But the bad news is his heart muscle has been scarred and his marathon time has gone from two hours and 20 minutes to two hours and 40 minutes. (I hope Julian is chuckling at that idea, especially if the marathon is in the heat and humidity of Singapore!) But he wants his 20 minutes back.

In theory, we could take human embryonic stem cells, turn them into heart muscle cells, put them into Julian, have them fit in place, and then his heart would work perfectly. And that's actually been done in some rodents. It hasn't worked out in humans, yet, but even if it did, the heart muscle cells derived from embryonic stem cells would likely trigger an attack by Julian's immune system. And so that concern led to a clever idea: Let's not take just any human embryonic stem cells but let's make an embryonic clone of Julian, not so it could grow up to be a bioethicist but for its embryonic stem cells. We want to destroy that embryo at about six days, harvest the inner cell mass cells, turn those into human embryonic stem cells, turn those into heart muscle cells, and put those cells in Julian. And since they have his DNA, his immune system will be perfectly happy with them.

That was the fascinating idea behind therapeutic cloning. What happened to it? Shinya Yamanaka did. This Japanese scientist figured out, in 2006 with mice and in 2007 with humans, how to make induced pluripotent stem cells. These cells seem, like human embryonic stem cells, to be able to become all human cell types but they do not require destroying an embryonic clone of Julian. Now we don't have to make an embryo of Julian and destroy it; we just have to take a few of Julian's skin cells, grow them up into a cell line, feed them the right factors, turn them into induced pluripotent stem cells, turn those into the heart muscle cells, and put those in Julian. Voila! His marathon time miraculously gets shorter. The idea of therapeutic cloning disappeared because the science changed—not the science of human embryonic stem cells, but the science of induced pluripotent stem cells.

I will talk about a few more examples, some of which are going to be talked about later in this conference. Professor Gyngell is going to talk about the genetic disease, spinal muscular atrophy ("SMA"). A long time ago I had a law student with SMA, who had to use a wheelchair. There has been a lot of interest in gene therapy to correct the flaws that cause SMA. But the last decade has seen great progress with drugs to treat SMA. Professor Gyngell's talk is about choosing between treating the disease after birth, using genetic selection to avoid the birth of babies would have the

disease, curing the disease in an embryo by genetic editing? The long hoped for “traditional gene therapy” for SMA may not be the common treatment.

This may turn out to be true of a lot of gene therapy because other therapies or interventions will replace it. My personal favorite example is Cystic Fibrosis. When human germline genome editing became an issue, I argued was I didn't think it was going to be very important, because almost everything you'd want to use it for could be achieved through embryo selection by preimplantation genetic diagnosis. But I always noted an exception. Imagine two people who have the same autosomal recessive disease. They live long enough, and they're healthy enough, that they want to have children, but they don't want their children to have their disease. Because each of them has two copies of the pathogenic variant of the gene, their children would *have* to get two pathogenic copies and have the disease. The example I used was cystic fibrosis. People with that disease, who used to rarely live to become teenagers, are living into their thirties, forties, and beyond and doing well. In just the last four or five years, cystic fibrosis treatment has been revolutionized by old fashioned small molecule drugs. has undergone an old fashioned small molecule chemical revolution. Miraculous drugs have allowed people with cystic fibrosis (and good health coverage) to live long and healthy lives.

I had a student this year, a healthy looking young man about 185 cm tall and weighing about 90 kilograms who told me he had cystic fibrosis. At first, I couldn't believe him. He told me that until he got the drugs three years ago, he weighed 80 pounds less, had almost no muscle, and had to spend many hours a day trying to keep his lungs clear. That's another situation where an expected science, gene therapy for cystic fibrosis, may have been preempted by great improvements in alternative approaches.

This kind of unanticipated change will happen in many cases. Just today Stat News had a short article about how the bariatric surgery for obesity might disappear because of new anti-obesity medications, with effects on the surgeons and the firms that make the medical devices used for that bariatric surgery.

It is an amazing time in bioscience right now because of all the different plausible approaches to disease. Consider failing kidneys. We can plausibly think about fixing kidneys with drugs or with devices, including possibly implantable mechanical kidneys. We might be able to increase the availability of human kidneys for transplant by changes in transplant rules. Or perhaps we will transplant pig kidneys into humans, but pig kidneys that have been genetically edited so that patient’s immune system doesn’t reject them. Or maybe we will use actual human kidneys that were grown in pigs. And, ultimately, we could transplant human kidneys that are grown from the patient’s own cells in the laboratory. We don’t know how to do any of these technical solutions yet and we probably will never be able to do all of them. Almost certainly, though, we will to be able to do one or more of them. It's a time of almost infinite possibilities, which means many challenges for who specialize in one approach, whether they are pharmaceutical companies, medical device companies, surgeons, or regulators. And if you have become specialized in using the genetically modified pig organs and somebody else is able to do a better treatment using human kidneys made in the laboratories, your field may disappear. And, if you are a regulator, your rules and guidelines can become obsolete.

WHEN THE WORLD CHANGES IN UNEXPECTED WAYS THAT AFFECT THE REGULATED SCIENCE

The last of my three big issues is when the world changes. This can happen in a variety of ways. I'm sure most, if not all, of you are familiar with the Collingridge dilemma. This states that the time when it is politically easiest to regulate it a new technology is at its beginning, but at that point you don't know enough about it to regulate it well. After a few years, the problems that need regulation become clearer, but by that time, vested interests that built up around the technology that make regulation very, very difficult. So that's the regulatory dilemma: You can try to regulate early when it's politically possible but you don't know enough or try to regulate later when you know better what to do but it's politically hard. That's one example of the society changing.

Another from my own country, is how various prenatal genetic interventions took on a different meaning in 2022, one year ago, when our Supreme Court abolished the federal constitutional right to abortion. Since then, over 20 states have greatly limited or banned abortion, which makes issues of prenatal genetic diagnosis or of embryonic genome editing much more salient than they were when abortions were easily available for everyone as one way to deal with fetuses with genetic diseases.

Another consequences is that now that abortion is illegal in many states, some advocates for embryos are attacking in vitro fertilization ("IVF") because it leads to many human embryos being created but never transferred into a uterus to get a chance at becoming a baby That might have worked forty-five years ago, but now about 10 million people, all around the world, are alive only because of IVF. Those people, their parents, their siblings, other people who know them and care about them constitute a change in the culture that changes what kinds of regulation of the technology are possible.

Another important social change has been increased interest in disability issues, particularly, but not exclusively, those around neurodiversity. The ethical debate about genetic selection, or genetic editing, or prenatal testing, with respect to Down syndrome, has changed dramatically in the last 20 or 30 years as advocates for Down syndrome, including, occasionally, people with Down syndrome, have made the case that they aren't disabled, they're just different. They're neurodiverse. And we also hear that from people on the autism spectrum, that they don't have a disability, they have a different way of thinking. That sort of social change then feeds back and affects the policy issues on science.

My last example was important to my own career. Thirty-two years ago I made a choice whether to focus my career on energy law or health law. I sometimes wonder if I made the wrong decision, as it seems increasingly clear to me that climate change is the most important issue of this century. But , climate change is not just an energy issue, it's also a biological issue. The urgent need to deal with climate change is going to change the regulation of some biosciences. For example, I predict that in a decade or two or less, Europe will no longer ban genetically modified food, because it will prove much easier to change the genes of wheat, maize, rice (or wine grapes) to let them tolerate heat better than to move all that agriculture 500 kilometers north. Climate change force changes in how we think about the ethical, legal, social and policy implications of some of the biosciences.

CONCLUSION

So, what does all this mean? There is a line often attributed to Niels Bohr, although it appears to have been said first by other Danes: “It's always hard to predict things, especially the future.” Those of us who work on the ethical, legal, social, policy, and political implications of advances in the biosciences need to take that to heart. We have to make predictions about the future in order to make ethical conclusions or policy recommendations about new technologies. But the future we're predicting is not only hard to see, but it's hard to see in ways that are changing every minute. Every time a new paper comes out in a journal someplace, it may change the future of the technology you're trying to influence, or to regulate.

So what should we do? We need to be open-minded. We need to be open-eyed. We need to pay attention. We need to put even more caveats in our papers about assuming that the technology develops in this direction. We need to be better at monitoring events, paying attention to what's happening and to make needed adjustments nimbly.

The last thing I will urge may seem an ironic comment to make to a roomful of people working in bioethics areas. Some people might even say that it’s a particularly ironic comment coming from me. We need to be humble. We need to realize the important limits of our knowledge and of our ability to predict the future and the consequences those limit can have for the ethical, policy, and legal analysis we make with respect to these new technologies.

Thank you for your time and attention.

2) Unproven Stem Cell Interventions in Japan under the Act on the Safety of Regenerative Medicine

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My name is Misao Fujita from Kyoto University. I'm so grateful to the Uehiro Foundation on Ethics and Education, Julian, and the organizers for giving me the opportunity to speak at this prestigious event today. My talk is about unproven stem cell-based interventions in Japan under the Act on the Safety of the Regenerative Medicine.

Unproven stem cell-based interventions are now globally acknowledged as the serious problem. And in this slide, the color-coded map indicates the number of website advertising unproven stem cell-based interventions by country. The country with the highest number of such websites is the United States, with 187 websites.

Moreover, administration of unproven stem cell-based interventions can cause acute or chronic complications, even deaths in extreme cases. A review article published in 2018 detailed 35 adverse events in 14 countries, including Japan, where one Korean patient died after receiving an unproven stem cell-based intervention. I will talk a little bit about this case later. Also, this review paper had cited our previous study on the Japanese court case of a patient who experienced numbness and became wheelchair-bound after receiving an allogeneic adipose-derived mesenchymal stem cell infusion. At that time, such interventions were not regulated in Japan except for research and clinical trial.

This is our empirical data. Before the Act on the Safety of Regenerative Medicine (ASRM) was enacted, we identified 74 private clinics administering 247 interventions using stem cells or somatic cells. These interventions were used to treat various diseases, such as cancer, cardiovascular diseases, gastrointestinal diseases, and for other purposes, such as cosmetic/anti-aging treatment and breast/buttock argumentation. However, this was the situation before the implementation of the ASRM, which regulate private practices, as well as research involving the administration of human cells.

Yet, even five years after the implantation of ASRM, a Nature article published in 2019, criticized the Japanese policies as the policies might give people false hope about how effective the therapies are. However, in order to accurately evaluate the policy, we should identify the situation of Japan with regards to cell-based interventions after the ASRM was enforced.

This is the outline of my talk. First, I will briefly describe the ASRM, which regulates all cell-based interventions in Japan. Next, I will present our data about the current situation in Japan after the enactment of ASRM. Then, I will discuss various studies on the quality of review by Certified Special Committees for Regenerative Medicine, which is a sort of ethics committee under the ASRM. And finally, I will summarize the outreach activities. I'm not sure if I could call it public engagement, but at least we can call them the outreach activities conducted by us thus far to educate the public on such issues. So let me move on to the first topic.

CARNEGIE COUNCIL The Voice for Ethics in International Affairs 上廣倫理財団 UNIVERSITY OF OXFORD Oxford Uehiro Centre for Practical Ethics NUS National University of Singapore Centre for Biomedical Ethics Yong Loo Lin School of Medicine

As some of you may know, in 2010, a Korean patient died of pulmonary embolism after receiving a stem cell-based intervention by the Korean company, RNLBio, at private clinic in Kyoto. During that period, there were three ways of providing cell-based interventions in Japan. The first was through clinical trials aimed at developing commercial products. All clinical trials were strictly regulated by the Pharmaceutical Affairs Act. The second was through research conducted at universities or hospitals. Research had to be performed in accordance with national guidelines. The last was in private practices through medical treatments not covered by public insurance and paid out of pocket by the patient. And at that time, Japan had no regulations regarding the administration of cell-based interventions in private practice. Therefore, such unsafe and unproven cell-based interventions, which are prohibited in many countries, including Korea, could be easily administered in Japan.

However, the situation had changed in 2014. The Act Concerning the Advancement of Comprehensive Measures for Citizens to Promptly and Safety Receive Regenerative Medicine was proposed in April 2013. Based on this act, two more acts were proposed: the Pharmaceutical Medical Devices and Other Therapeutic Products Act and the ASRM. All these acts took effect in 2014, which was called as the "New Year of Regenerative Medicine."

So, let me explain a little more about these regulations. When companies develop and sell cellular products, the process is classified as a clinical trial and is subject to the Pharmaceutical Medical Devices and Other Therapeutic Products. And both research and private practice regulated by the ASRM. Thus, any cell-based intervention needs approval and must be reported to the Ministry of Health, Labour and Welfare (MHLW) prior to initiation of the intervention. In addition, more stringent regulations are placed on cell-based interventions with greater risk, and the penalties are imposed for violation. I will now explain about this point in more detail.

The ASRM classifies all cell-based interventions into three types of regenerative medicines. For example, for Class I Regenerative Medicine, the use of ES or iPS cells and gene therapies is considered to be a high-risk procedure. In this case, a Certified Special Committee for Regenerative Medicine examines the provision plan and that provision plan is submitted to the MHLW. And after a recommendation by the Health Science Council, research or therapy can be initiated. For Class II Regenerative Medicine, the use of somatic stem cells is considered to be a medium-risk procedure. These differ from Class I Regenerative Medicine, in that no recommendation by the Health Science Council is required. For Class III Regenerative Medicine, the use of somatic cells is considered to be a low-risk procedure. These differ from the other two approaches in that research or therapy can be started after the provision plant is examined by a Certified Committee for Regenerative Medicine and submitted to the MHLW. The Certified Committee has more lenient competition requirements than the Certified Special Committee. In this manner, cell-based interventions administered in private clinics seem to be successfully regulated by the ASRM.

However, unlike many countries, the ASRM does not prohibit the administration of such interventions for therapy, which I think is very problematic. So, to illustrate this point, I will show you a little data from our empirical study on the situation after the enforcement of the ASRM.

First, our research team investigated the type of cell-based interventions administered by private clinics in Japan. We use the public documents available on the MHLW website since 2017, when the Regulation for Enforcement of the ASRM was partially amended. We analyze the more than

3,000 informed consent documents submitted by more than 2,000 medical institutions. We found that cell-based interventions were offered for various diseases and conditions. The most common interventions were the use of platelets for dental treatment, administration of autologous immune cells to cancer patients, and cosmetic medicine. Several treatments targeted diseases of the musculoskeletal system. You can see that hair loss and menopause are also targeted.

However, some medical societies are against the administration of stem cell "therapies" based on their literature reviews. For example, the Australasian College of Sport and Exercise Physicians said that there is still little evidence of mesenchymal stem cell-based interventions for musculoskeletal conditions such as osteoarthritis, tendinopathy, and osteochondral defects. Similarly, the American Society for Aesthetic Plastic Surgery and the American Society of Plastic Surgeons reviewed more than 9,000 papers and concluded that scientific evidence is very limited in terms of the safety and efficacy of stem cell-based interventions in aesthetic purposes. However, as shown in the previous slide, stem cell-based interventions for musculoskeletal diseases and for cosmetic purposes were widely and legally available in Japan.

Furthermore, we found several websites of private clinics in Japan that included sales messages explaining that cell-based interventions were eligible for "medical expense deductions." Medical expense deductions are a tax system in which the government pays a refund to compensate for the tax burden of people who must pay large amount of the cost of treatment. Therefore, we estimated the total annual amount of refund that the government could pay for cell-based interventions by private clinics. And as a result, estimated by the "number of patients" who received the interventions, the refund ranged from 94,000 US dollar to 73 million US dollar in fiscal year 2017, and from 1.7 million US dollar to 135 million US dollar in fiscal year in 2018. Also, estimated by the "number of the injections" of cell-based interventions, the amount was 1.8 million US dollar to 140 million US dollar in fiscal year in 2017 and 3 million US dollar to 2.2 billion US dollar in fiscal year in 2018. Of course, this amount does not represent the actual amount of refunds paid, as not all patients who receive interventions undergo the process of receiving refunds. However, these data suggest that there are fiscal risks to society as a whole, in addition to health and financial risks to individual patients.

But all the cell-based interventions that I presented have been reviewed and approved by the Certified special Committees and/or Certified Committees for Regenerative Medicine, which are review committees complying with the ASRM. So next, to examine the quality of the committee's review, we conducted the following studies as part of the Ministry's commissioned research.

To assess the quality of the committee reviews, which is quite difficult to define, we first examined whether the provision plan approved by the committees were reviewed on the scientific basis. Under the ASRM physicians are required to indicate in the provision plans, including scientific references, why they believe that the intervention is safe and applicable. On August 1, 2019, we obtained 351 provision plans for Class II therapies with more than 2000 references, such as articles, books, and websites. The results showed that the 20 provision plans did not cite any references, 15 provision plans cited references but were not academic studies or did not have clearer bibliographic information, 8 provision plans cited articles published in so-called predatory journals, and 45 provision plans did not cite clinical research articles that confirmed safety. This means that one-quarter of the provision plan did not have a clear safety rationale. But all these plans were approved by the Special Certified Committee for Regenerative Medicine.

Next, we examined whether the committees reviewed the qualification of physicians, which are essential for the safe and appropriate implementation of the interventions described in the provision plans. We reviewed each provision plan to determine if the target disease and the expertise of the physician implementing the interventions matched. In July 2019, 391 plans were examined, with 15.9% of all plants having a presumption of a mismatch between the diseases covered and physician expertise, and 14.1% of plans having a strong presumption of a mismatch between the diseases covered and physician expertise. In other words, about 30% of the provision plans have results that raise doubts regarding the expertise of the physicians who will implement the interventions. Specific examples include a neurosurgeon treating atopic dermatitis; an ophthalmologist and an industrial physician treating liver disorders; an obstetrician/gynaecologist treating myocardial infarction, spinal injury, cerebrovascular diseases, and osteoarthritis.

We were very curious about the reasons behind the committee's approval of such provision plans and scrutinized the informed consent documents for patients available on the MHLW website. We found that more than 60% of the provision plans had other plans with provision plans with exactly the same title, and the contents of the documents were identical among provision plans with the same title. These findings suggest that many private clinics that provide cell-based interventions use duplicate plans and informed consent documents. These duplicate documents were reviewed by a subset of committees.

So next, we investigated these subsets of committee in terms of the addresses, members and minutes. We searched the internet for information, and it was confirmed in four cases that there was a Company X. They were different companies in each four cases, but a Company X connected private clinics and the Certified Special Committees for Regenerative Medicine that reviewed their provision plans. For example, a Company X sells its cells to private clinics and provides the services to create prohibition plans. At the same time, the company operates a committee to review the plans submitted by the clinics. With such a tripartite relationship, there was a concern that the independent and fair review required by the ASRM could not be expected.

Finally, we examined 254 private clinic websites that provided Class II therapies. As a result, more than a half of the clinic websites could fall under the category of exaggerated advertising prohibited by the Medical Care Act. These websites included such expressions as “strict adherence to the ASRM procedures,” “approved by the MHLW,” or “reviewed by a nationally certified committee.” All private clinics performing cell-based interventions must comply with these requirements. Therefore, labelling them as if they had a special authorization is legally considered hype.

In Japan, cell-based interventions offered at private clinics are often provided without proper scientific verification and advertised as special treatments. Moreover, in fiscal year in 2021 alone, according to the MHLW, more than 60,000 patients received such interventions in Japan. Therefore, outreach activities are very important to educate the public about these issues. We made a Japanese translation of the “Informed Consent Standard for Stem Cell-Based Interventions Offered Outside of Formal Clinical Trials” issued by the International Society for Stem Cell Research in 2019. This document outlines the information that must be provided to patients to make an informed decision regarding such interventions. We have also provided lectures to the general public, training for local bar associations, and study sessions to the media. We will continue to raise awareness regarding these issues in the future.

This is my last slide. We conducted these studies with the cooperation of many individuals. In particular, I would like to say thank you to Dr. Hatta, a former lab member and now at the Shizuoka Graduate University of Public Health, who has made great efforts to collect and analyze data with great patience. I would also like to thank Dr. Ikka at the National Cancer Center who led some of the studies discussed today. Thank you very much for your time and attention.

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3) Regulatory Dynamics of Gene and Cell Therapies in Japan

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Thank you very much for giving me this great opportunity. I also appreciate all the staff and the organizations that prepare and support this wonderful conference. My name is Jusaku Minari, and I am from Kyoto University. Today, I offer a presentation entitled "Regulatory Dynamics of Gene and Cell Therapies in Japan." Along with other countries, Japan has considered and enacted various ethical and legal regulations for medical research and clinical care. In this conference, I would like to share some of the key characteristics and lessons of these regulations, which we have learned in Japan. I hope this talk will be useful for you.

In today's presentation, I have three topics. First, I will touch on the current international landscape of cell and gene therapies. This is very important because we must grasp the specific context when considering appropriate regulations and institutions. Second, I will discuss a previous historical analysis of regulations in Japan using an example of genome research. In this section, using the lens of the regulations surrounding genome research, I try to show some specific challenges regarding the handling of regulations. Finally, I will present a recent analysis of regulations on regenerative medicine and genome editing therapy. Let's start with the first topic.

I am very interested in the initiatives of the ISCT, the International Society for Cell and Gene Therapy. The ISCT published a global regulatory report on cell and gene therapy on June 22, 2023. This report shows not only representative developing and approved drugs related to cell and gene therapy, but also some of the regulatory issues, including the current situation of the Good Clinical Practice (GCP) and EU pharmaceutical legislation.

This slide shows the number of gene therapies, genetically modified cell therapies, and nongenetically modified cell therapies by phase. As of June 1, 2023, the majority of therapies were in preclinical development. Eighty percent of gene therapies, totalling 739 therapies, are in preclinical development, and 23 therapies are in preregistration or Phase 3. Genetically modified cell therapies stand at 70%, or 804 therapies, in preclinical development, and 14 therapies in preregistration or Phase 3. A total of 44 nongenetically modified cell therapies are in Phase 3 or preregistration. The slide indicates that most of the therapies are under review, while some have already been reviewed at preregistration or Phase 3.

This slide shows an overview of the approved products of these three therapies. As of June 1, 2023, 87 products have been approved globally. Sixty-two nongenetically modified cell therapies, 11 genetically modified cell therapies, and 14 gene products were approved. That is, while the majority of the approved products are nongenetically modified cell therapies, 25 genetically modified cells and gene products have already been approved.

This is the list of genetically modified cell products approved over the past ten years. One of the representative products is Kymriah, which was first approved in 2017 and is currently approved in the US, the EU, the UK, Japan, Australia, Switzerland, Canada, and South Korea. Indeed, many of these cell products are autologous CAR-T, chimeric antigen receptor T cells, like Kymriah.

This is the list of gene products that have been approved over the past 10 years. One of the representative products is Zolgensma, which was first approved in 2019 and is currently approved in the US, the EU, the UK, Japan, Australia, Canada, Brazil, Israel, Taiwan, and South Korea. Like Kymriah, which I referred to on the previous slide, many countries have approved this product. In

Japan, much attention was paid to this drug in 2020. This is because Japan's health ministry set the price of Zolgensma at about 167 million yen, or 1.17 million dollars, making it the most expensive medication funded by the public system. Such a relationship between emerging drugs and medical fees will be increasingly discussed in the future.

Regarding the regulations of these therapies and drugs, a revision of the GCP, Good Clinical Practice, is planned. This revision will occur due to the development of designs and technologies of clinical trials and may provide innovators with additional benefits. The scope and application of the revision will address the incorporation of diverse trial types and data sources in clinical trials.

On the other hand, EU pharmaceutical legislation will also change, representing the largest reform in over 20 years. The aim of this revision will be to make medicines more available, accessible, and affordable through supporting innovation. The revision includes proposals for a new directive and new regulations. Currently, six key elements of the proposal are shown. The intention of these elements includes facilitating better access to new drugs and establishing a more simplified regulatory framework. From these regulatory changes in GCP and EU pharmaceutical legislation, it can be said that conventional regulatory systems must come to a turning point to be significantly reconsidered and revised.

Here, I want to revisit the meaning and significance of regulations. There are various types, such as legal regulations and nonlegal binding regulations, such as governmental and professional ethical guidelines. Regulations also include both fundamental concepts and specific procedures. If these characteristics of regulations are used, appropriate regulations are established and implemented, and the regulations can contribute to the promotion of science and technology and the creation of social benefits while avoiding negative risks and side effects. This, by some measures, indicates that regulations can be regarded as social constructions. In this case, it is possible to have various relevant perspectives on regulations, such as the structure of regulations, regulatory architecture, and the engineering of regulations.

In addition, when regulations are shaped and formed, various philosophies, social values, and concepts, including equality, diversity, respect, justice, and tolerance, are considered, and incorporated into the regulations. This indicates that the fundamental concepts and incorporated social values among various regulations cannot always be identical.

Dr Mathews and her coauthors have mentioned, through this paper, that our current laws, regulatory bodies, and other governance structures—both 'hard' (such as legally binding laws and regulations) and 'soft' (such as voluntary guidelines, standards, and norms)—were largely built for a research, development, and market landscape that has changed substantially over recent years. As a result, our current approach to governance is no longer fit for purpose. I somewhat agree with their opinions, and to address the current challenges of regulations, I am interested in the nature of regulations.

Here, I want to share a conventional characteristic of regulations for biomedical research in Japan. In Japan, until recently, soft laws, namely non-legally binding guidelines, have been widely adopted in Japanese medical research to ensure regulatory responsiveness and flexibility regarding scientific advancement and societal changes. I would like to clarify this point further in terms of Japanese soft-law culture.

This paper, published in 2004, is entitled "Administrative Legislation in Japan: Guidelines on Scientific and Ethical Standards." Dr. Akabayashi and his coauthors, through this article, showed that many regulations, including legal regulations, non-legal binding regulations, and ethical

guidelines, were set around 2000. There was a strong tendency at that time for ethical guidelines, namely soft laws, to be proactively adopted and established by relevant ministries. In this table, we can see various sets of ethical guidelines for genome research, research using ES cells, gene therapies, epidemiological research, and clinical research. An example of a legal regulation is the Human Cloning Prohibition law. In the article, they argued that "a further problem is that the presence of several guidelines...has caused difficulty and confusion for researchers."

Another researcher, Dr Tashiro, published an article in 2010, entitled "Unintended Consequences of Soft Regulations: The Social Control of Human Biomedical Research in Japan." In the article, he pointed out several things. First, the Japanese framework for the regulation of biomedical research has generally been shaped by discussions in ad-hoc committees. Second, this inevitably leads to a situation in which there are no fundamental principles integrating a number of rules. Finally, the case-by-case response also leads to a confusing situation for researchers. In fact, having many guidelines without harmonization creates discrepancies among their provisions. These sentences indicate that a case-by-case approach can be useful for a particular type of research, but there is a negative risk that fundamental rules have not been shaped and formed, causing discrepancies in the stipulations between different regulations.

Based on the perspectives obtained from these papers, I will explain the second topic, an analysis of regulations for genome research in Japan.

We published this article in 2021. In it, we focused on two sets of regulations for genome research. One is the Fundamental Principles of Research on the Human Genome, established in 2000 by the Bioethics Committee of the Council for Science. The other is Ethical Guidelines for Human Genome/Gene Analysis Research, established in 2001 by three ministries. The former, the fundamental principles, clarifies the conceptual ethical framework for the human genome and its related research; the latter, genome guidelines, presents concrete practical procedures, including the specific requirements for informed consent, research protocols, and ethical review. In the article, attention was paid to changes in the regulations over the last 20 years, their challenges, and opportunities to improve the regulations. In particular, we identified three key challenges regarding regulations.

The first challenge concerns the relationship between fundamental concepts and specific procedures. While the fundamental principles remain unchanged and are referenced less in the practice of genome research, ethical guidelines have been repeatedly and dynamically revised to address scientific, ethical, and social issues, becoming more detailed and procedurally concretized. These phenomena could be partly regarded as a formalization of the principles elaborated on in the fundamental principles and an increase in procedural formalities (not necessarily linked with the conceptual background) of the ethical guidelines. Therefore, there is an increasing gap between fundamental principles and ethical guidelines and an increase in the procedural formalities of ethical guidelines.

The second challenge concerns the relationship between non legally binding regulations and legally binding regulations. This challenge mainly comes from the specificity of the ethical guidelines themselves. As I previously mentioned, non legally binding regulations, also called soft laws, have been widely adopted in medical research in Japan to ensure the regulatory flexibility of scientific and societal changes. However, due to the nature of soft laws, they should complement relevant hard laws, such as the Act on the Protection of Personal Information (APPI). The ethical guidelines were revised twice to comply with the APPI. In such situations, there is potential regulatory-related instability in research developments due to the amendment of both ethical guidelines and related hard laws, namely, the APPI.

On a related note, this slide shows the history of governmental ethical guidelines associated with three medical research fields in Japan: genome research, epidemiological research, and clinical research. Two of the three sets of guidelines were integrated in 2014, and a unified set of guidelines, Medical and Biological Research Involving Human Subjects, was established in 2021 as a result of the integration of the three sets of guidelines. These guidelines have been strongly influenced by the APPI. The APPI increasingly influences the nature of ethical and legal regulations.

The last challenge concerns biomedical ethics and the protection of personal information in regulations. This challenge is primarily associated with the conceptual nature of human-derived data. Biomedical ethics has mainly been established based on considerations of physical rather than informational harm. Based on this perspective, specific informed consent, withdrawal of consent, and potential risks are stipulated in regulations. While this approach can be useful for protecting research participants, it can raise challenges in the promotion of data sharing, biobanking, and data-driven research. On the other hand, increasing attention to the protection of personal information is required. As a result, the concepts of (bio)medical ethics and personal information are currently mixed in the ethical guidelines. Thus, there is an increasing need to explore the ethical and legal norms of human-derived data in (bio)medical research.

Here are five key lessons learned from the Japanese regulatory experience of genome research for cell and gene therapy. The first concerns careful consideration of case-by-case approaches. The second is to address optimizations for the coexistence of hard and soft laws. The third is to constantly connect fundamental concepts with specific procedures. The fourth is preparation to address conceptual confusion, for example, regarding human-derived data. The last is related to the securement of regulatory stability, with some flexibility. Potential factors that could lead to regulatory instability include research and technological developments, social changes, frequent revisions and integrations of regulations, and international coordination of regulations. These things are very important for adjusting and optimizing existing regulations on the one hand; on the other hand, they could possibly destabilize the current regulatory orders. Therefore, careful management is needed for these adjustments of regulations.

Lastly, I will present the final topic, an analysis of recent regulations for regenerative medicine and genome editing therapy.

In Japan, there are at least two key legal regulations specifically related to regenerative medicine, both of which were passed in 2013 and came into force in 2014. One is the Act on the Safety of Regenerative Medicine, or ASRM, which regulates unproven medical technologies and interventions using processed cells. The other is the Act on Pharmaceuticals and Medical Devices, or PMD Act, which regulates products seeking marketing approval. We first focused on the left one, ASRM, to gain an understanding of the concepts and ideas of the law due to its uniqueness. Regarding the PMD Act, further discussions are increasingly needed in that several key regulations, such as Good Clinical Practice and EU pharmaceutical legislation, will be revised, as I mentioned earlier.

Regarding the ASRM and PMD Act, this perspective is very important. It is that Japanese oversight of stem cell-based interventions thus distinguishes clinical trials for pharmaceutical marketing authorization and approval from all other clinical research (e.g., academic research) and unapproved therapies. The former is covered by the PMD Act and the latter, including SCBI provision by healthcare professionals, hospitals, and private clinics, by the ASRM. In this presentation, I focus more on the necessity and implications of the ASRM, but not the PMD Act.

Regarding regenerative medicine, we recently published an article entitled “Reflection on the Enactment and Impact of Safety Laws for Regenerative Medicine in Japan.” In this article, we focused on one set of regulations for regenerative medicine, the ASRM. Two specific reasons for focusing on the ASRM are that this law includes unique regulations that broadly cover unproven interventions and therapies in regenerative medicine—in other words, it covers both research and clinical care—and the revision of the ASRM was planned within five years after its enactment.

The article addressed the origin, process, and impact of the regulations and the challenges and possibilities of improving them. Before the implementation of the ASRM, there were Guidelines on Clinical Research Using Human Stem Cells for Research, established in 2006 by the MHLW and Director Notification, set in 2010 by the MHLW for clinical care. At that time, this indicated that stem cell-based interventions for clinical research and clinical care were separately managed through two different regulations. In this situation, the progress of regenerative medicine and increasing concerns about the safety of unproven therapies mainly required robust legal regulations for both research and care, leading to the establishment of the ASRM.

However, there was significant concern about setting additional regulations. That is, that while the safe provision of stem-cell based interventions needed to be managed by additional regulations, both academic freedom in research contexts and the broad discretion of medical professionals in the context of clinical care had to be carefully ensured under the Japanese Constitution and other specific laws. I would like to clarify this point further.

The Japanese Constitution stakes out a broad commitment to individual rights and freedoms, including access to healthcare, in Article 13, and it protects freedom of occupation (associated with physicians’ discretion) and academic freedom in Articles 22 and 23, respectively. Again, the Japanese Constitution covers individuals’ free access to healthcare in Article 13, physicians’ discretion through clinical care in Article 22, and academic freedom in Article 23.

In this situation, the committee, associated with the formation of the legal regulation, eventually advocated that it is acceptable for these freedoms and discretions to be limited in the interest of prioritizing the protection of human life and health. This helped to justify additional regulation of medical practice, namely the ASRM. This indicates that the protection of human life and health can be clearly prioritized in comparison to individuals’ free access to healthcare, physicians’ discretion through clinical care, and academic freedom.

In the committee discussions, two of the main focuses were determining the ASRM’s scope and shaping terminology. We clarified the discussion in this slide. Which term is better: regenerative medicine or cell therapy? In the case of regenerative medicine, the term is used to convey the purpose of a given medical treatment or the outcome of that intervention. If it were defined solely in terms of the aim of the intervention, the concept could apply to interventions with little or no efficacy in achieving regenerative functions (namely, the regeneration of biological functions and bodily organs and tissues). In this case, there was concern that non-evidence-based interventions could easily fall within the official definition of regenerative medicine. If the term were defined from the perspective of therapeutic outcomes, however, it would exclude from the act all regenerative therapies in development, including innovative clinical research and practices.

The term “cell therapy” was considered to present an understanding of a given treatment’s methods to the public. However, it was felt that it might undervalue the concept of regeneration, which was relatively familiar to the Japanese public, and mislead patients or the public to think that it included nonregenerative cell and tissue transplants. This contradiction reflects the emergence and development of new, unfamiliar, and unclarified medical interventions.

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Eventually, “regenerative medicine, et cetera” was adopted for consistency with other legal instruments. This term indicates medical intervention using processed cell products for two purposes. This definition encompasses a tripartite structure using a specific method and two aims. “Two aims” mean reconstruction, repair, or formation of the structure or function of the human body, or treatment or prevention of human diseases, respectively. This approach, which includes both medical intervention using processed cell products with the aim of reconstruction of the structure or function and the aim of treatment and prevention of diseases, plays a key role in broadly covering unproven stem cell-based interventions in research and clinical care.

The emergence and development of genome-editing technologies occurred around the same time that the ASRM was being considered and developed. In 2015, New Scientist reported that gene editing saved a girl dying of leukaemia in a world first. In fact, genome editing technologies were expected to cover many applications, such as cell therapy, organ transplants, and gene drive. There was a partial revision of the ASRM in 2020, in which it was decided that gene-edited cells (with ex vivo genome editing) would be regulated in the same manner as gene-transferred cells, namely iPS cells, and ES cells. Therefore, the ASRM can achieve some degree of flexibility through a tripartite structure composed of a method and two aims.

However, regarding genome editing technologies, ASRM covers ex vivo but not in vivo genome editing. This is because in vivo, namely, the direct injection of the technologies into bodies, is different from medical intervention using processed cell products and is therefore not covered by the tripartite structure.

This is a tentative map of the regulations associated with genome editing in Japan. After the emergence of genome editing technologies (i.e., CRISPR-Cas), many regulations were established or partly revised. Ten years were needed for these adjustments of regulations. Here is the point that I am now explaining. Regarding clinical applications for somatic genome editing, ex vivo genome editing and in vivo genome editing are regulated differently.

This point is a key challenge of stem cell and gene therapies in clinical research and care and is related to regulatory consistency. Regarding stem cell therapy, including ex vivo genome editing, the ASRM covers both clinical research and clinical care. Regarding gene therapy, including in vivo genome editing, specific guidelines, such as soft laws and two laws, cover clinical research but not clinical care. These regulations include the Guidelines for Gene Therapy Clinical Research, the Clinical Trials Act, and the Japanese Cartagena Act.

Recent discussions about ASRM revisions have noted that the ASRM will cover both gene therapy, including in vivo gene therapy, and stem cell therapy, including ex vivo gene therapy. In addition, under the ASRM, these two therapies will be recognized differently, so an additional regulatory framework for gene therapy will be included in the ASRM. However, we are facing a situation where further discussion will soon be needed to consider the relationship between the ASRM and other relevant therapies, such as mRNA vaccination and exosome therapy.

In this situation, I think that more attention must be paid to diachronic aspects that reflect the perspective (or nature) of regulations to bridge the past, present, and future. In the current scenario, while ad hoc regulations are important short-term solutions, fundamental regulations must be established over time. Moreover, the two types of regulation must always be compatible with one another.

This concludes my presentation. While rapid developments in cell and gene therapies have occurred, model changes in conventional regulatory frameworks have been initiated. In this regard,

careful consideration of the current regulatory culture is needed, where the coexistence of fundamental and contextual perspectives should be ensured. In addition, I believe that more attention should be paid to the diachronic aspects of regulations.

4) The Identity Problem, Gene Editing and the Two-Tier Deontic View
Dr Dominic Wilkinson, Professor
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So I should start by thanking the Uehiro foundation for supporting this conference and of course for supporting the Uehiro centre, Julian and NUS for supporting my visit to NUS as a visiting professor in Biomedical Ethics, it's fantastic to be here. I'm going to take this discussion in a different direction. We've had some very applied, very practical discussion of regulations, I'm going to wind back to thinking about some fundamental philosophical questions.

So I want you to imagine that you're a decision maker considering ways of preventing a genetic problem. The particular genetic problem that I have in mind is a condition called familial adenomatous polyposis, FAP. This is an autosomal dominant genetic disorder, a nasty genetic disease that causes a predisposition to cancer. Seventy per cent of those who are affected by this gene will have polyps that develop into cancerous lesions in early adult life. Without intervention, 100% of them will die from cancer in early adult life. And the decision makers are contemplating two different ways of dealing with this serious genetic disease. One is a type of intervention that we've been talking about: gene editing, So this is Joanne. Joanne has this disorder. She's had parts of her own colon removed. And she's undergone IVF in the hope of having an embryo without FAP. Unfortunately, she only has affected embryos, and she's unable to have further cycles of IVF because of limited access to funding. So she wants to gene edit one of her affected embryos so that they won't have this condition which she has suffered from. So that's option one. But here's a different option that the policy makers consider: which to offer funded embryo selection – so that parents who carry the gene can afford IVF and are able to choose unaffected embryos. So which of these would be better?

Here's a different type of choice. This is a population level choice. You're in charge of a public health program, and are aware that a commonly used anti-epileptic and I have in mind sodium valproate, causes a significant rate of malformations, about four in 10. Women who become pregnant while taking sodium valproate, their fetus could be affected some with very severe abnormalities, but quite a lot have milder abnormalities affecting their development and learning. And the decision-makers are considering two different options for preventing these malformations. One is to identify women taking this drug early in pregnancy and then switch them to an alternative drug, or those who are about to start on the on the medication but who are pregnant to stop them starting on the valproate and start on a different drug instead. Or option B is pregnancy prevention, and to mandate as occurs in the UK, that women who are taking sodium valproate take contraception. As a consequence, women who are taking Valproate will delay their pregnancy until a point in time that they're not taking Valproate and fewer children will be born with these malformations. So these are the two types of problems.

If we're thinking about a single gene disorder like this cancer gene, we could try and treat it with gene editing or try to prevent it with embryo selection. If we're trying to prevent birth defects, we could try and do so with pregnancy detection or with pregnancy prevention, which should we choose?
And one thing that many of you will be aware is there's a crucial or arguably crucial difference between these types of interventions. So, in terms of the first of these, if we gene edit an embryo, we change a scenario where a child, we can call him Jack, is born with a genetic disorder. If we edit

a gene, edited Jack will be born instead who will not have this, this phenotype, not have the predisposition to cancer. Compare this with embryo selection, where a different embryo will be implanted instead of Jack with familial adenomatous polyposis. Joe will be born who has who doesn't have this gene.

And the same for our public health program: if we embark on pregnancy detection in early pregnancy, instead of developing these malformations, these children will be born without these malformations. But if we embark on pregnancy prevention, instead of this group of embryos, a different group of children will be conceived instead, who will be born without these malformations.

Now one attractive answer to which of these we should choose simply says whichever of these is going to be most effective, whichever is going to be most likely to prevent the genetic problem or most effective at preventing the genetic problem, whichever is going to prevent the most number of cases. However, as I've alluded to already, these are different types of choices. And philosophers have highlighted that these are different in a potentially morally relevant way. In some of these cases, the same individuals will exist regardless of the decision that we make. We might call these individual affecting choices or cases or reasons. The other type are non-individual affecting cases, where different future individuals will exist, depending on what we decide. For example embryo selection, or pregnancy prevention. And as Derek Parfit famously described, when we make decisions that affect who exist, if we fail to make those choices those decisions can't be criticized on behalf of the children who are born with the malformations, or with the genetic disorders, because if those decisions had been made, those children would not have been born, a different children would have existed instead. This is the challenge of the non-identity problem.

Famously, there are three different ways of responding to the non identity problem. One is to think of these two types of choices, the individual affecting choice, the non-individual affecting choice as being very morally different, there's a huge moral significance. Indeed, there is on some accounts, there is no moral reason to choose between embryos, or to choose to delay a pregnancy as there will be no children who will be benefited or harmed if we simply prevent pregnancy. So this is what might be called the “great difference view”. And on this basis, we should morally make individual affecting choices. For example, thinking about embryo selection versus embryo editing, we've got no moral reason to select between embryos, but we have a strong moral reason to embryo edit. That's going to favor genetic modification or pregnancy detection. The alternative view which was the view that Derrick embraced, was the no difference view: claiming that there's equal moral reason to choose greater or lower or lesser well being in non-individual affecting or individual affecting cases. So we might toss a coin, or indeed, we might look at whichever of these is going to be more effective, which is going to have the greatest chance of preventing the cancer. Which of these is going to prevent the greatest number of birth defects. Well, there's a third view, and this is a view that a number of philosophers have been drawn is some sort of compromise in between. The third view, some difference view, also sometimes called the two tier or midway view, is an attractive sort of compromise, which says, look, there's greater moral reason to make an individual affecting choice than a non-individual affecting choice, but it might be outweighed by the numbers. So that's going to tend to favor gene editing or pregnancy detection. But it will depend on the numbers, on just how different they are in terms of the numbers that will be affected. The ‘two tier’ in the title refers to the idea that there's this higher tier or the stronger moral reason for individual affecting and this lower tier of non-individual affecting cases. And there

are a number of reasons for being drawn to this type of compromise view. The great difference view seems to have some implausible implications for thinking about climate change, or major policies that will cause much worse lives to be lived by people in the future, but will affect the conception of many individuals. And the great difference view appears to suggest that there is nothing wrong with risky forms of gene editing like that done by He Jianqui or negligently preventing failing to prevent teratogenic malformations because different children would be born. But the no difference view also has seems to have some challenges. It seems to suggest that it's very wrong to fail to select an embryo with a malformation. In fact, it's equally wrong, as deliberately causing harm. If we deliberately conceive a child with a disability or we deliberately deafened a child, for example, in cases of hereditary deafness, it's equally wrong. So the no difference view also seems somewhat unattractive. So we might be drawn to this compromise.

But the problem which I've come to call the two tier problem is the difficulty of deciding. If we think there are these two classes of reasons, how much difference is there? These are really significant practical questions. We're interested in practical questions, regulation, questions, policy questions here. We need to know how different these tiers are. There's good reason to think that pregnancy prevention is probably going to prevent more cases. But how many more cases does it have to prevent before we choose this given that it's on the lower tier?

There are a series of problems, in fact, for the two tier view, and I'm going to run through some of these and suggest a way of responding to them. One of the problems, which I've already alluded to, is to identify how many non-individual affecting cases or harms are equivalent to an individual affecting harm? One of one of the challenges is that the nature of the harm here, and the nature of the reason seems to be different. And it seems very difficult to answer. Nobody that I know of has been able to come up with any plausible weighting. It just seems utterly arbitrary to say how different these are. It's unclear, even how we would begin to generate some sort of weighting between these two types of reasons.

Next, if we think that, that non-individual affecting reasons are less moral important than individual affecting reasons, it potentially has some absurd implications. Here's an example to bring it to light. A pharmaceutical company becomes aware that one of its best selling medications is associated with rare teratogenic side effects. The company decides to mitigate the problem by combining the medicine with a harmless second agent that has the side effect of altering the timing of ovulation. As a consequence, any children who develop malformations related to the drug will be different from children who would have been conceived if the mothers had not taken the medicine. Now, the idea that this is in some ways a moral improvement, or that the pharmaceutical company has done something good just seems bizarre.

For another example, we might think that more significant phenotypic changes, for example, those affecting the brain might be identity altering, rather than minor changes. But if that's the case, it seems to suggest that there's a moral reason to make lesser changes or to deal with minor problems or non-brain problems, because individual affecting choices are more morally significant than non-individual affecting choices. Again, that seems deeply counterintuitive.

One of the challenges is uncertainty about which cases the same individuals will exist or not. Sometimes, this is because of challenges with understanding the timing of conception. So Derek Parfit, made the argument that even small delays in the timing of when parents conceived us

would actually have resulted in a different individual existing rather than us. But at least within a one month period, when there's a single ovum, there's going to be a degree of uncertainty. There's a possibility, even if very small, that the same sperm and egg could have combined. How do we deal with cases where it's possible that that the same individual would have existed? There are real uncertainties, not only in whether the individual would have existed, but also which counterfactual we think is the relevant one for deciding whether this is an individual or non-individual affecting case. And I've alluded already to the idea that, depending on the nature of the genetic intervention, we may or may not think that that affects the identity of the individual who exists. But it's, again, it's very difficult to, to know, in individual cases, whether that will effect that will mean that a different individual will exist. Presumably, very small, genetic modifications won't lead to a different individual existing, while very large will. But in between, there's going to be significant uncertainty. Should we treat these as on the high or the lower tier? I think there's, it's very difficult to know.

One of the challenges that Derek Parfit identified for this view, which he explored in his final paper, published in Philosophy and Public Affairs after he died, were some intransitivities if we think that that that these reasons are on different tiers, and we're considering different options. We may be led to paradoxical sequences of choices where Option A is inferior to Option B, option B is inferior to Option C, but option C is inferior to Option A. One of the things that, in particular, these intransitivities seem to be a problem for is a view that we might call the Two Tier Telic view. And that's the view according to which the outcome of individual affecting choices is of greater value than the outcome of non-individual affecting choices with equivalent effects on wellbeing. This is the claim that the outcome, and when you've got a child who's been gene edited, who doesn't have the cancer gene is better than the outcome of a different child existing, who doesn't have the Adenomatosis Polyposis gene. When you have these notions that there's different value to these outcomes, it leads to these particular problems of intransitive choices. But this particular way of interpreting Two Tier views is not the only way that we might interpret Two Tier views. In particular, we might be led to think that the reason for responding to these different choices in a different way, comes from a different source.

So here's an example, that is developed from an example of Derek's but is one I developed a bit further. It's a case that I call Death at 60. Geneticists have recently identified a rare genetic disorder that's asymptomatic until it causes sudden death at age 60. There's no cure for this genetic disorder. But with costly medical treatment, it's possible to postpone the effect of this genetic disorder for a short period, Jack has just turned 60 and has been identified with a gene. And I'm Jack's doctor. With treatment, I could enable him to live for a year to the age of 61. However, there's limited funding available for treatment of this disorder. And for the same cost. population screening could identify a couple who are carriers for this gene, enable them to undertake IVF and embryo selection. And if this is chosen, future Jane, who will live for 80 years, rather than future Sall, who would live for 60 years, will come into existence. Now, if we think about a case like this, should this doctor choose to prolong Jack's life, save Jack's life, give him an extra year of life, or cause it to be that a different individual, Jane, rather than Sally will come into existence and live for 20 years longer. It's very clear that the outcome of the latter would be much better. But nevertheless, if you're Jack's doctor, you have a very strong reason, I think, to save the person in front of you. And the source for that comes not from the value of the outcome, it comes from a different source.

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So this is the view that I call the Two Tier deontic view. And the idea is that the moral reason to make an individual affecting choice is stronger than the reason to make an equivalent non-individual affecting choice, if and to the extent that agents have special obligations to benefit or prevent harm occurring, to existing or to specific future individuals. So the idea is that the greater reason that we have to make individual affecting choices comes from our moral obligations, rather than from some difference in the value of the outcome itself. Here is another case which might provide some intuitive support for this for this view. This is what I call Future Death at 60. So, geneticists have recently identified this rare genetic disorder that causes sudden death at age 60. There is no current cure or treatment for the disease. Exactly as described before. there are limited resources available to research this disorder. In one option, resources are spent developing medical treatment, which is not yet currently available, and future Jack will be able to be treated and live to age 61 rather than dying at age 60. Or for the same cost, population screening could identify a couple who are carriers for this gene, enable them to undertake IVF and embryo selection. And if this is chosen, future Jane will live for 80 years, rather than future Sally will come into existence. So in this scenario, we're contemplating whether we should invest in developing a treatment that will be of limited effectiveness, or in identifying couples who carry this gene, enabling them to have embryo selection. These are not individuals who currently exist, they're not individuals to whom we at present have ethical obligations. And I think in this case, it seems much more plausible that we should choose to devote our efforts on pre Implantation Genetic Diagnosis, identifying the carriers and preventing the disorder through embryo selection.

Why should why should we be drawn to this two tier deontic view? Well, I think if there is a reason between these two tiers, between individual affecting and non-individual affecting choices, it can't be related to the outcome, because the outcome is the same, the same number of individuals, in these cases, will exist with disabilities or with serious disorders. And if it is, if there is a difference, it relates, obviously to the idea of causing harm or benefit to individual; it's a function of what we are doing to them. And potentially, it's agent relative because it's a function of our relationship to the individuals who will be thereby harmed or benefited. One advantage of this view is that it explains the significant intuitive difference. One of the puzzles of the two tier views is that in some cases, it seems that there's a big difference between these individual affecting and non-individual affecting cases. And in others, it seems that there isn't. So the public health program I described at the start of this talk is based on an example that Derek Parfit gave, where it seems really strikingly obvious that there isn't a big difference that you should go with whichever is going to be more effective. Whereas other cases, particularly the Death at 60 type case, but maybe some of these gene editing cases, we have a different intuitive response. And one of the reasons one of the explanations, I think, is because of our relationship to the individuals who will be affected. Here's a type of explanation that Julian might be sympathetic with, even though I'd suspect you won't embrace the conclusions that I come to. So we can think of these reasons that apply as vectors. There are two types of reasons that apply in these cases. One is in terms of the consequences, the other is in terms of our ethical duties to the individuals who will be affected. And when we think of them as vectors, we can see that sometimes these will converge, and sometimes these will diverge. It also explains why I think people come to different answers about these cases. Consequentialist, typically tend to focus on this particular reason (the outcome), and identify no difference between cases. But those who identify the significance of moral duties, even at a cost of consequences, have often said, that it feels different when individuals are harmed or benefited.

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What are the practical consequences if, drawing on this model, we adopt the two tier deontic view?

Well, I think in terms of public health policy, for programs like preventing birth defects, those policymakers have duties to the population to minimize the harms of drugs that are prescribed to prospective parents. They have duties to society, but they have low or no duty to specific individuals. And I think that they ought to, as a consequence, choose the option that will optimize the outcome, that will prevent the most cases of valproic acid associated fetal malformations. One of the attractions of this type of answer is that when we're thinking at a policy level, it takes away some of these headaches of working out, how many of these cases are actually individual affecting and how many are non-individual affecting? It takes away this concern that people will manipulate the reasons because actually, they're equivalent. And the challenge of indeterminacy, either of conflicting counterfactuals, or degrees of genetic manipulation no longer become as troubling.

What about fertility treatment and gene editing? We've had lots of talk about gene editing. Well, again, if we think about this at a policy level, I think there's a strong reason that we should think about gene editing versus embryo selection, in a parallel way, and look at which is going to be most effective, and most cost effective. In terms of preventing these significant genetic disorders, we shouldn't necessarily prefer non-individual affecting forms of gene editing because there'll be less likely to harm individuals.

However, it may be that particularly when you're thinking about the professionals who are involved in providing fertility treatment, and gene editing, that they may feel that they have some specific obligations to the individuals who will be conceived as a result of their actions. So they may be particularly concerned about the harms and benefits that will result to the individuals who they've been instrumental in conceiving. And it's possible, that legal liability might track individual affecting harm and benefit. Some of you may have encountered the case of Evie Tombes. This is a young Paralympian with spina bifida who is now 20, who sued her GP, because the GP had failed to give advice to her mother about taking folate during pregnancy. Her mother had been to the GP seeking conception advice, and the GP had not advised taking folate prior to conceiving her child. Her child developed Spina Bifida, a disorder that's significantly preventable by taking folic during pregnancy. It was absolutely clear and accepted by the court that if the GP had told the mother to take folate, that she would have delayed conception, because she got pregnant actually, very soon after seeing the GP. And so if he had given that advice, a different child would have existed. Evie Tombes would not have been born and nevertheless, in this case, the judge awarded a large amount of damages. Now, you can interpret this case in a number of ways, you could say that the judge was philosophically mistaken to award liability in this case; this is a non-individual affecting case. You could say, look, what they were identifying is that there was a significant wrong. They needed to compensate for it. They thought it was an important, albeit non-individual affecting wrong and that they didn't think that the fact that she wouldn't have existed changed the nature of the wrong. But in terms of the argument that I'm making, what this suggests is that liability may apply or may not differ in these types of cases, purely on the basis of, of whether the same individual will exist or not.

I've alluded to different decision makers. I talked about policymakers and professionals. But of course, parents make these types of decisions. And parents may have a consequentialist duty, Julian's duty of procreative beneficence to think about the well being of the different possible

children who they could bring into existence. But they arguably also have duties to the specific future children who they will conceive, and they may, on that basis, plausibly have a stronger reason to cause an individual affecting benefit to avoid an individual affecting harm. So from the point of view of individual prospective parents, they may have greater reason to choose gene editing than embryo selection, thinking about the children they may conceive.

I'm conscious of time, I'm going to run through the some of the potential counter arguments fairly quickly. So one of the obvious arguments against the two tier deontic view is that it will predictably lead to a worse outcome if you think that there's a, a greater reason, in at least some cases, to choose individual affecting choices, notwithstanding that will lead to more cases of disability more cases of, of harms from taking drugs during pregnancy, for example. But as I've alluded, that's going to be diminished, because I think these large scale choices, these policy choices, these choices about whether we should fund gene editing, or embryo selection, we should treat these symmetrically. When we make decisions at scale, we ought to treat them symmetrically. So that won't lead to, to, to worse consequences overall. And of course, it's inevitable that whenever we deviate from the consequentialist outcome for other reasons, that will have that will have negative consequences. And that in itself doesn't mean we're wrong to deviate from it. Again, it's a question of weighing up these vectors.

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5) Drugs, Genes and Screens: The Ethics of Preventing and Treating Spinal Muscular Atrophy
Dr Chris GynGell, Senior Research Fellow in Biomedical Ethics
The University of Melbourne

I want to thank the Uehiro Foundations for supporting this event. I also want to thank Julian, first for inviting me to talk, but also because this talk I'm giving is based on a paper which we've co authored, together, along with a medical geneticist at the Murdoch Children's Research Institute.

I'm going to be speaking about ethical considerations for cell-based interventions for spinal muscular atrophy. I'm hoping this talk sort of melds together some of the earlier practical and empirical talks with some of the philosophical issues raised by Dominic.

So first, a bit of background on spinal muscular atrophy. It's the most common inherited lethal neurodegenerative disease.

Carrier rates for spinal muscular atrophy (SMA) vary by ethnicity. In Australia, about one in 40 people are carriers. This results in approximately 30 babies being born with SMA annually. In Singapore, this number is slightly higher, with around 50 to 60 children born with the condition each year.

SMA is caused by a deletion or mutation in the gene responsible for the production of the survival motor neuron 1 (SMN1) protein. This protein is crucial for muscular function and facilitates communication between nerves and muscles. In severe cases, affected children can't produce this protein due to the gene's mutation. The outcome is heart-wrenching: children develop typically until about six months of age, after which there's a noticeable decline. By then, they stop meeting developmental milestones and eventually lose the ability to use their muscles. This can lead to fatalities from respiratory failure. In the most extreme cases, the maximum lifespan is roughly two years.

This genetic condition is intricate. Besides the SMN1 gene, there's another called the survival motor neuron 2 (SMN2) gene. Though it sometimes produces a functional protein, it does so at about 15% of the rate of the SMN1 gene. People have varying numbers of SMN2 gene copies, which leads to four different types of SMA, the severity of which depends on the presence and function of these genes.

Up until a decade ago, witnessing a child with SMA was heartbreaking as there were no available treatments. However, in recent years, interventions have emerged, providing some hope. One such treatment is Nusinersen, which costs approximately $750,000 initially, followed by yearly treatments costing around $375,000. It doesn't act on the mutated SMN1 gene but targets the SMN2 genes to increase the production of the functional SMN protein. Another significant breakthrough is Zolgensma, a gene therapy that introduces a functional SMN protein to cells. It was one of the most expensive treatments ever approved by the FDA. Yet, as time has progressed, similar therapies have been approved, some reaching up to $3.1 million for a single treatment.

While these developments are groundbreaking, we must also consider preventive measures. Pre-implantation genetic diagnosis (PGD) is a widely recognized method. Relevant for those with a family history of SMA, it involves producing embryos through IVF, testing them for mutations, and

only implanting the ones with a functional SMN1 gene. This process costs roughly $15,000. Another approach involves prenatal testing and potentially terminating pregnancies where SMA is detected. As technology advances, SMA could be a target for gene-editing techniques like CRISPR, providing another preventive avenue.

However, for any treatment or prevention strategy to be effective, early diagnosis is essential. Newborn screening programs, such as the one added to the US's recommended uniform screening panel and some in Australia, are critical for timely intervention. Similarly, for preventive measures, carrier screening programs, like Australia's "Mackenzie's Mission", are essential.

The availability of multiple options now raises questions for governments and individuals regarding prioritization. In a world with limited resources, challenging decisions need to be made. While I'll mainly focus on government policies, it's essential to recognize that individuals also face critical choices concerning their health and that of their offspring. In the subsequent discussion, I will delve deeper into the ethical considerations to provide a framework for these decisions regarding SMA interventions.

The first area of ethics I'll explore is the disability critique of disability screening. Evidently, a significant difference between ex ante and ex post approaches is that the former involves selecting against or preventing the birth of someone with a disability, while the latter treats the individual. There's an extensive discourse about the disability critique of such screening.

I've identified two primary considerations. The first is the expressiveness argument, which posits that when we select against embryos predisposed to disabilities, we may be conveying a prejudiced view towards disabled individuals. This could mirror the everyday discrimination faced by people with disabilities. However, applying this argument to conditions like SMA, which can be fatal in early childhood, is challenging. Some types of SMA might allow a person to live longer, but conditions causing death before age two express a different sentiment.

The second critique is the intolerance argument. It suggests that by screening against disabilities, we display an intolerance for diversity, not valuing the insights and contributions disabilities might bring. For instance, some argue that conditions like autism or dyslexia bring cognitive diversity beneficial to society. Yet, it's challenging to extend this viewpoint to diseases like SMA that lead to early death. While diversity is valuable, not all diversities, especially those causing early mortality, should be preserved or regarded neutrally.

To summarize this section, while the disability critique literature offers valuable perspectives, it doesn't decisively guide our decisions on SMA interventions.

Turning to fundamental ethical principles, autonomy stands out. This principle underscores that individuals should have the autonomy to make decisions about their lives. In the context of SMA, this means providing people with various options. In essence, all the interventions expand the options available to individuals, especially compared to a decade ago.

However, to genuinely make informed choices about all treatments, one needs to know their carrier status for the SMA mutation. We argue that this is only feasible with carrier screening options. Without carrier screening, options like PGD and potential future gene editing treatments

are not genuinely accessible. Thus, if we aim to support maximum autonomy and offer individuals a full suite of options, prioritizing carrier screening seems essential. This would allow individuals to understand all available treatment options and make informed choices among them.

Let's consider beneficence. The central idea is that we aim to benefit people through these interventions. The concept of benefit can be segmented into two primary facets: the duration of life and the quality of life.

Comparisons between ex post treatments are straightforward. For instance, consider the gene therapy which introduces a functional plasmid into your bloodstream to produce the necessary protein, versus nusinersen which necessitates annual spinal injections. Preliminary studies suggest the gene therapy yields more significant benefits, potentially extending life by anywhere from 19 to 74 years compared to nusinersen's 5 to 20 years. Additionally, the gene therapy is less invasive.

However, it's more challenging when comparing the beneficence of ex post and ex ante interventions. Pre-implantation Genetic Diagnosis (PGD) results in a child with a functional SMA gene, leading to normal life expectancy and motor function. Moreover, PGD is considerably more cost-effective than ex post treatments. Yet, the catch is that PGD alters the identity of the child that would be born. For instance, if a couple chooses nusinersen and has a child, Julian, with SMA, the treatment can prolong Julian's life from an expected two years to potentially seventy. However, if the couple opted for PGD, they might have a different child, Kathy, with a normal lifespan. While Kathy benefits from a standard life expectancy, it's not because of the PGD.

Essentially, ex ante methods offer an "impersonal" benefit; they don't provide person-specific advantages or disadvantages. How one approaches the philosophical 'non-identity problem' will influence how one prioritizes these treatments. Some might argue PGD doesn't benefit anyone, while others may deem its benefits equivalent or even superior to ex post methods due to its outcomes and lesser invasiveness.

Now, shifting to justice. When contemplating health resources, an intuitive perspective is that we should maximize the number of people who benefit. In public health systems with limited resources, choosing an expensive therapy comes with the opportunity cost of forgoing treatment for another condition. Therefore, justice often necessitates the selection of the most cost-effective option, a principle rooted in distributive justice.

This necessitates an examination of the economic efficiency of possible medical treatments. Knowing one is an SMA carrier presents a compelling case to endorse preventative measures, like PGD and prenatal testing and termination, rather than post-diagnostic interventions such as nusinersen. There is a need for further empirical studies to evaluate the cost-benefit analysis of carrier screening, particularly for SMA. However, when this screening is paired with tests for other Mendelian disorders, it becomes increasingly apparent that advocating for such programs is justified on ethical grounds. Moreover, there is a compelling argument rooted in distributive justice to provide carrier testing, PGD and IVF, or prenatal testing and selective termination at no cost to the couples affected.

In summary, A variety of new strategies are emerging that aim to alleviate the impact of SMA on affected families. These developments bring about complex issues concerning the allocation of

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resources. The ethical principles of autonomy, beneficence, and justice favor addressing SMA through preventative measures, such as PGD, prenatal testing, and termination.
A couple opting for PGD to have a healthy child—especially when their subsequent child is at risk of SMA—bestows significant advantages upon their future child, granting them the prospect of a life without disability and with normal longevity. This benefit is substantially more pronounced than what is typically achieved through post-diagnosis treatments, which are not expected to entirely eradicate SMA. Prenatal testing and termination also emerge as highly advantageous options for couples likely to conceive again. However, the ethical principle of beneficence doesn't uphold these measures in scenarios where termination doesn't pave the way for the birth of another child.

Justice-based arguments also advocate for preventative measures. PGD and prenatal testing and termination are considerably less expensive than post-diagnosis SMA treatments. Prioritizing cost-efficient solutions facilitates a fairer distribution of medical resources across the population.

The superiority of preventative measures underscores the importance of enhancing SMA carrier screening. Prospective parents, when informed of their carrier status, are empowered to make well-informed decisions regarding the choice of treatments. Autonomy is thus bolstered by carrier screening initiatives. Furthermore, as these screenings bring prenatal testing and PGD to the fore for at-risk couples, they concurrently foster beneficence and autonomy.

Thank you for your time, and I again want to express my thanks to the Uehiro Foundation for supporting this conference.

6) Moral Obfuscation: The Sad Story of Synthetic Embryos
Dr Julian Savulescu, Chen Su Lan Centennial Professor in Medical Ethics
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Scientists this year have created embryo models. According to *The Guardian* newspaper ("Synthetic human embryos created in groundbreaking advance", June 14, 2023), scientists say these model embryos, which resemble those in the earliest stages of human development, could provide a crucial window on the impact of genetic disorders and the biological causes of recurrent miscarriage.

However, the work also raises serious ethical and legal issues as the lab-grown entities fall outside current legislation in the UK and most other countries. The structures do not have a beating heart or the beginnings of a brain, but include cells that would typically go on to form the placenta, yolk sac and the embryo itself.

Prof Magdalena Żernicka-Goetz, of the University of Cambridge and the California Institute of Technology, described the work in a plenary address at the International Society for Stem Cell Research's annual meeting in Boston in 2023.

"We can create human embryo-like models by the reprogramming of [embryonic stem] cells," she told the meeting.

The motivation for the work is for scientists to understand the "black box" period of development that is so called because scientists are only allowed to cultivate embryos in the lab up to a legal limit of 14 days.

Robin Lovell-Badge, the head of stem cell biology and developmental genetics at the Francis Crick Institute in London, said: "The idea is that if you really model normal human embryonic development using stem cells, you can gain an awful lot of information about how we begin development, what can go wrong, without having to use early embryos for research."

…scientists in the UK and elsewhere are already moving to draw up voluntary guidelines to govern work on synthetic embryos.

"If the whole intention is that these models are very much like normal embryos, then in a way they should be treated the same," Lovell-Badge said. "Currently in legislation they're not. People are worried about this." (*The Guardian*)

There is also a significant unanswered question on whether these structures, in theory, have the potential to grow into a living creature…. Scientists say it is not clear whether the barrier to more advanced development is merely technical or has a more fundamental biological cause.

"That's very difficult to answer. It's going to be hard to tell whether there's an intrinsic problem with them or whether it's just technical," Lovell-Badge said. This unknown potential made the need for stronger legislation pressing, he said. (*The Guardian*)

…So far, no one has made embryo models that have the capacity to develop into human beings, but a recent study on monkey embryo models showed that such models could induce pregnancy (which terminated spontaneously soon after) if placed in the uterus.

… Research on natural human embryos tends to observe a widely adopted guideline — enforced by law in many countries — that human embryos should not be cultured in the laboratory beyond 14 days.

But because in most countries' embryo models do not meet the formal definition of an embryo, they are not subject to such restrictions.

"We sought to develop a tool to ask specific questions about the second week of human embryo development, since using actual human embryos in research is ethically and technically challenging," says Zernicka-Goetz (*The Guardian*)

David Albert-Jones, writing in *Bioedge* ("Why are scientists boasting of creating 'synthetic human embryos'?, June 20, 2023), observed,

"If this really is an embryo, and it looks a bit like one, then this is a new way of generating an embryo without fertilisation. If cells from an adult could be used, then synthetic embryos would be a new form of cloning. This would be wrong for all the same reasons that the old way of cloning a person … was wrong.

"A synthetic embryo is not a 'model' of an embryo, it is an attempt to make an embryo. If this attempt is successful, scientifically, then it will be wrong ethically, but if it is not successful scientifically then it will not be able to tell us much about normal human development."

"So far they have not succeeded even in mice in getting 'synthetic embryos' to develop to birth. So perhaps this is not an embryo but an uninteresting clump of cells. On the other hand, if we have any doubt then the embryo-like being should be given the benefit of the doubt."

That is an argument I have made in relation to brain organoids and chimeras.

Moral Obfuscation

One of the work-arounds scientists have employed is to develop these with genetic modification to ensure they cannot form a placenta. Thus they do not have the potential to form a human being. But this kind of work-around is essentially disabling something with the potential to form a human being so that it no longer has the potential to form a human being. This argument would not be persuasive if we took a normal human embryo and genetically engineer it so it could not produce a placenta, and then saying, "It no longer has the potential to form a human being so we can experiment on it as we would on non-embryos." Clearly, it would involve the destruction of a human embryo.

This is what I call "moral obfuscation." Obfuscation means to intentionally confuse. What scientists want to do, quite legitimately, is to experiment on human embryos. But because of the restrictions on research on human embryos, and the limitations of the current definitions of human embryos, they create new life forms: embryoids, blastoids and synthetic embryos. They argue that these are not embryos, so research is permissible.

However, in all likelihood these have, or will have in the future, the potential to create a human being.

One objection is that synthetic embryos lack the potential to form human beings because of imprinting problems. However this is likely or at least possibly only a current technical limitation.

Indeed, such potentiality arguments rest on very tenuous, empirical grounds. The central claim is that synthetic embryos, embryoids, blastoids and the like lack the potential to develop into a human being. (Interesting, Australia has treated blastoids as if they are embryos.) But this is likely due to limitations in technology at this time. Whether something has a right to life, or a special moral status, should not depend on whether technology can keep it alive. It is determined by its intrinsic properties.

Consider an analogy. Whether a human being at the end of life is said to have a right to life, or a special moral status, is not determined by the state of technology, whether technology at a particular time can keep that person alive. Perhaps the person has an incurable disease – they are still said to have a right to life in virtue of their nature as a person, even if this right cannot be respected or fulfilled.

Another moral obfuscation is the 14 Day Rule which has dominated the regulation of embryo research (which scientists are also trying to overturn). This was introduced by the Warnock Committee in the 1980s to delineate a point of moral significance in embryonic development which would determine the point until embryo research could be conducted. Indeed, as another example of moral obfuscation, the embryo was redefined as a "pre-embryo" before 14 days.

But 14 days is morally irrelevant. It is similar to the Texas Heart-Beat Rule which determines when abortion is permissible – not morally hands on when a heartbeat happens to be detected, as I have argued elsewhere (Haining CM, Keogh LA, Savulescu J. The Unethical Texas Heartbeat Law. Prenat Diagn. 2022 May;42(5):535-541. doi: 10.1002/pd.6136. Epub 2022 Apr 9. PMID: 35357014; PMCID: PMC9320804)

There are two reasons that 14 days was thought to be morally significant. The first is that twinning is no longer possible after that point. As Mary Warnock roughly put it, "Up until that point, the embryo has not decided whether it is one or two." But imagine replication became possible and full grown human beings could divide into identical twins, as in science fiction. It would be absurd to suggest that a person no longer had moral status once the replicator was produced, just because of the *possibility* of division. While that individual continues to exist undivided, that individual has moral status. Moral status is not affected by the possibility of division.

The second argument used by the Warnock Committee was that the nervous system does not begin to exist before 14 days. Around 14 days, the neural streak forms, which is the precursor to the nervous system. However the mere organisation of primitive neuroepithelial cells is of no moral significance. At that point there is no brain, just a streak of cells. Most importantly there is no consciousness or any other mental phenomenon of moral significance. The embryo prior to 14 days is morally equivalent to the embryo after 14 days.

What does matter is consciousness. The reason we can treat a rock anyway we please is because the rock is inanimate. The reason why we can pull plants up, or do what we please with them, is because they are not consciousness. The reason why we shouldn't do certain things to non-human animals, like beating or whipping them, is because they are conscious and experience pain from those actions. And the reason we should not kill innocent human beings is because they have high levels of consciousness, such as self-consciousness.

But mere consciousness, the ability to perceive stimuli as painful, does not begin until much later in fetal development, around 20 weeks. So actually research on human life should be permissible until that point, when early termination of pregnancy (without analgesia) is permissible.

The 14 day rule was an example of moral obfuscation. If we rejected it, and instead allowed creation of and research on embryos for the first trimester, there would be no need to create "embryo models." And embryos would be more informative scientifically. Gene editing and cloning could be used to create embryos with maximally informative profiles, such as displaying certain diseases. Provided these embryos were not implanted, this should be ethically permissible.

Notably, the US and UK allow the creation and destruction of embryos for research. If the 14 day rule was relaxed, there would be little impetus to create synthetic embryos.

Of course, this raises the question of the moral status of the human embryo. When does it achieve moral status?

The Puzzle of Moral Status

One way to answer to this question is to ask when does a human being's life become devoid of value, so that it is permissible to end that human being's life. The definition of death has been changed from a cardiorespiratory definition to a brain death definition. If life ends, in the morally significant sense, when our brains cease to function, then it begins in a moral significant sense when our brains start to function. That is considerably later than 14 days.

Indeed, life prolonging treatment is frequently withdrawn from patients who not brain dead but are permanently unconscious. Such patients have been said to no longer have interests. If our biography ceases when we become permanently unconscious, it begins when we become conscious, which is not until around 20 weeks of gestation.

Debates around moral status seem intractable. However, law and public intuition suggest a way forward in the debate around the moral status of the embryo. Consider the case of Manishkumar Patel.

In 2007, in the USA, Manishkumar Patel's partner fell pregnant with their second child.
He did not want a second child because their first had medical difficulties and he was afraid this child would too. He put abortion drug RU486 into her smoothie, but she did not drink it, instead sending it for testing.

In the meantime, the pregnancy ended in a miscarriage.

Patel was charged with attempted first-degree intentional homicide of an unborn child. He fled for India, forfeiting a $750k bond but in 2017, he was arrested in New York. He was sentenced to 22 years in prison for the attempted homicide. (https://www.insideedition.com/man-gets-22-years-prison-slipping-abortion-pill-pregnant-girlfriends-drink-47528, "Man Gets 22 Years in Prison for Slipping Abortion Pill Into Pregnant Girlfriend's Drink" October 11, 2018)

While it was not a crime at the time to procure an abortion, it was a crime to attempt to kill a wanted fetus, as Patel did. This suggests that the fetus does not have intrinsic value, but instrumental or conditional value – conditional.

This view of the moral status of the fetus is supported by a previous case in March 2006. A 21-year-old Cleveland man, Christopher Challancin, was driving home from a party with his 17-year-old girlfriend, Jessica Karos.

She was four months pregnant.

They began to argue about her ability to care for their child. Challancin, who had been drinking, became angry and began to weave at high speed through traffic. He lost control of the car and crashed. Karos was left paralysed from the chest down, and the baby died. Challancin was unhurt.

Because he killed the baby, he was charged with homicide, as well as assault for "ruining her life," as her father put it. (http://blog.practicalethics.ox.ac.uk/2011/01/solving-the-puzzle-of-the-moral-status-of-the-embryo-and-fetus/)

Again, in this case, there was a crime because the fetus was desired by the mother.

Similar judgements have been made in relation to embryos. In January 2005, Alison Miller and Todd Parrish sued their fertility clinic, the Centre for Human Reproduction in Chicago. They had been having IVF treatment in 2002 and had stored nine embryos, one of which was "mistakenly" discarded. The clinic apologized and offered the couple a free cycle of IVF, but they sued the clinic for the "wrongful death" of their embryo.

However, at the other extreme, abortion is freely available in many parts of the world. For example, every year in Australia, about 100,000 fetuses are aborted. This is not a crime because the pregnancy is not desired. Nearly all of these are normal and healthy fetuses. No one is charged over these deaths.

It is a similar situation with embryos. Thousands of embryos are destroyed in Australia each year. In fact, the law on IVF in Victoria, Australia requires their destruction after five years.

How can killing a fetus at once be homicide and yet no crime at all? How can the destruction of embryos at the same time be required by law and widely practiced but also, in some places, be the crime of wrongful death and a moral abomination? How can the one act – killing early human life – be both right and wrong?

We have polar opposite attitudes, moral norms, and laws relating to embryos and fetuses. How can this conflict be reconciled? I have previously called this the Puzzle of the Moral Status of the Embryo and Fetus (http://blog.practicalethics.ox.ac.uk/2011/01/solving-the-puzzle-of-the-moral-status-of-the-embryo-and-fetus/)

There are two solutions to this puzzle.

First Solution: Extrinsic, Not Intrinsic Value (or Small Intrinsic Value)
The embryo or fetus has value or moral status when couples or one of the parents wants them.

We should distinguish between intrinsic value or "final" value when an entity has interests and a life of their own. The fetus

Extrinsic of instrumental value is value which resides in the capacity of an entity to produce intrinsic value. The fetus has instrumental value in terms of its ability to produce a human person later. It also has conditional value – conditional on the parents' desires. It is possible to give a "relational account" of embryonic status – determined by the relations of that embryo or fetus to its future self and others.
If the embryo or fetus has instrumental, conditional or relational value, then it is not wrong to create embryos for research, provided it accords with the desires of those who produce them. That is, there is consent.

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One might argue that there is a harm to future a person if an embryo is destroyed. However, if the embryo is destroyed, there is no harm so it is not wrong on these grounds.

Consider an analogy with art. Someone creates a beautiful painting but chooses to destroy it. They are perhaps doing the wrong thing because other people could have enjoyed it. They fail to maximize value. But it is their prerogative. The painting only has extrinsic value.

This argument has one counterintuitive implication. It is wrong to destroy embryos if they are of value to someone. Often a couple completes their family and they have spare frozen embryos. Other couples are unable to produce their own children. It is wrong to destroy these spare embryos if others want them (Fuscaldo, G. and Savulescu, J., 2005. Spare embryos: 3000 reasons to rethink the significance of genetic relatedness. Reproductive biomedicine online, 10(2), pp.164-168). The same applies if scientists wish to use them for research. Of course, it is the prerogative of the couple to destroy, them just as it is the painter's prerogative to destroy his painting. But it remains morally wrong and they should be encouraged to give them to others who want them.

Second Solution: Embryo Ownership

A second way of resolving the embryo and fetal moral status puzzle is to view the embryo and fetus as the property of the couple (or woman?) who produced it. "It is my embryo and I will do what I want with it."

Ownership is, of course, a human invention. We need to invent rules on who has right to control embryos. This is an ongoing problem of embryos in clinics, when the couple has discordant wishes for the fate of their embryos, property in tissue, etc.

One obvious route is to establish that parents own their embryo and can dispose of it however they prefer. In cases of discordant wishes, the default could be that the party who wishes to keep the embryo can keep the embryo.

Notably, the state has taken away that control by requiring destruction of frozen embryos. This shows the fluidity of ownership. The embryo might belong to an individual, a couple or a community, or some combination. And we might or might not allow a market in the sale of embryos. All of these issues are to be resolved if we view embryos and fetuses as property.

Other Arguments against Embryonic Moral Status

So far, I have considered two solutions to the embryo and fetal moral status puzzle: the embryo/fetus as having extrinsic value and couples having property rights in embryos.

On both these accounts, there is nothing necessarily wrong with creating embryos for research, if the couple consent.

There are many other arguments to supporting the view that the embryo or fetus has low moral status.

a. *Embryo rescue cases*

   Bernard Williams imagines a case where there is an embryo storage facility on fire and a human person trapped in the building. Firepersons can either rescue the human person or many frozen embryos. Williams intuits it is obvious they should rescue the person.

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b. *The Scourge*

Toby Ord points out that around 200 million embryos never develop each year because of abnormalities. If these were persons with moral status, this would be the most catastrophic scourge afflicting humanity. Vast amounts would be spent in preventing or curing the scourge. Yet virtually nothing is spent preventing these embryo deaths because people do not view them as equivalent to the death of a human being.

c. *Twinning*

When twinning occurs, one individual ceases to exist and is replaced by two different individuals. No one is concerned by the ceasing to exist of the original individual. It is not viewed as the death of a person. Twinning is increased in IVF but no significant money is spent in trying to prevent it. These attitudes suggest the ceasing to exist of an embryo is not a major moral concern.

d. *Moral Theories*

Many moral theories could support embryo research. Preference Utilitarianism would straightforwardly support it. Hedonistic Utilitarianism would support it if the utility of the research outweighed the loss of utility in terms of happiness of a future person who could be created from the embryo. This is doubtful when there is a person willing to gestate the embryo.

Embryo research is also supported on contractualist grounds. If we did not know whether we would be an embryo destroyed in research, or an embryo or person who would benefit from that research, would we want the research to occur. It would be rational to choose embryo research from behind a veil of ignorance if the chance of benefitting was sufficiently higher than the chance of being destroyed and not producing a person (Savulescu, J., 2002. The embryonic stem cell lottery and the cannibalization of human beings. Bioethics, 16(6), pp.508-529). Of course the latter is also dependent on whether there are couples willing to gestate that embryo.

e. *Dog Analogy*

Scientists want to create dog embryos to experiment on them to understand development and develop drugs. This is permissible. There is nothing wrong with creating and destroying dog embryos. But that doesn't mean we can do what you want to dog. We now appreciate the dog has value because it can experience pain, etc. It has moral status because it has a life of its own. Humans are no different – can feel pain, conceive of themselves existing across time. We can create and destroy human embryos while also respecting human persons.

Social practice and attitudes, law and ethics all support the view that the fetus or embryo has low or no moral status. Provided people do not wish to create children from embryos, it is morally permissible to create and destroy them for research with the consent of those who produced them.

Conclusion – Against Moral Obfuscation

There is nothing wrong with embryo models or synthetic embryos. They MIGHT lead to unexpected valuable findings. It is difficult to see their advantage over embryos, including cloned embryos, for research. Their creation represents moral obfuscation.

We should bite the moral status bullet. Embryos have extrinsic value and could be viewed as the property of those who create them. We should create and use embryos for sound scientific research. Cloning and gene editing are also acceptable, though that is the topic for another talk.

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We need better ethics, not merely more science.

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7) Gene Editing, Identity and Benefit

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I have one aim here: to challenge the claim that gene editing in human embryos is morally preferable to genetic selection, because it benefits the child, whereas selection doesn't benefit the child. The ideas I'm presenting are based on a paper I published with Professor Thomas Douglas from the Oxford Uehiro Center for Practical Ethics[1]. They form part of an ongoing discussion and touch upon fundamental philosophical issues about human reproduction, and benefit and harm.

To begin , I invite you to think about two hypothetical cases. The first case is that of

> *Edited Larry*. Lesley and Lex, both carriers of cystic fibrosis (CF), have produced one viable embryo via IVF. A genetic test shows that it has two copies of the CF allele. Lesley and Lex decide to subject the embryo to GE to replace the faulty alleles. The gene-edited embryo is implanted, and nine months later a child, Larry, is born. Larry does not have CF, nor can he pass it on.

Lesley and Lex employed gene editing to prevent a genetic disorder in their child. We can say they 'edited out disease'. Consider now the second case, that of

> *Selected Barry*. Bellamy and Blair, both carriers of CF, have produced two viable embryos via IVF. A genetic test shows that one embryo has two CF alleles, while the other one has none. Bellamy and Blair select the embryo without CF alleles for implantation, and nine months later a child, Barry, is born. Barry does not have CF, nor can he pass it on.

Bellamy and Blair 'selected against disease'. Many have argued that editing out disease, as in *Edited Larry*, is more morally problematic than selecting against disease, as in *Selected Barry* since it poses greater risks to the resulting child and their offspring (e.g., risks due to off target effects). But others have argued that GE also has moral advantages over genetic selection.

Chris Gyngell and Julian Savulescu wrote that:

> "...even when selection can be used to avoid disease, germline gene editing may provide a more desirable option. Selection prevents disease by changing who comes into existence; whereas gene editing ensures those who come into existence have the best shot of living a full life. Using germline gene editing to avoid disease thus seems more analogous to curing a disease than genetic selection via pre-implantation genetic diagnosis."[2]

The thought is this: in *Edited Larry*, editing out disease benefits Larry – it is better *for* Larry – because, had such gene editing not occurred, Larry would have been born with CF. He would have been, in at least one respect, worse off than he is. In that respect, gene editing is like treating a disease.

But selecting against disease, as in *Selected Barry*, does not benefit the child who comes into existence as a result – it is not better *for* Barry that he was selected, since it is not the case that he would otherwise have existed with the disease. Had Bellamy and Blair made a different selection

[1] Douglas, T and Devolder, K (2022). Gene Editing, Identity and Benefit. *Philosophical Quarterly* 72 (2):305-325.
[2] Gyngell C and Savulescu J (2017). The Simple Case for Germline Gene Editing, in *Genes for Life*, 28–44. Melbourne: Future Leaders.

decision, presumably Barry would not have existed. So, there would be no benefit – at least not the sort of benefit that people have in mind when they think about these issues.

It is often assumed that, other things being equal, we have stronger moral reasons to benefit particular people than we do to bring about impersonal improvements We do not commit ourselves to this view, but let us assume, for the sake of argument, that it is correct. One could then argue as follows:

The benefit argument
(1) Editing out disease benefits the future child
(2) Selecting against disease does not benefit the future child, though it may produce an impersonal improvement (i.e. it will bring about a better state of affairs)
(3) Other things being equal, we have stronger moral reasons to benefit particular people than to produce impersonal improvements
Therefore
(4) Other things being equal, we have stronger moral reasons to edit out disease than to select against disease.

In this paper I want to challenge the 'benefit argument'. I argue that premise (1) fails to hold in relation to many likely future instances of editing out disease, and that restricting the scope of premise (1) to avoid this problem deprives the argument of much of its practical significance.

Qualifications
Before I proceed to this critique of the benefit argument, I want to make two qualifications. A first one concerns premise (1). There will be cases in which editing out disease does not confer a benefit on the gene-edited child because either (i) the gene-edited embryo never gives rise to a child (e.g. a miscarriage occurs), (ii) the editing procedure alters the numerical identity of the child, (iii) unusually, the genetic disorder would have increased rather than diminished the wellbeing of the child, (iv) the editing procedure has unintended effects that result in lower wellbeing for the child than she would have had without the procedure.

So, (1) will need to be restricted to cases in which none of these circumstances obtain. We capture this restriction by revising (1) to

(1'). *If all goes according to plan*, editing out disease benefits the future child.

This change presents the benefit argument in the most charitable light.

Consider next premise (2), according to which selecting against disease does not benefit the child created as a result. There are certain kinds of benefit that selecting against disease arguably can confer. The selected child may for example enjoy non-comparative benefits. These are benefits that consist in being in a state that is in one respect good for you, not compared to some alternative scenario in which you might have been or were in, but in an absolute sense. In *Selected Barry*, selection may provide a non-comparative benefit to Barry because it allows him to live a good life, or a life containing good elements. Selection can be *good for* Barry. But it can't be better for Barry, because there's no alternative state of existence for Barry. Had the parents taken a different selection decision, he wouldn't have existed. With this distinction, it may seem that we can rescue premise (2) by adjusting it. Selecting against disease does not confer a comparative benefit on the future child, though it may produce an impersonal improvement or confer a non-comparative benefit.

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Combining the adjustments to both (1) and (2) leaves us with the following formulation of the benefit argument:

> (1∗) If all goes according to plan, editing out disease confers a comparative benefit on the future child
> (2∗) Selecting against disease does not confer a comparative benefit on the future child, though it may produce an impersonal improvement or confer a non-comparative benefit
> (3∗) Other things being equal, we have stronger reasons to confer comparative benefits on people than to produce impersonal improvements or confer non-comparative benefits on people.
> Therefore (4∗) Other things being equal, and if all will go according to plan, we have stronger moral reasons to edit out disease than to select against disease.

In the remainder of this paper, I will used the unqualified term 'benefit' to refer to comparative benefits.

The Problem

Let us return to *Edited Larry*: the case in which Lesley and Lex edited out CF alleles. The proponent of the benefit argument (who believes that editing out disease benefits Larry) seems to have one particular counterfactual scenario in mind. They envision that, had the parents not edited out disease, Larry would have had CF. He would thus have been worse off than he is now. But why think that this is what would have happened had the parents not edited out disease? Consider this alternative counterfactual scenario in which the parents change their mind about GE: Suppose Lesley and Lex planned to use GE to ensure their child would not develop CF, but at the last moment they became worried about the risks of GE and cancelled the procedure. Would they then have decided to have the CF-affected embryo implanted into Lesley's uterus? We think that's not all that likely. After all, it is natural to assume that Lesley and Lex (a) want to become parents, and (b) want their child to be free of cystic fibrosis. If they decide to *not edit out* disease, then they can still opt for other means for realising both these goals (e.g. IVF + genetic selection, donor gamete/embryo, adoption). It is plausible to assume that, if Lesley and Lex had not edited out disease, they would have opted for one of these alternatives, none of which would have resulted in Larry coming into existence. If this is right, then their actual action of editing out disease did not benefit Larry since, had this not occurred, Larry would never have existed. There is no comparative benefit.

Let's return to Premise 1 of the Benefit Argument. This is most naturally read as a general claim—'editing out disease *invariably* confers a benefit to the future child'—but as we have just seen, this general claim does not hold. Editing out disease doesn't confer a benefit where the edited child would otherwise never have existed. And, as *Edited Larry* suggests, there may be cases where the alternative to GE would have been discarding the embryo.

To rescue the benefit argument, we could restrict the scope of this premise. We could adjust it to

> (1#) Editing out disease benefits the future child, *provided that the parent(s) would in any case have brought the embryo to term*
> (2) Selecting against disease does not benefit the future child, though it may produce an impersonal improvement
> (3) Other things being equal, we have stronger moral reasons to benefit particular people than to produce impersonal improvements
> Therefore
> (4#) Other things being equal, and if everything goes according to plan, we have stronger moral reasons to edit out disease than to select against disease, *provided that the parent(s) who edit out disease would in any case have brought the embryo to term.*

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But this change substantially limits the practical significance of the benefit argument. That's because many situations in which parents would consider editing out disease are ones in which, if the editing does not take place, the embryo will be discarded, and parents will opt for alternative ways to have a child free of the disease they're trying to avoid. In all of these cases, the restricted version of the benefit argument will not apply.

And there's something else: restricting the scope of the benefit argument also has a surprising implication - one that limits the practical significance of the argument even further. Which counterfactual scenario would have obtained in a given case largely depends on the importance the prospective parents accord to the genetic trait the GE is intended to avoid. There is reason to believe that the more serious the disorder, the more plausible it is that the parents would have discarded the afflicted embryo had they not employed GE and would instead have pursued alternative means of having a child. Because presumably, prospective parents are generally more motivated to avoid severe genetic disorders in their child than less severe disorders, or, e.g, carrier status.

Consider a modified version of *Edited Larry:* In the modified case, the embryo from which Larry developed had two alleles not for cystic fibrosis, but for Gilbert's syndrome, a common, mild and usually asymptomatic genetic disorder of the liver. As in the original version of the case, Lesley and Lex choose to subject the embryo to GE and as a result Larry neither develops Gilbert's syndrome, nor is a carrier of the condition.

In this scenario, it seems plausible that the relevant baseline counterfactual scenario for determining whether there's a benefit, is one in which Larry is born with Gilbert's syndrome**.** This is because, had Lesley and Lex not edited out the disease for some reason, it is plausible to assume that they would have decided to carry the (non-gene-edited) embryo to term anyway.

Gilbert's Syndrome would not be considered a serious enough disorder to outweigh the burden, risks, and possible moral costs associated with discarding the embryo and choosing an alternative way to have a child (e.g. by undergoing another round of IVF treatment and selecting against Gilbert's syndrome).

This has a surprising result: the more serious the disorder the prospective parents wish to avoid in their child, the less likely it is that editing out disease benefits the future child, and thus, the less likely it is that the benefit argument establishes a moral advantage for editing out disease over selecting against disease.

In other words: the putative moral advantage for editing out disease is more likely to obtain in relation to less serious disorders than in relation to more serious ones. This further diminishes the practical significance of the benefit argument. Why? It applies most likely in cases in which the disorder is not serious—the case for using GE may not be very strong – the benefit argument may be a easily outweighed by other considerations, such as considerations about the risk of GE.

The main concern that has been raised about editing out disease adverts to its risks, either for the edited individual or her descendants. These risk-based concerns are most likely to be decisive when there is in any case a weak argument for editing out disease, since the disorder in question is not serious or even is trivial.

Conclusion

The benefit argument fails because, in some cases, editing out disease does not benefit the edited child (since that child would not otherwise have existed). Restricting the argument to avoid this problem deprives it of much of its practical significance:

In many circumstances where gene editing is likely to be employed, the child would not otherwise have existed, so the restricted argument does not apply.

The cases in which the argument is most likely to apply are those in which gene editing is used to prevent a mild disorder, and these are precisely the cases in which the standard, risk-based objections to editing out disease are most likely to outweigh the moral advantages posited by the benefit argument.

An objection

Julian Savulescu and Jeff McMahan think Thomas Douglas and I are using the wrong sort of counterfactual in our analysis[3]. According to them, what matters is not what the parents would have done had they not done GE but what they *could* have done.

Suppose parents used IVF, did PGD, discovered deafness, but implanted the embryo without editing, thereby having a child with deafness, when gene editing was possible. (They use this example.) Suppose that had they not implanted the unedited embryo, they *would have* discarded the embryo and either not had a child or tried embryo selection.

According to McMahan and Savulescu, the deaf child has a complaint: what the parents did was *worse* for the child because they *could have* caused the same child to exist without deafness. If the parents implant the defective embryo without gene editing when gene editing was possible, the *normatively salient* alternative is implantation following gene editing to enable the subsequent child to hear.

Thus, McMahan and Savulescu conclude that if the implantation of the embryo without GE was *worse for* the child, even if the parents *would* otherwise have discarded it, then it seems to follow that, if they had implanted the same embryo *with* GE, that would have been *better for* the child, even if the parents *would* otherwise have discarded the embryo.

I disagree, however, with this conclusion. I agree that if parents implant the embryo without GE, thereby creating a deaf child, the normatively salient thing to do was to implant the same embryo *with* gene editing.

But in the cases Douglas and I are interested in, parents want to have a healthy child. Suppose they use IVF and PGD. They have two embryos. One that will result in Deaf Dylan [E(d)], and one that will result in Hearing Henrietta [E(h)]. Suppose their options are:
(1) Do gene editing on E(d) to enable Dylan to hear and discard E(h).
(2) Discard E(d) and implant E(h).
(3) Implant E(d) without gene editing and discard E(h).
(4) Discard both.

In this scenario, the normatively salient thing to do is (2): discard the embryo that will result in Deaf Dylan and implant the other embryo. But if that's correct, the gene editing didn't benefit the child. In the relevant counterfactual scenario, Deaf Dylan wouldn't otherwise have existed.

[3] McMahan J. and Savulescu J., Unpublished draft. McMahan J., unpublished notes.

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8) Lost in Translation: The Ethical Complexities of Going from Bench to Bedside Using Novel Gene and Stem Cell Therapeutics

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I've been really enjoying this conference. Thank you so much to the organizers for having me here with you today. This discussion so far has been so fascinating. It has been very philosophical. I feel a little bit like coming back home, how am I hearing my native language again. I've been away from philosophy for a while.

I'd like to give you an idea of my approach to doing bioethics. If scientists are farmers working in the field, and philosophers are up on Mount Olympus, I am sort of that little bird flying up and down between the two. You'll get a sense of that, today. I'm going to give you a bird's eye view of three big areas in biotechnology that are very exciting and also converging in really interesting and dynamic ways. It will draw on the work I've been doing for a long time, with researchers in the field and doing that collaboration, you know, kind of with the farmer.

The three big areas that I want to focus on are stem cells, cell and tissue engineering, and gene editing, in the hopes that these will lead to new therapies for patients with very intractable conditions that are not easily treated with current methodologies. These typically are the hardest cases where it's like everything that's left, that medicine cannot currently address. So, the new modalities are going after that.

I will unpack what I think are some really interesting ethical issues. The other thing I want to convey is that when I started doing a lot of work with scientists, typically they would have an attitude like, “Well, Dr. Hyun, you'll do the ethics and we'll do the science. And I found it really hard to keep that separate. I think good science is ethical science - and that raises some really interesting ethical questions. It's very hard for me to tease apart when someone is doing ethics and when someone is doing science, and you'll, I think, get a flavor of that as I go through the three main areas.

So, we'll start with stem cells. Of course, the dream is to have more stem cell therapies in the clinic. Currently, the standard of care (the only thing that's really prevalent) is stem cell transplantation for blood disorders. Now, the typical view is to in order to get to a new therapy, you have to go through the clinical trials process. Now, what's interesting to me about this is the clinical trials approach had been developed historically for the development of new drugs. And so the question is whether this pathway an appropriate one for cell based biologics, which are not like drugs. The first way in which there's a really sharp difference for me, is that in phase one (this is where you do your toxicity study, your dose toleration studies) for drugs, you often use healthy volunteers who are compensated for their time and inconvenience, who will take drugs to know what is the tolerance level. If you're using a stem cell based biologic, this should ideally graft onto the patient for their lifetime, to replace cells that have been lost in a heart attack, or even for people who have diabetes. You really can't use healthy patients; you can't use healthy volunteers. One of the things we know about stem cell biology is that the niche environment matters for how the transplanted cells behave. It's very important and it forms this dynamic, interactive relationship. If it's not an injured site, the biologic is probably not going to behave the way you're intending it to in a patient. For example, if there's no spinal cord injury, why would you put lab grown neural cells in the spinal cord? Ideally, the product's going to last for the lifetime of the patient, so you can't withdraw a

healthy volunteer from that study like you'd normally would. So, there are technical challenges or differences. But what's really interesting is that gives rise to some deeply ethical questions. And it's hard to kind of tease apart the ethics from this scientific problem.

Thus, if you have to use patients, if you have to use persons who have the disorder, in your tolerance stage, just to see after one or two years, whether this is a success and nobody develops a tumor, or nothing bad happens, then you don't want to use a super high dose of cells for that. You want to use the minimum amount to get your data that this is tolerated in the body. So, it's going to be a patient that has some sort of disorder, that's going to get a clinically irrelevant dose of cells. It's not going to do anything. If it does, that's a happy accident. But that's not how it's designed. How do you convey to the patient, you're going to get this stem cell therapy, but you're really a testbed, a human testbed, to see how the product behaves in the body? Researchers, they don't intend to kind of dehumanize people this way. But when they present their data, let's say they show the initial platform when they went to the animal model -- that the product does this. Now they're going to go to human; they're really looking at the patient just like a human biological testbed. So how do you convey that? Which stage of the degenerative disease do you put the product in? You probably want to use relatively healthy people, because they have all kinds of other issues if they're deep into the decline. So the question is at what stage you do this? Now, as a doctor, I would not want my patient to enroll in something like that, if they have lots of other good options. A phase one trial might interfere with their standard of care down the road. I'm thinking of Parkinson's disease, for example. But for the investigator, that's not the person you want to test. You don't want all these other confounding adverse events and other things to happen that are may be associated with the disease, but you're not exactly sure. You really want to use the people who have early signs. So it's sort of like a mismatch, right? From the patient welfare interest point of view, you want to wait until much later; for an investigator's point of view you want to push earlier. Where's that sweet spot? See how this is an ethical question? And a technical one; it's both. You can't tear away the ethics and the science.

Another issue is that, as you're going through the different phases, you have to scale up your product by a lot and maintain quality of that product. That's a big challenge. And it's very expensive to do that. You have to get investment from industry to get to phase two, phase three. And that can also raise some really interesting challenges for conflict of interest and hype and all that. I wanted to also briefly touch on that last box, you need three clinical standards to get to the phase one. And the pre clinical standards are not well articulated for these kinds of very complex biologics as they are for drugs. Let me give you an example of how the FDA is building the ship while it's sailing at the same time. This is the last box now moved up to the top. You have to have these types of standards. And it's not always clear what the standards might mean. For drugs, you have to know what's the purity of the drug, right? And potency of the drug. But purity and potency for cell based products is hard to determine. What do you mean by purity? Sometimes you don't want all the same cell type. In the bone marrow transplants that are now standard of care, it's a mixture of cell types of works best, and it's not pure. Thus the better term is perhaps "contaminated or not contaminated." One may need to redefine some of these categories, because biologics are dynamic, and they work together. What does potency actually mean? You can measure that in a drug but these cell products are supposed to interact. These are philosophical, metaphysical questions, but also deeply scientific.

Once you get to the middle box, you have to scale up. And unlike pills, which you can just scale up in massive amounts, and you can just leave on the shelf without causing any change, cells are genetically dynamic things that could accrue mutations over time. How do you maintain quality? How do you know that when it leaves your processing center and goes to the clinic, it hasn't changed in that process? When I give versions of this talk, especially in front of patients, they get kind of depressed because they realize how far away this dream is. Because somebody needs to be working on the distribution plan. Nobody's worked that out. It's basically like Amazon, where you have to have these fulfillment centers all across the US where they're prepared there and sent to the clinic. Or maybe it's like those meal preparation kits, where you prepare the last bit at the bedside. How are you going to distribute this product and maintain quality? What's the shipping container like?

So even if you have this clinical breakthrough, how are you going to get cell based products out to patients? How are you going to produce enough? When I point that out, people say, okay, yeah, you're right, it's kind of far away. And then there's proof of concept. You have to use animals for a number of reasons before you can go to humans, and this raises all sorts of questions about chimeras, creating them in the lab, especially for neurological disorders – a lot of controversy about putting human cells in an animal. That's a necessary step for development for FDA, so it's really hard to avoid that. Chimeras also raise some conceptual problems. Therefore it's always hard to know, what am I supposed to be working on and what are the scientists supposed to be working on? How do I divide up this labor? I think we just have to have the conversation constantly together about this.

Now, we're going to hear a little bit later about this other pathway – medical innovation – because it's essentially a myth that everything has to go through clinical trials. Actually, medical innovation outside of a clinical trials system historically has been an extremely important avenue for getting things in the clinic. But with stem cells, this presents a very difficult problem, because the stem cell clinics that you've been hearing about – those commercial, fraudulent clinics, -- are presenting themselves as medical innovators that are going outside the FDA.

On the other hand, you have to have some room for responsible medical innovation, because historically that's how so many things have made it to the clinic. In the US, there's a lot of off label prescribing of drugs. Off label prescribing means you're using a drug in populations that the FDA did not approve the drug for. It is up to the physician's judgment to use it in a new way. If you didn't allow for off label prescribing, we would not have psychiatry, pediatrics, and a lot of treatments for cancer. Also, without medical innovation, you wouldn't have surgical innovations. You wouldn't have had laparoscopic surgery, whole organ transplant, deep brain stimulation. None of these happened through clinical trials.

I'm not going to say much more about this except to say that it is quite challenging to tease apart what is responsible and irresponsible medical innovation. What's the difference between stem cell tourism and somebody at the Cleveland Clinic offering cell therapy? I tried to map out the differences there in a Science article quite a while ago. But one thing that I did find completely fascinating from this work is that we have been, I think, and this is where philosophy comes in, I think we've been misdiagnosing the problem of stem cell tourism for a very long time. If you want to have a good prescription or a solution to a problem, you have to have the right diagnosis. What is the problem for which we have to come up with a solution? When I was working with

International Society for Stem Cell Research (ISSCR) on these guidelines, we had all been thinking that stem cell tourism was a marketplace type problem. So at first, it was seen as a kind of fraud problem in the marketplace. To fight this, you need better consumer information: patients need to be armed with information. ISSCR tried to deal with the demand side of this a bit. And then ISSCR also thought we have to have higher regulation or tighter regulation to control the supply side. People were making wild claims, and people were being fooled, and the product wasn't good. We all looked at it that way. And we tried to confront the argument that adults should be able to spend their money how they want and also make their own decisions about their own bodies.

But that marketplace analogy started to fall apart for a number of reasons. One of them was that we're finding that many of the people taking patients to these clinics in Mexico, in Russia, for example, and all these places, many of them are children who don't fit that nice, buyer beware and personal autonomy model that the marketplace model is assuming. Stem cell tourism was actually getting worse, it wasn't getting better. We were providing a lot more information, creating patient handbooks and the ISSCR distributed information and asked local regulators to be more consistent. But we realized maybe we were misdiagnosing the problem. I got thinking about this because I started getting emails at this time from patients like some scientists constantly were getting emails from desperate patients. "Where should I go for this? What should I do for that?" One of these emails was so memorable for me. I got an email from somebody in Italy. He said, Dr. Hyun, I'm thinking of taking my son, my little boy to Russia to a clinic for this degenerative brain disorder he has. What do you think about that plan? I began answering his email the way I normally answered such emails. I said, here's the patient handbook about stem cell therapies, the facts, all translated into Italian. And I said, right now, there's no other standard of care outside of maybe some skin grafting and maybe, hematopoietic stem cell transplantation. I wrote him all this information, information, information, information, I put it all there. And then I decided to try one thing different on this email. I decided to add a sentence at the end of my usual answer. I said, if you are asking me what I would do if I was you, I wouldn't take my son to Russia. I would spend the rest of my time with him doing what he wants to do. And then I hit send, and he was the only one that ever responded to me. So next morning, he emailed me back and said, Dr. Hyun, I was afraid you were going to say that, but I think you're right.

The next day, I went to an institutional review board meeting, and the chaplain of the hospital who's also on the committee was walking with me. He asked me how things were going. I told him about this whole email exchange. He said, Oh, yeah, well, that's a family under spiritual distress. I asked him what that was. He said that as a chaplain he had to deal with this all the time. It's not that patients have religious questions. They usually have needs because they're under a state of spiritual distress. I asked where can I learn more about this? He said people have written a lot about this in oncology, and in nursing. There's a lot of literature on this. I ended up reading a lot on this.

That's when I thought, well, this might be the misdiagnosis. It's not that patients need more information, they need support. They need support because they're in crisis. A lot of their own family is in crisis. The antidote to spiritual distress is therapeutic hope – in order to pull yourself out of this feeling of distress, the feeling that I am not looking forward to the things that normally give me meaning in my life. In order to pull yourself out of that you have to fixate on hope. Therapeutic hope has a three part structure: (1) I have a goal, (2) I can identify a pathway to that goal, and (3) it's up to me to pursue that pathway. Those three things are called the architecture

of therapeutic hope. In bringing these ideas forward, I was I wasn't doing anything extremely creative. I was just bringing these ideas into stem cell tourism. If you tell a patient, don't go to Mexico, don't do this, don't do that, as their doctor, you close a pathway that they were fixated upon. But then you better give them another goal, another pathway, and empower them to try to pursue that. Otherwise, they're going to either just ignore you and just go to a stem cell clinic anyway, and it could possibly be much more harmful for them to do that, or they're going to slip further into spiritual distress. It's a really interesting dynamic, and I think more attention needs to be paid to it, so I wrote that up in a paper, and I submitted it to Cell Stem Cell.

It's funny, because this is a high level science journal. The term "spiritual distress" was in the title of my manuscript, and the editor asked Do you mean religion? I said, No, no, just read it. It's not religious spirituality. It's about what gives your life meaning. It could be religion, it could be your relationships, it could be the arts, it could be lots of things. When you feel disconnected from what gives your life meaning, that's when you fall into an existential crisis. Sot that's what I really wanted to say about the tourism part of stem cell therapies.

The other big area now that's really interesting, besides trying to go to the clinic through medical innovation, or trying to go to the clinic through clinical trials, is the amazing ability to use stem cells and their derivatives to do all kinds of great things in the lab. This other type of work isn't necessarily to create biologics to go into patients, but it's for scientific study, or to get new tools for discovery. A really interesting thing that we can now do with IPS cells has to do with disease modeling in a dish. Through this you can compare healthy controls and how those cells develop and compare them to the disease specific cells and see where things start to go wrong. You can do that in 2D in a dish. Of course, you can do that with screen new drugs, because you can have an endless supply of disease specific cell types. You can add different chemicals to these cell types and do the readouts on the cells. Sometimes you may start to see some combinations that seem to work well in altering or stopping progression. Very fascinating. I remember in the earlier days of human embryonic stem cell research at the ISSCR, there was very little industry interest in our meetings because the work was too controversial. It was all embryonic. When iPS cells came on the scene, in the front rows were now Pfizer all these companies because they were really interested in this technology for drug screening.

That said, I think the benefits of stem cell research are not going to be direct, as people imagine, in the form of cell-based therapies and transplants. Rather, it's disease modeling and drug screening that will enable the more traditional routes to the clinic with drugs to go faster. When people say they haven't seen the benefits of stem cells, they don't know about this.

Okay, but tissue and cell cultures in two dimensions are not very realistic. Organs and tissues are complex, they're three dimensional and involve many cell types. This motivates the move to complex self-organizing human systems that we didn't have before. As you know, animal models are not perfect because they're not humans. And two dimensional cell systems are human, but they're not realistic. Therefore the move now it to create 3D structures that mimic basic organ functions.

But the more realistic you make these models, the more concerning they may be to people and what you do with the models, especially tissue systems that are associated with moral status – gonads and brains. Hank Greely, who you saw yesterday, loves to say that brains and gonads are

all that people care about. I think he's right. Brain organoids are where I started focusing on with NIH support, working with the researchers who are doing this research. Now researchers can make organoids that recapitulate a particular region of the brain. No one organoid can recapitulate everything, so you must put them together like Lego blocks. You can build more complex systems called assembloids. Sergiu Pasca, one of my colleagues at Stanford, is famous for this. Now think about organoid systems in the dish, human organiod systems. In addition their being linked together, after a while you start asking, What is that in the dish? What if researchers made a brain organoid and connected it to a heart organoid? There can be a lot of really interesting philosophical questions about what is in the dish. What is the moral status of that?

Our institutional research review committees are set up to oversee research with common natural kinds. Take human subjects research, for example. We know what a human being is. And animal research. We know what animals are. But these new organoid combinations are not natural kinds. Many of these new things don't exist in nature. They are biological artifacts. Who reviews this work? These are quite unnatural.

Many people are also really hopeful about iPS cells offering more personalized diagnostics and personalized therapies. The big problem here however is how are you going to move these through to the FDA? Right now the FDA cannot approve, quickly, each individual iPS cell derived personalized intervention, because by definition each of these cell-based interventions have different DNA, making them each different products. It takes years and years for approval for products. Thus, the FDA would have to approve a *process*. Here's the dream, right? If someone has a disease, you can make an organoid, or you can make some representation of the body in a dish. It would be like their personalized system, you can then screen drugs on that, and you might even be able to create tissue from them that are transplanted back. That would be a super personalized way of providing care. If you have a process approved, how specific would this process have to be? If it's for blood disorders, then can it be for any blood disorder? Or would there be a difference between leukemia and sickle cell? It is quite unclear what's going to happen. It is all very complicated when you wake up to all the reality checks.

My last area is gene editing. As you know, there's a distinction between editing of somatic cells and germ cells. With the latter there's another interesting distinction that carries some unique issues. Let's begin with germline editing.

So the current consensus seems to be that one type of germline editing is now acceptable. You heard Hank say yesterday that the promise back in Asilomar Conference, was that researchers would never cross into the germ line. But now the view is that germline editing is ok as long as you keep it in the dish. The new line in the sand seems to be the uterus; you can study the embryos or sperm or eggs in a dish and try to edit out genetic defects. No transplant into the uterus for reproductive use.

I want to pause here to point out that I think there are some big potential problems with somatic cell gene editing. We all know about the Jessie Gelsinger case. That was a gene therapy trial and somebody died. Somatic cell editing is not ethics free.

Back to germline editing in a dish. This too is controversial. In the US context, in Canada, and in Australia as well, you can't make embryos for research. It's illegal now in the US. It is illegal to pay

this research with federal funds. But whether you have federal funds for this or not in Canada and Australia, it's illegal to make an embryo solely for research purposes. You have to use extra embryos from fertility clinics. Well, how are you going to do this research in the germline if you can't use frozen embryos from a clinic and edit those because they are too far along (as I explained yesterday)?. Scientists don't want to use those, the ones that are frozen in a clinic or too far along. So, you got to make your own. That's an ethical issue.

Another related issue is that you got to use human eggs. How are you we're going to get the eggs? We saw in the stem cell experience that this is very controversial. If you don't pay research egg donors the way you normally paid women for fertility services, then nobody will volunteer. I actually think it would be unethical to ask a woman to donate eggs for research without financial compensation because the physical and emotional burden is so high. Every other healthy volunteer who donates biomaterials for basic science – bone marrow, bronchoscopy, all these like really painful things – get compensated for their time, effort, and inconvenience.

In closing, the US response for human genome editing resulted in this report. I just want to point out what I find fascinating about this, because they offer this whole traffic light system. I call it the traffic light system: somatic cell green light; germline editing in a dish gets a green light. But instead of giving reproductive germline editing a red light, they gave it a flashing yellow light. It's a flashing yellow light because right now you can't do that. It's not permissible for now, but it might be possible in the future.

9) The Ethics of Human Epigenome Editing

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Hi everyone. Good morning to all of you. I am very honoured to have this opportunity to present at the Uehiro-Carnegie-Oxford Ethics Conference. I would like to thank the Uehiro Foundation for their generous support and I also thank Julian for inviting me. It's been a long time since I've been to a face-to-face international conference, and I've enjoyed it immensely so far thanks to the wonderful host and presentations.

Today I am going to talk about the ethics of human epigenome editing.

This presentation is an ongoing collaboration with a genome editing researcher who is also a muscular dystrophy patient, so it is a good opportunity for me to share what my collaborator and I are thinking. I hope that my work stimulates thoughtful discussion and invites your valuable feedback.

Let me begin by confirming a premise I have made when discussing the ethics of human genome editing. The most controversial aspect of human genome editing is germline genome editing. The reason that germline genome editing is the most controversial issue is that it may have long-term effects on future generations and also some would say it is morally wrong to edit human germline, especially embryos, in the first place.

The former issue, that is long-term effects on future generations may be good or bad, and germline genome editing is often called as heritable genome editing because the effects of the intervention are unexpectedly passed on to the next generation. Needless to say, the ethical pros and cons of heritable genome editing are still being actively debated.

On the other hand, it is often said that somatic genome editing avoids the heritability issues that have plagued germline genome editing by not targeting germline cells. Therefore, it is generally assumed that somatic genome editing does not pose any additional ethical challenges to those already raised by conventional somatic gene therapy.

In this talk, however, I would like to emphasize that even when germline cells are not targeted by somatic genome editing, the possibility of indirect germline effects should not be overlooked. The risk of somatic genome editing indirectly affecting germ cells is currently considered quite low, but the concerns have not been fully addressed.

Today's main topic is epigenome editing. Epigenome editing is as you may know "a technology that regulates gene function by artificially controlling epigenetic states at specific locations on the genome."

I will talk about the details later, but the overall functional regulatory information of the genome (not involving genetic changes) is known as the epigenome. Epigenetics, the regulatory mechanism of the epigenome, is responsible for the quantitative control of gene expression.

This presentation aims to raise questions for academic discourse concerning the ethics of human e-GE, rather than to derive a normative conclusion regarding human e-GE.

S Fragile X syndrome is a good example of epigenome editing in a pathological context and its

potential clinical application. Fragile X syndrome is a genetic disorder that causes a range of developmental problems, including learning disabilities and cognitive impairment. The disease affects approximately 1 in 4,000 males and 1 in 8,000 females.

In the FMR1 gene locus of healthy individuals, DNA methylation is low and this gene is expressed. However, in the FMR1 gene locus of Fragile X syndrome patients, DNA methylation is high and this gene is silenced. Currently, there are some established pharmacological therapies, but the therapies don't cover all the clinical features of Fragile X syndrome.

In 2018, researchers used dead Cas9-system for editing DNA methylation, and they succeeded in rescuing the pathological gene suppression of FMR1 without direct gene editing.

This is the differences between CRISPR-Cas9 and dCas9. As you know, Cas9 has two basic function; first is binding to a targeted region on the genome, and second is cutting the DNA strand. dCas9 itself maintain an ability to bind to a targeted region on the genome but has no ability to cut the DNA strand. If the effecter domain was fused with dCas9 system, dCas9 bind to a targeted regions on the genome and regulate epigenetics and gene expression.

e-GE does not manipulate the genome sequence so the results of epigenome editing interventions are temporary. Four epigenome editing listed here are examples of what I call transient interventions. This type of epigenome editing intervention and oral medicine are thought to share the similar level of reversibility in effects. Within the e-GE, functions and applications are varied.

First, dCas9-Tet1 reactivates silenced genes and improves neural function in models of diseases such as Fragile X syndrome which I mentioned earlier. Second, dCpf1-CTCF alters local chromatin structure and helps reactivate genes in diseases such as Rett syndrome, a neurodevelopmental disorder. Third, CRISPRa activates disease-causing genes and disease-modifying genes, leading to improved disease phenotypes, as demonstrated in a mouse model of muscular dystrophy. Forth, CRISPRi is a transcriptional silencing system that has been successfully used to silence disease-causing genes associated with muscular dystrophy and cancer. A clinical trial based on this principle is currently being planned.

Hit-and-run silencing/CRISPRoff is an example of a different type of e-GE. CRISPRoff introduces local heterochromatin signatures and maintains gene silencing even after the editing tool is removed. So it offers the potential for long-lasting effects without continuous intervention. This differs from the previously introduced e-GE in the sense that the main feature is that the effects of the intervention are long-lasting. For this reason, I call this e-GE as a persistent intervention.

These are some diseases associated with epigenome abnormality, so the listed diseases can be potentially treated by e-GE.

So far, we have pointed out that there are two main types of e-GE. One is the "transient" type of e-GE and the other is the "persistent" type of e-GE. Both have their advantages and disadvantages, and their use can create dilemmas. This type of epigenome editing intervention and oral medicine are thought to share the similar level of reversibility in effects. So the dilemma here is which intervention to take between the advantages and disadvantages. Transient type of e-GE intervention and oral medicine are thought to share the similar level of reversibility in effects.
But if you want to maintain the effect, you should go for persistent type of e-GE intervention.

Here I would like to point out two issues that have been overlooked in SGE/SGT. One is that, as mentioned in the background, SGE and SGT have traditionally been discussed under the assumption that the effects of the intervention are not inherited because they do not target germ cells. In particular, for adult somatic genome editing, it is currently considered unlikely that epigenome editing tools could inadvertently enter germ cells via systemic intervention. Indeed, the fact that it is unlikely does not mean that there is no risk.

On the other hand, genome editing and gene therapy of prenatal fetuses and postnatal infants may indirectly affect germ cells as a result of the intervention, although empirical data are currently lacking. Particularly when it comes to genetic interventions in prenatal fetuses, some concerns have been raised about the side effects of such interventions.

For example, in the paper titled “prenatal gene therapy for the early treatment of genetic disorders”, one of the risks of prenatal gene therapy is the "theoretical risk of germ-line transmission" and the related ethical concern is that "germ-line transmission may induce transgenerational mutations or secondary infertility.” Although these points are made in other papers, they are limited at this time and seem to be points that should be carefully considered as we move from research to clinical practice in the future.

The paper on the left is the result of a study reported this year showing transgenerational epigenetic inheritance in mammals. This suggests that if e-GE directly or indirectly affects the germ cells, the editing effects can be passed on from generation to generation.

S One of the concerns in CRISPR-cas9 is whether genetic change in germline inherit trangenerationally or not. In case of e-GE, it makes no genetic change and some epigenetic changes, so it used to be unknown whether those epigenetic changes can be “transgenerationally inherited” through germline development or not, but now it can be.

So, given the traditional concerns about heritability, the potential for inheritance of effects from SGE/SGT or “persistent” somatic e-GE (Se-GE) respectively would be a key concern for scientists and others. That is, when such genetic interventions are used on fetuses, infants, and even adults, the consequences of the interventions may be inadvertently inherited.

Again, while the risk of germline effects of genetic interventions in adults is thought to be quite low, the risks of interventions in fetuses and infants have not been adequately studied empirically. It may also be desirable to intervene in the germline to make the effects of e-GE more permanent. In such cases, the heritability issue would be an important concern, as it is with conventional genome editing. So, as the field of GE/GT moves from research to clinical application, there is an urgent need for accurate safety evaluation of SGE, including Se-GE.

As far as I know, two papers have been published on the ethics of e-GE. Both of papers are dealing with the ethical issues raised by human somatic e-GE and partly human germline e-GE. And there are like right one is done by who are in there and colleagues. Actually I am not sure I pronounce my name correctly. But both of the papers are doing with the ethical issues raised by human somatic cell genome editing and pottery are human germline genome editing.

In light of the ethics literature of e-GE, I roughly identified ethical issues, although this is by no means exhaustive. The first is a safety issue. As long as the Cas9 system is used, off-target problems cannot be avoided. It is also not entirely clear what can be achieved with e-GE, and there are still uncertainties in the technology. The second is the problem of unexpected side effects in future generations as a result of targeting or consequently affecting germline cells. The third is the issue

of interventions for non-medical purposes (e.g., enhancement or sex selection). The fourth is the issue of informed consent when genetic interventions are performed on children. Fifth is the problem of genetic deterministic reduction, that presenting epigenetics as if it were the underlying "cause" of health conditions and presenting as if epigenetics were the (often sole) cause of disease. Sixth is the problem of social inequality caused by the high cost of genetic interventions. As literature shows, these are not necessarily specific to e-GE, but are issues common to SGE/SGT, GGE, and even stem cell therapy.

If we divide the future use of e-GE into three types, that is, transient Se-GE with no inheritance, Persistent Se-GE with inheritance, and Persistent Ge-GE, the safety and ethical issues seem to fall into one of these categories. Transient Se-GE without Inheritance should be treated basically the same as SGE/SGT. On the other hand, Persistent Ge-GE should be treated basically like GGE. Persistent Se-GE with inheritance is more difficult to handle. As for this, the safety and ethical issues depend on the uncertainty factor of the presence or absence of germline integration/editing. I think it is reasonable to take precautionary measures, as with GGE, when there are uncertainties, until they are demonstrated by scientific research.

Finally what I want to consider is the problem of genetic inheritance itself. As we have already seen, persistent types of Se-GE and Ge-GE could have heritability problems. As mentioned earlier, if persistent type of Se-GE could be inherited, it would seem that, as with existing GGEs, it would be best to consider the safety risk to the maximum extent possible until the safety risk has been scientifically verified to some degree. However, the question here is to what extent we should take the heritability issue seriously. In considering the heritability issue, I would like to open the discussion by briefly touching on three cases. The first is GGE. The second is SGE/SGT. The third is a nuclear disaster. These situations, including nuclear terrorism, seems to be possible in the future.

I tentatively classified the three cases on a pilot basis using four criteria. For GGE, the nature of the intervention is intentional, the germline changes are intentional and direct, it is heritable, and unanticipated adverse effects are possible. In contrast, for SGE, we share all the criteria with ND case except for the nature of the intervention. If we look at the heritability issue based on whether the nature of the intervention is intentional or not, then we can distinguish between GGE or SGE/SGT and ND. In other words, even if there is a germline change in ND case, it would be permissible for that change to be transmitted to future generations. Also, if we look at the issue based on whether the germline change is intentional or not, we can distinguish between GGE and SGE/SGT or ND. In other words, GGE may not be acceptable, but SGE/SGT would be. If heritability per se is not morally important, then it may be appropriate to discuss the ethical pros and cons of genetic interventions, taking into account other ethical issues. Of course, safety issues should be addressed in the most scientific way possible.

Safety evaluation is essential for the clinical application of SGE, including persistent Se-GE. Given the challenges and prospects of e-GE, even persistent Ge-GE may also be necessary, although it has not yet been well-investigated. We should seriously consider whether the inheritance of genetic interventions to future generations is morally important. In contrast to the conventional arguments, the heritability concerns may not be morally significant in and of themselves if other heritability case considered. Nonetheless, we should consider safety and other ethical issues raised by SGE and GGE in general.

Given the nature of evolving (epi)genome editing and the content of this presentation, an updated ethical discussion of human e-GE in the broader context of genetic intervention seems to be important.
Thank you.

10) A Framework for Encouraging Responsible Innovation with Autologous Stem Cells

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Introduction

Regulators internationally are faced with challenges in providing timely access to innovative therapies with stem cells while delivering safe and effecting stem cell-based products. In the absence of clear pathways for innovation, an industry has flourished globally marketing 'stem cells' direct to the consumer (DTC) for products and services that have not been approved for marketing or demonstrated as safe and effective in formal clinical trials. This industry has raised many concerns around patient safety and exploitation, conflicts of interest, trust in science and medicine, professionalism and institutional practices that legitimates the market. Even so, regulators remain under pressure to accelerate the approval process with the introduction of programs that allow early market entry for products demonstrated as having likely, but still uncertain, benefits and safety.

In this paper, I draw on over 10 years of research conducted in Australia, Japan and Singapore to identify some of the ethical challenges in regulating innovation with autologous stem cell therapies. The research included comparative reviews of regulatory frameworks and international trends, content analyses of websites marketing stem cells DTC, stakeholder workshops, interviews with patients and medical professionals and roundtable discussions with experts in bioethics, health law, product regulation, stem cell science and regenerative medicine. I describe the challenges regulating innovative uses of autologous stem cells in clinical practice and propose solutions within a co-operative regulatory framework. I conclude with a discussion of the opportunities and impediments for applying this framework at the national level and across transnational contexts.

Methods

1. Scoping reviews of ethical and regulatory challenges of the direct to consumer (DTC) marketing of stem cells [1,2]
2. Documentary analysis of regulations applicable to the use of stem cell-based products in the Australia, Japan, Singapore, United Kingdom, and United States of America [3-5]
3. Content analysis of websites offering autologous stem cell-based products in Australia, Japan, and Singapore [6]
4. In depth interviews with patients seeking autologous stem cell-based products in Australia [7,8]
5. Roundtable discussions with stakeholders and regulatory authorities from Australia, European Union, Japan, and Singapore [9]
6. Normative analyses of regulatory frameworks for the use of stem cell-based products in clinical innovation [10,11]

Key Findings

Our analyses have articulated the many ethical and regulatory challenges of the global industry selling "stem cells" through DTC marketing in major health economies. While initially framed as a form of medical tourism [12,13], where patients typically travel from higher to lower income countries to access more affordable heathcare, evidence demonstrates that the DTC stem cell industry has penetrated the domestics markets of major health economies and is most prevalent in the USA [14-16], Australia [17,18], and East Asia [19-22]. Our analyses of websites marketing autologous stem cells DTC in Australia and Japan were consistent with international studies that have identified an implausibly wide range of diseases and conditions they claim to treat with little to no scientific evidence of safety and efficacy [6]. We also showed that the majority of "stem cells" being marketed

were sourced from the patient's adipose (fat) tissues from lipoaspirate and infused back using some form of 'injection', which included both intravenous and intrathecal. The safety of these administration routes is not supported with scientific evidence.

What is the harm of this industry? Besides the documented experiences of patients who have expended significant amounts of financial and emotional resources on accessing unproven therapies and have not benefited [7,8], we described the case of Sheila Drysdale who died after being administered an autologous adipose-derived procedure at an Australian clinic [23]. This patient was 75 years old and suffering with advanced dementia when her husband approached the owner of the clinic, cosmetic surgeon Ralph Bright, after hearing about the procedure on the radio. Mr Drysdale had the procedure for his arthritis and felt he had benefited from it. He had seen the procedure being marketed on the Internet overseas for other neurodegenerative disorders and asked Bright if it would help his wife. Bright agreed to provide Mrs Drysdale with the procedure, who was taken to the clinic out in Sydney and sent back to her nursing home but then died within sort of 10 hours from blood loss. Her death resulted from Bright's failure to ensure his patient had ceased taking blood thinning medications for hypertension and not keeping her in observation long enough after the lipo-aspiration to monitor for such an adverse event.

While this case could be viewed merely as a medical error that any conscientious doctor could overlook, the Deputy Coroner and medical registration tribunals did not. Bright was found to have displayed reckless disregard for patient safety by administering an experimental intervention that had no clinical support or scientific justification. He also was not specialist in neurological conditions and failed to disclose the experimental nature of the procedure. Put simply, he had no business offering the procedure to this patient, who would not have bled to death in her nursing home follow an intervention that had no benefit, had Bright not been marketing so called 'stem cells' on the Internet and radio. The NSW Medical Council found Bright guilty of negligence in his duty of care and would have cancelled his registration, but Bright relinquished his medical license before the proceedings ended. His Sydney clinic continues to operate although its website no longer markets 'stem cells'.

Our comparative analyses identified weaknesses and siloes in how therapeutic products are regulated in clinical trials or research and their uses in clinical practice as partly enabling the DTC stem cell industry to flourish in countries that are ordinarily seen as well-regulated [3-5]. One exception we found was Singapore, where the industry has never established itself [9]. Upon closer examination of the regulatory context in Singapore, we found the centralisation of therapeutic product regulation and professional governance of medical practitioners under a single government authority (Ministry of Health) to be important in enforcing laws and disciplining unethical behaviour of doctors marketing unproven medical interventions with stem cells. We describe this approach as cooperation between regulators with authority over the marketing of stem cells and their use in clinical practice.

Conclusions

Based on these findings, we have constructed a cooperative regulatory model for encouraging responsible innovation with stem cell-based products without promoting an industry marketing unproven interventions DTC [10,11]. This model comprises of three overlapping spheres of prohibitive, permissive and positive regulation under an umbrella framework. Prohibitive regulation comprises of traditional laws (e.g. consumer protections) and are punitive in action when enforced and permissive regulation are the legitimate pathways that allow for product marketing and manufacturing. Positive regulation is the area of professional governance that we argue needs the greatest attention with guidance that rewards practitioners for ethical conduct.

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11) A Demoralizing Approach to the Ethics of Cell and Gene Therapy

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1. Welfarism and Demoralization

Imagine a causally isolated world, inhabited by a single, intelligent, mentally and physically healthy, rational human being. The world contains resources for survival. If this individual does not act, they will die. So what should they do? In the short term, of course, they must provide themselves with sustenance and shelter. But why should do that? To advance their own well-being. So one relevant consideration is what well-being consists in. If hedonism is correct, then the rational way for this individual to act will be to maximize the balance of pleasure over pain, across the rest of their life as a whole. But if well-being is constituted by more than pleasure, and, say, accomplishment or achievement also matters, then they may, given that they have the talent to do so, be better off producing some impressive work of art, even if that is overall hedonically costly.

Well-being, however, is not the only relevant consideration here. From the prudential point of view (and the example is of course intended to rest on some conception of that point of view), personal identity is also relevant. Now consider two variations on the example. In the first (*World 1*), the experiences of the individual over time will be continuous and very tightly connnected over the whole of their biological existence. They remember everything, their beliefs and desires do not change, their actions all emerge from previous intentions, and so on. On anything like a standard Humean or reductionist position on personal identity, the rational strategy for this individual at any time is to act so as to maximize their well-being across the rest of their mental and biological life. Animalists will agree, as will those who accept anything like a 'Cartesian' view, according to which personal identity depends on the continuing existence of the soul. Now consider a very different case (*World 2*). At the end of each 24 hours, the maximal number of the individual's individuating beliefs, desires, intentions, and so on, that can rationally change do so. On one day, they continue to believe that the sky is blue, for example, can remember how to think, and naturally feel thirst and hunger. But they remember nothing of the previous day, have quite different dispositions (are, say, cheerful rather than phlegmatic), form entirely new projects, and so on. If we also assume some lack of continuity of experience during sleep between one day and another, many reductionists will claim that the person on the previous day has been replaced by a new person, or at least that the radical lack of connectedness has implications for the degree of concern the first-day-person should have for the second-day-person (especially if we assume that the first-day-person is aware of the relevant metaphysical facts in their world). The animalist and the Cartesian, however, may be more inclined to think that the first- and second-day person are identical.

In *World 1*, where nothing changes, all that matters is which theory of well-being is correct, on the plausible assumption that the individual has a reason – indeed overall reason – to promote their own well-being. In the second world, more is required: the truth about identity over time, *and* the truth about whether rational egoism is correct or whether there are reasons to promote the well-being of other persons that may on occasion override egoist reasons. If the individual in *World 2* has knowledge of the metaphysics, they might have an opportunity towards the end of a day to take steps to make the existence of the next day's individual more comfortable, steps which would be overall costly to today's individual to take.

I have described one world, *World 1*, in which most would agree that what matters is only, or primarily, the correct theory of well-being. That world is far from our own, in which individuals are

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in a constant state of flux. In *World 2*, two more things matter: the correct theory of personal identity, and whether there are non-egoistic reasons of sufficient strength on occasion to override egoistic reasons.

It may be tempting to think that, on, for example, a reductionist view of personal identity, *World 2* requires us to ask 'moral' questions. Given the mental switches, for example, would it be *wrong* of the earlier individual not to take steps to help the later? Is it required by morality that they do so? Would it be generous, or kind? Do they have a duty, and, if so, are they blameworthy if they do not help?

I now want to suggest there are strong reasons to resist this temptation. The practical questions raised for the agents in these worlds *can* be answered without using moral terminology, and I believe that they *should* be so answered. On the face of it, it is hard to see what more these agents need. The answers to their questions about what to do are fully answered by a position which provides complete accounts of well-being, personal identity, and reasons for action. The view that these are always sufficient to answer any practical question might be described as *welfarism*: all that matters is well-being, who gets it, and how much. Practical or ethical decisions, then, are best seen as ultimately distributive, where the only *distribuendum* is well-being.

The world we inhabit is of course highly complex, and we need many concepts to explain and describe it. But it is dangerous to think that because some concept is widely accepted and natural to us, we need it to answer particular questions. At one point, many people thought there were witches, and acted in accordance with that belief. Until we are offered a plausible case for using moral terminology, we should treat it as potentially equivalent to witch-talk. It may be merely unnecessary; but it could also be misleading, causing us to think and act in ways we have reason not to think or act. Imagine some group of rational beings living lives very similar to us, except that they think about how to act using only non-moralized concepts concerning well-being, identity, and reasons for action. Insisting to them that they are missing something of huge importance – morality – may be analogous to someone's claiming in the C14 that the concept of 'witch' is required to understand the origin of the Black Death.

Of course, by using the word 'morality', I am myself using the concept. But that is true of what I said about witches. The concept of 'witch' is now very rarely heard; am I recommending that we treat the concept of 'morality' in the same way? I am, but primarily (though not only) within philosophy. What we might call 'the morality system' – extending Bernard Williams's notion to cover all moral terminology – has been and is hugely important in human life. It may be that, in time, we, or our successors on the planet, might move beyond it, but for the moment I see little advantage, and indeed some danger, in encouraging people in general to stop using moral terminology. And because of its historical and cultural significance, philosophers should continue to reflect upon it, as they might do on religion (even if they are inclined towards atheism). We can think of morality as some so-called 'positivists' think of the phenomenon we call 'law'. There is no 'ideal', 'natural' (or 'super-natural') law, existing independently of human practices, against which we might assess those practices. There are just the practices themselves, and, we might consider legal practices without strictly *using* legal terminology – we might, ask for example, whether trial by jury in some species of case is overall beneficial or harmful, elucidating 'trial by jury' as 'what is called "trial by jury"', or more directly in non-legal terminology, though that approach would certainly complicate matters usually for no good reason. 'Morality', then, can be seen as a set of practices which have emerged over time, through cultural evolution, and which may plausibly be thought highly beneficial – at least in certain respects (like law, morality is without doubt also seriously harmful, and continues to be put to bad uses). Most modern moral philosophers think of morality in the same way that natural lawyers think of positive law. Natural lawyers are now in a

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small minority in the philosophy of law, and it is time that moral philosophy followed the lead of jurisprudence. In other words, just as we can ask practical questions about legal practices without using legal terminology at all, or at least without committing ourselves to the existence of legal entities existing metaphysically independently of human practices as in principle to be understood without use of legal terminology, so we can ask practical questions of the morality system.

Moral terminology may, then, be unnecessary in discussing practical or ethical issues. Whether it is helpful will depend on the case, though as yet I have not found any issue where it seems likely to be so, and hence recommend a strategy of *demoralization*. It is worth noting also at this point a fact about morality which does not apply to other non-referring concepts, such as 'witch'. There is a huge amount of disagreement about morality which does not boil down to disagreement about the genuine underlying issues on which it supervenes. Take just one notion: rights. Are there rights? Do animals or embryos have rights? How do rights relate to duties? What are human rights, non-legally construed? Are some rights inalienable? And so on. Some discussion is fairly immediately translatable into the language of what matters. For example, two people arguing about whether utilitarianism is true can be understood as arguing about whether the only ultimate reason we have is to promote overall well-being. But much discussion is not translatable, or at least not easily translatable, and therefore it is worth avoiding the concepts involved entirely.

A final reason for demoralizing is that the morality system has at its heart a number of emotions, in particular, forms of anger directed at perceived wrongdoers (blame, resentment, indignation) and of fear, disgust, and self-hatred, serving as sanctions and deterrents to immoral action (guilt, shame, remorse). These are negative emotions, often extremely distressing, and are likely to distract impartial and rational attention to the plausibility of premises or arguments. A good deal of philosophical ethics employs moral language, often of a rather portentous kind, for rhetorical purposes, either to attract agreement from others, or to encourage disagreement with opponents. Rhetoric is out of place in philosophy. (I have been focusing especially on philosophy, but I do believe there are occasions beyond philosophy when demoralizing is justified, e.g. when considering how to allocate some scarce health resource, and I shall say more about this with reference to cell and gene therapy below.)

2. Some principles

According to the view sketched above, what we need in our toolbox before considering the ethics of cell and gene therapy are accounts of identity, well-being, and the reasons governing the distribution of well-being.

The issue of identity is metaphysical, of course, but it is also ethical. The question is essentially one of ethical or practical status (the demoralized notion of 'moral status'). Who or what matters? The most common view is that what matter are diachronic individual sentient beings, where sentience is usually taken to involve phenomenal consciousness. But we might also wish to consider Buddhist-influenced views according to which selves are not diachronic, but are constituted merely as subjects of experience at a time, as well as views according to which zombies might have a well-being, even though they entirely lack phenomenal consciousness or awareness. But for our present purposes, we might most productively work with the idea that what matter in the cases under discussion are primarily the individual recipients of cell and gene therapy, and those affected by particular distributions of such therapy.

What about distributive principles themselves? In *World 1* above, perhaps the most plausible view is that the agent has overall reason to maximize their well-being across the whole of their life, since there seems no plausible justification for discounting the future at the theoretical level,

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though of course a maximizing strategy might well involve actual discounting in practice. Are there principles other than egoism? This seems hard to deny. Consider a case in which I can prevent billions suffering the most exquisite suffering for decades, at no cost, or perhaps some minor cost (an annoying itch for a few seconds), to myself. So I have a reason to maximize my own happiness, but also that of others. That reason is not itself overriding, however. Consider a case in which I can prevent many others – all of whose lives will go hugely better overall than mine – experiencing some fairly brief period of exquisite suffering (say, 10 seconds) at the cost of experiencing that suffering myself for five decades. There is here a dualism of the practical reason, which requires judgement in particular cases. When it comes to the suffering of others, should I maximize impartially? I think not: there is often a strong case for diverting well-being to those who are worse off, if they are below some threshold at which maximization seems more reasonable than diversion.

So we now have in place a theory which may provide answers to questions about cell and gene therapy, according to which any agent has reasons to: 1) maximize their own well-being; 2) maximize the well-being of others; 3) give priority to those below a certain threshold. Note one further upshot of demoralized welfarism (DW) as defended above. Many accept the so-called 'acts and omissions' doctrine, according to which, say, killing some innocent person is morally worse than allowing some innocent person to die. Now we understand practical reasons properly, we can see this doctrine as itself an unjustifiable aspect of the morality system. What matter are well-being, and who gets it. How they get it is entirely irrelevant, and so the causal history of any state of affairs under evaluation is itself irrelevant. All of us do tend to put special weight on our own agency, but that is merely a product of biological and cultural evolution which we might well want to resist in practice, at least on occasion. Certainly the acts and omissions doctrine should be excised from philosophical discussion.

3. Cell and Gene Therapy

We are now at the point at which we can examine the implications of DW for moral or ethical issues in cell and gene therapy. One immediate result is that there are no moral issues! But, of course, this conclusion is not as dramatic as sounds on first hearing, because there may well be issues often described in moral terminology which, once restated within DW, are significant. These we might call ethical rather than moral issues, using 'ethics' to cover practical reason in general, and to be distinct from the morality system.

Consider, then, the position that, since all innocent persons have a right not to be killed or left to die, and human embryos are persons (albeit embryonic persons), experimentation on human embryos in stem-cell research is wrong. Within DW, that position might be restated as follows: there is a reason not to kill and a reason to save those with ethical status, embryos have ethical status, and hence there is a reason not to use human embryos in stem-cell research. It is quite often said that early embryos have no well-being, and hence no ethical status. This may be true, but whether it is so depends on which conception of ethical identity we should employ. On a plausible version of the animalist view, a sentient adult is identical with the embryo from which they came (if it did not split). But on the standard psychologically reductive view of persons, their ethical status began at the very earliest when sentience developed. On the animalist view, then, if one believes that, other things being equal, there is a reason not to kill or to fail to save a sentient adult, on the ground that this will deprive them of future well-being, there is also a reason – indeed a stronger reason – not to kill or to fail to serve an embryo, since it will be deprived of an even greater amount of well-being, other things equal. This might be thought to put pressure on the animalist view itself, but that is not the case. What appears doubtful is the great significance attached to killing or failing to save those with ethical status. Any reasons we have not to kill or to fail to save post-birth individuals, then, cannot plausibly be ultimate; they are grounded in

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impartial reasons to promote well-being overall. (In that respect, then, the most plausible DW position on killing will be broadly analogous to act utilitarianism, though of course that position is usually stated in moral terminology and DW will also include a distributive principle favouring the worse off.)

DW also enables us to distance ourselves from ethically irrelevant debates, such as that concerning the treatment/enhancement distinction. Imagine that you are in a position to benefit me, as an individual with a well-being and hence ethical status, to degree *d either* by treating me for some illness *or* by enhancing me in some respect (such as improving my memory, which will enable me to gain more enjoyment from, say, bird-watching). As far as I am concerned, other things equal, it is irrelevant which you decide to do. There may of course be reasons for a state to focus its health budget on what is usually described as treatment rather than as enhancement, but these reasons will again not be ultimate. The actual distinction we draw between treatment and enhancement is highly contingent on what we take to a norm for our species, such as cognitive capacity, height, or life span. But it is at least plausible to claim that well-being in some existing society is likely to be greater overall (and appropriately targeted at the worse off) if some basic health minimum is a defeasible legal right. But it has to be admitted that such calculations will be extremely difficult, and perhaps even quite out of place if one thinks that those with little capacity for well-being – such as maggots, to use Ingmar Persson's example – should be given very high priority over those with much greater well-being.

Other issues can be addressed – or rather side-stepped – in the same way. Consider for example the claim that there is something inherently objectionable in creating human chimeras. It is true that we would have some ethical responsibility towards them, if they have a capacity for well-being, but the distinction between a human being and a chimera is merely one of biology, and in itself irrelevant to ethics. The ethical weight current human beings tend to place on the human/non-human distinction is clearly too great – consider, say, our tolerance of the factory-farming of billions of chickens. But that distinction also may have some value, in the sense that it inhibits our tendencies to harm or kill other humans. Any changes we seek to bring about in our attitudes here will have to be carefully thought through, but in the case of factory-farming I would imagine that the compassion we might show in abolishing it would be likely to benefit our fellow humans rather than put them at greater risk. It has been claimed that beings such as chimeras, or certain forms of genetically engineered humans, would be deeply alienated from others. This is certainly relevant from the DW point of view, but what matters is the effect of that alienation on them, and their place in the eudaimonic economy of the world as a whole. It may be, that is to say, that benefiting the better off at some cost to the worst off is justified overall, if the benefit to the better off is sufficiently great.

The somatic-germline distinction is in the same category as that between human and human-chimera. What matters are the effects of any action on the well-being of those with ethical status, whether they exist now or in future. There clearly are risks here, and – unsurprisingly – the DW view is that these have to be weighed against one another, and against the opportunity costs of the actions in question. Should cell and gene therapy and research continue? I believe it should not at present, but only because the resources it uses could be put to better use. If the question is taken to be – as it usually is, if only implicitly – whether it would be better to use those resources for such therapy and research or to destroy the resources in question, I have no doubt that both should continue, though of course not without careful oversight and monitoring.

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