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The rise of biological engineering: does the end justify the means?

The views and opinions expressed in this article are solely my own.

Abstract

The 21st century will be the century of biology and medicine, fueled by the rapid accumulation of biological engineering breakthroughs such as viral vectors, gene editing, and reproductive medicine, which are drastically reshaping human healthcare. But does the end justify such technological means?

First, the R&D and manufacturing costs of these complex technologies lead to hefty price tags: how can governments and payers ensure that patients in need access those treatments, while keeping healthy incentive systems for innovation? Second, as science offers increasingly practical challenges to fundamental societal frameworks such as genetic transmission and family structures, how can we ensure they are being regularly revisited and debated? Third, how can we collectively address breakthrough events such as the first genome-edited human embryos engineered by Chinese scientist He Jiankui in 2018? Fourth, with the advent of direct-to-consumer solutions such as genetic tests, how can we ensure citizens are not left to themselves?

The recipe for success will neither be to hand over societal and ethical choices to technologists, nor to shy away from the multiplication of such use cases. Far from trying to gauge whether the end justifies the means, the overarching question becomes instead: can we put in place appropriate global governance structures to promote a healthy dialogue between scientific progress and ethical guidance, so that societies can truly choose the medical and biological future they want to live in?

If the 20th century has been the century of chemistry and physics, the 21st century will be the century of biology and medicine, with the promise of a flurry of medical innovation stemming from a better and deeper understanding of fundamental biological mechanisms underpinning the human body and mind. In order to understand how such technological progress provides challenging use cases for ethicists and policymakers today, we can come back to the very birth of the century, in 2003, with the completion of the Human Genome Project and mapping of the entire human genome. [1] This was actually a product of successful global scientific governance, with genome sequencing being performed over the span of several years across the US, Europe, Japan, and China, and the resulting work being immediately published and accessible to all. But did that mean it was truly a public good? Such answer came a decade later, in particular through the landmark US Supreme Court case *Association for Molecular Pathology v. Myriad Genetics Incorporated*, in 2013.[2] Myriad Genetics discovered the precise location and sequence of the *BRCA1* and *BRCA2* genes, whose mutations are now known to dramatically increase the risk of breast cancer, and sought to patent *BRCA1* and *BRCA2* for their relevance to the market of breast cancer genetic tests. However, the US Supreme Court unanimously ruled that human genes could not be patented because "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated", and further added that "Myriad did not create anything (…) it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention". [3] This landmark case provided an answer to one of the most pressing ethical questions: in one of the rare cases of the history of biotechnology, the global scientific effort of unlocking the code to the human genome was deemed a public good.

In parallel, the rapid accumulation of technological breakthroughs in biological engineering further accelerated the field of cell and gene therapy:

1. Viral vector technologies allowed to genetically alter cells of patients suffering from genetic disorders by making them express healthy versions of the mutated genes. The concept relies on leveraging viruses' ability to infect host cells and integrate their genetic material into the host cells' DNA. By reprogramming a virus to add in its DNA a healthy copy of a mutated gene, it is possible to integrate such DNA in the patients' cells and restore normal genetic function. These approaches have already led to approved therapeutic products to treat certain monogenic disorders (AveXis' Zolgensma® is relying on an adeno-associated virus to deliver a healthy copy of the *SMN1* gene to treat spinal muscular atrophy, [4] Spark Therapeutics' Luxturna® is also relying on an adeno-associated virus to deliver a healthy copy of the *RPE65* gene to treat inherited retinal disease[5]), or in cancer immunotherapy (in particular with autologous CAR-T cells such as Novartis' Kymriah® or Kite Pharma's Yescarta® and Tecartus® for blood cancers[6]).
2. Gene editing technologies such as meganucleases, zinc finger nucleases, transcription activator-like effector nucleases (TALEN®), and most recently and crowned by a 2020 Nobel Prize, clustered regularly interspaced short palindromic repeats (CRISPR), allowed any

[1] International Consortium Completes Human Genome Project, Press Release, https://www.genome.gov/11006929/2003-release-international-consortium-completes-hgp
[2] ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL., PETITIONERS v. MYRIAD GENETICS, INC., ET AL., Opinion, https://casetext.com/case/assn-for-molecular-pathology-v-myriad-genetics-inc-2
[3] *Op. cit.*
[4] Zolgensma FDA package insert, https://www.fda.gov/media/126109/download
[5] Luxturna FDA package insert, https://www.fda.gov/media/109906/download
[6] Kymriah FDA package insert, https://www.fda.gov/media/107296/download; Yescarta FDA package insert, https://www.fda.gov/media/108377/download; Tecartus FDA package insert, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel

research center or biotechnology company to seamlessly copy, cut and paste human genes.[7] These tools can be engineered at will to recognize a chosen location of the human genome, and coupled with an enzyme that makes a break in DNA at that specific location. This break triggers a cellular repair mechanism (known as non-homologous end-joining), where the cell tries to repair such break but generally fails, leading to a complete knock-out (inactivation) of the gene. With such tools, it is therefore possible to edit out virtually any gene in the human genome, as well as knock-in (insert) other genes at their place (for instance, in a monogenic disorder, knocking-out the mutated version of the gene to knock-in its healthy version). These approaches have already shown clinical promise to treat additional monogenic disorders such as sickle cell anemia, or in cancer immunotherapy (in particular with allogeneic, or off-the-shelf, CAR-T cells). [8]

3. Reproductive medicine technologies drastically opened up the toolbox available to humans to address their fertility. A range of pharmaceuticals and surgical procedures are now routinely used, as well as assisted conception (through intrauterine insemination or in vitro fertilization, including with egg or sperm donation). In 2017, 2% of all infants born in the United States were conceived with the use of assisted reproductive technology (defined as fertility treatments in which either eggs or embryos are handled, i.e. excluding intrauterine insemination for instance).[9] By allowing the possibility for fertilization to occur in a laboratory ex vivo (outside of the human body), and combined with the abovementioned technologies, these approaches are opening up the way for mankind to operate on its own germline.

It should be noted that the COVID-19 pandemic provides a fantastic use case of such acceleration, with a recent and innovative technology, synthetic messenger RNA (mRNA)-based vaccines, being at the cornerstone of the first two FDA-approved vaccine from Pfizer/BioNTech and Moderna. Such vaccines are made of mRNA coding for the spike protein, one the key proteins of SARS-CoV-2. Upon injection, such mRNA will make the recipient's cells express the spike protein, thereby triggering an immune response that will protect them against a potential subsequent SARS-CoV-2 infection.[10]

The ethical questions raised by these technological evolutions are certainly not new, but the practical applications are. First, while the initial use cases of cell and gene therapy are hardly debatable (treating certain forms of cancer or inborn genetic disorders), the R&D and manufacturing costs of these extremely complex technologies lead to hefty price tags. The first gene therapy, Novartis' *tisagenlecleucel* (commercially known as Kymriah®), was approved by the US FDA in 2017. It is made of autologous CAR-T cells, a customized cancer treatment created using an individual patient's own white blood cells, which are genetically modified to target and kill leukemia and lymphoma cells, and carried a $475,000 list price. [11] Just two years later, in 2019, the US FDA approved AveXis' *onasemnogene abeparvovec-xioi* commercially known as Zolgensma®, another gene therapy to treat spinal muscular atrophy, a rare neuromuscular disorder, in small children. With a list price of $2.125

[7] Gene-editing pipeline takes off, *Nature Reviews Drug Discovery*, https://www.nature.com/articles/d41573-020-00096-y
[8] *Op. cit.*
[9] Assisted Reproductive Technology Success Rates, US Centers for Disease Control and Prevention, https://www.cdc.gov/art/successrates/index.html
[10] How the Pfizer-BioNTech Vaccine Works, The New York Times, https://www.nytimes.com/interactive/2020/health/pfizer-biontech-covid-19-vaccine.html; How Moderna's Vaccine Works, The New York Times, https://www.nytimes.com/interactive/2020/health/moderna-covid-19-vaccine.html
[11] Primary analysis results from Novartis pivotal JULIET trial show Kymriah (tisagenlecleucel) sustained complete responses at six months in adults with r/r DLBCL, a difficult-to-treat cancer, Novartis, https://www.novartis.com/news/media-releases/primary-analysis-results-from-novartis-pivotal-juliet-trial-show-kymriahtm-tisagenlecleucel-sustained-complete-responses-six-months-adults-rr-dlbcl-difficult

million,[12] this became the world's most expensive drug, and explained AveXis' acquisition by Novartis for $8.7 billion.[13] What are currently isolated pricing cases are bound to become the norm in the coming years, with close to 400 cell and gene therapies being in development in the US alone. In many cases, such treatments also require highly complex manufacturing and supply chains in order to be customized for each patient and delivered in a timely manner. Therefore, the questions of access that are being particularly acutely felt for COVID-19 vaccines and treatments will continue to rise together with the tide of cell & gene therapy. Since most of these developments initially come from academic institutions and biotechnology companies, and are generally taken at a later stage by pharmaceutical companies, how can governments and payers better coordinate and negotiate to ensure that patients in need access those treatments, while keeping healthy incentive systems for biotechnology innovation? From a manufacturing perspective, how can efficient technology platforms and supply chains be built across the globe to further industrialize and make these highly complex technologies truly accessible, off-the-shelf, to those in need?

Second, profound societal changes are to be expected from the rise of these technologies. The evolution of the concept of family and parenthood has been partly driven by technology, starting with the first in vitro fertilization baby in 1978. Indeed, in vitro fertilization is a highly complex set of medical procedures which require in particular medication for ovulation induction, surgery for egg retrieval, sperm retrieval, conventional insemination *in vitro* (in the laboratory), and finally surgery for embryo transfer. With the possibility to rely on donors for both egg and sperm, the traditional concept of the family unit was severely undermined. Yet today, the questions are infinitely more complex. In 2016, the first "three-parent baby" was born from mitochondrial transfer. This intervention involved a prospective mother with diseased mitochondria, the structures that provide energy to cells, which were exchanged by mitochondria of a healthy, unrelated donor. The new-born thereby carried genetic information from three "parents": the sperm donor, the egg donor and the mitochondria donor. This came from a very ethically acceptable principle: offering mothers the ability to avoid passing on metabolic diseases caused by faulty mitochondria to their offspring. [14] Yet, this technological prowess triggered the need to rethink once again our preconceived notions of parenthood, genetic transmission, and family structures. Today, countries across the world battle with the place to give to culturally complex situations rendered possible by modern reproductive technology, such as IVF or surrogate pregnancies. How can we ensure that such core cultural concepts are being regularly revisited and debated at a local and global level, as scientific innovation offers increasingly practical challenges to fundamental societal frameworks?

Third, more debatable use cases are coming to life, such as the first genome-edited human embryos by Chinese scientist He Jiankui in 2018. Interestingly, this has led to a rapid Chinese and international outcry, but one must remember that the original purpose of such intervention, at least on paper, was as much a medical one as the others previously highlighted. Indeed, the purpose was to offer an HIV-positive father and an HIV-negative mother the possibility to have children that would be free of infection. To do so, the embryos were edited by the CRISPR gene editing technology to inactivate the *CCR5* gene, which encodes a protein that HIV uses to enter and infect human cells. [15] The purpose of this was to reproduce a naturally occurring rare phenomenon seen on the so-called Berlin patient and London

[12] AveXis Announces Innovative Zolgensma® Gene Therapy Access Programs for US Payers and Families, Novartis, https://www.novartis.com/news/media-releases/avexis-announces-innovative-zolgensma-gene-therapy-access-programs-us-payers-and-families
[13] Novartis enters agreement to acquire AveXis Inc. for USD 8.7 bn to transform care in SMA and expand position as a gene therapy and Neuroscience leader, Novartis, https://www.novartis.com/news/media-releases/novartis-enters-agreement-acquire-avexis-inc-usd-87-bn-transform-care-sma-and-expand-position-gene-therapy-and-neuroscience-leader
[14] Genetic details of controversial 'three-parent baby' revealed, Nature, https://www.nature.com/news/genetic-details-of-controversial-three-parent-baby-revealed-1.21761
[15] Genome-edited baby claim provokes international outcry, Nature, https://www.nature.com/articles/d41586-018-07545-0

patient, where a mutation on *CCR5* conferred innate resistance to HIV. [16] Here, the world quickly asked the difficult question: did this commendable end justify the means of human germline editing? Thankfully, this led to a rapid global response through the creation of the International Commission on the Clinical Use of Human Germline Genome Editing which provided guidance at a global level this September 2020. Their key conclusion was that "no attempt to establish a pregnancy with a human embryo that has undergone genome editing should proceed unless and until it has been clearly established that it is possible to efficiently and reliably make precise genomic changes without undesired changes in human embryos. These criteria have not yet been met and further research will be necessary to meet them." Some of the key concerns included the specificity of gene editing, that is the ability to avoid off-target, undesired gene edits; mosaicism, which is a situation where not all cells continue to carry the genetic mutation during embryo development; as well as chromosomal abnormalities, which can lead to severe genetic defects. [17] The evolution of gene editing tools is very likely to reduce or eliminate these issues. But importantly, this review did not wish to conclude on whether these interventions should be permitted once the technology matures. It called to continue ongoing national and international conversations on ethical, moral, and religious views for potential long-term societal implications, without forgetting issues of cost and access as highlighted previously. It essentially aimed to provide a sound scientific foundation for ethics to be "guided by action", "confronted with cases" and "produced on the fly" in the words of Professor Daniel Andler, in order to aim for global, science-driven consensus, while avoiding the dramatic pitfall of ethics dumping.

Fourth, it is important to remember that all our previous case studies, even the most controversial, fell under the supervision of physicians and medical practitioners. At least in our modern societies, each patient is being guaranteed informed consent, that is their right to choose a given medical intervention with the appropriate knowledge on its benefits and risks provided to them by experts. But what happens when complex biological information is being directly provided to individuals, without clear guidance on the underlying medical significance of such data? The advent of direct-to-consumer genetic testing, pioneered by companies such as Ancestry, 23andMe, FamilyTreeDNA or MyHeritage, provides an interesting use case to such question. Such companies offer a paid service accessible to everyone, without prescription or medical supervision, where the customer is expected to provide a personal saliva sample which forms the basis of a process of DNA extraction and sequencing. The company is then able to analyze individual variations in the DNA sequence called single-nucleotide polymorphisms (SNPs) which can be more or less powerful predictors of the customer's ancestry and predispositions to certain health conditions. [18] While the former offering already raises a number of ethical questions (by revealing to a given customer genetic links to other customers – or lack thereof), the latter is of particular interest as it provides access to raw genetic knowledge without any medical interpretation. Indeed, the understanding of the significance of SNPs is still being the object of numerous studies, with certain SNPs (such as the ones on the apolipoprotein E, tightly linked to heart disease or Alzheimer's disease[19]) being more relevant to predictive medicine than others. Is it ethically acceptable to provide unrestricted access to such knowledge, knowing that most customers will not have the relevant scientific background to assess the relevance of the data provided to them? Is it medically relevant to exploit genetic data to provide an individual with precise risk factors of contracting currently incurable diseases such as Alzheimer's, if there are no actionable solutions to offer? Certain countries clearly answered no to both questions, with restrictive legislations on recreative genetic testing. In France for instance, direct-to-

[16] Timothy Ray Brown, First Patient Cured of H.I.V., Dies at 54, New York Times, https://www.nytimes.com/2020/09/30/health/timothy-ray-brown-first-patient-cured-of-hiv-dies-at-54.html
[17] Heritable Human Genome Editing, International Commission on the Clinical Use of Human Germline Genome Editing, https://www.nap.edu/read/25665
[18] The Science Behind 23andMe, 23andMe, https://www.23andme.com/genetic-science
[19] APOE, SNPedia, https://www.snpedia.com/index.php/APOE

consumer genetic testing for health purposes is banned. [20] In the US, pioneer companies like 23andMe had a difficult start with the regulators (in 2013, the FDA's suspended 23andMe's tests over concerns "about the public health consequences of inaccurate results", [21] with such tests being resumed only in 2015). Additional concerns around privacy and the importance of personal genetic data followed suit when companies like 23andMe announced partnerships with pharmaceutical companies centered around drug discovery and development.[22] More generally, many countries are still debating about the consequences of affordable, direct-to-consumer genetic testing, and the impact this will have on the relationship of citizens to their genetic makeup.

It is evident that, with the rapid progress of technology and absence of international consensus on ethics, such dilemmas will flourish in the future and our societies will need to understand and address them. The risk otherwise is to fuel a rising tide of scientific defiance and misinformation, as we have seen for instance with anti-vaccine movements, which would be extremely damageable to healthcare systems across the world. Instead, the recipe for success will neither be to hand over societal and ethical choices to scientists and technologists, nor to shy away from the multiplication of such technological use cases. The middle ground will require to keep building bridges between scientific, medical, technological expertise and political systems. It will require strong and trustworthy fora where biotechnologists, the 21st century's technologists, will keep a constant and healthy dialogue with politicians and lawmakers to ensure that each have a say in shaping the path of tomorrow's medicine. Far from trying to gauge whether the end justifies the means, the overarching question becomes instead: can we ensure that appropriate global governance structures are in place to promote a healthy dialogue between scientific progress and ethical guidance, so that societies can truly choose the medical and biological future they want to live in?

[20] In France, it's illegal for consumers to order a DNA spit kit. Activists are fighting over lifting the ban, STATnews, https://www.statnews.com/2019/11/14/france-consumer-genetic-testing-ban
[21] F.D.A. Orders Genetic Testing Firm to Stop Selling DNA Analysis Service, New York Times, https://www.nytimes.com/2013/11/26/business/fda-demands-a-halt-to-a-dna-test-kits-marketing.html
[22] GSK and 23andMe sign agreement to leverage genetic insights for the development of novel medicines, GSK, https://www.gsk.com/en-gb/media/press-releases/gsk-and-23andme-sign-agreement-to-leverage-genetic-insights-for-the-development-of-novel-medicines