# EXTREME GENETIC ENGINEERING and the HUMAN FUTURE

## Reclaiming Emerging Biotechnologies for the Common Good

CENTER FOR GENETICS AND SOCIETY

Friends of the Earth

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### About Center for Genetics and Society

The Center for Genetics and Society is a nonprofit information and public affairs organization working to encourage responsible uses and effective societal governance of human genetic and reproductive technologies and other emerging technologies. The Center supports benign and beneficent medical applications of these technologies, and opposes those applications that objectify and commodify human life and threaten to divide human society. A resource list of articles and statements about human germline gene editing can be found at **www.geneticsandsociety.org**

### About Friends of the Earth

Friends of the Earth-U.S., founded by David Brower in 1969, is the U.S. voice of the world's largest federation of grassroots environmental groups, with a presence in 75 countries. Friends of the Earth works to defend the environment and champion a more healthy and just world. Through our 45-year history, we have provided crucial leadership in campaigns resulting in landmark environmental laws; precedent-setting legal victories; and groundbreaking reforms of domestic and international regulatory, corporate and financial institution policies. **www.foe.org**

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# Contents

## Executive Summary

The idea of genetically modified children was once the stuff of science fiction, but recent developments in genetic engineering and "synthetic biology" could make it a reality. Scientists are bringing together a new generation of technologies that enable them to artificially redesign life — everything from yeast cells to people. And now, with recently developed techniques for "gene editing," the prospect of redesigning humans is much closer.

This is a brief overview of the current range of synthetic biology techniques and approaches, particularly gene editing, that are being proposed for use on humans. We discuss the challenges and concerns that arise from these proposals, including their unprecedented ethical, social and health implications.

Researchers hail synthetic biology – a new set of genetic engineering techniques – as "the future of manufacturing, engineering and medicine."[1] Amid big dreams are fast-paced investments. The synthetic biology market is expected to reach close to $39 billion by 2020.[2] Already products of synthetic biology, such as synthetic biology-derived vanillin, stevia and oils, are entering food and consumer products ahead of independent environmental and safety assessments, oversight and labeling — a worrying precedent for human applications.

But much more far-reaching proposals are in the pipeline. For example, one prominent synthetic biologist, Stanford's Drew Endy, has asked, "What if we could liberate ourselves from the tyranny of evolution by being able to design our own offspring?"[3]

Prominent voices, including some scientists working in the field, are deeply concerned about the unforeseen consequences that human genetic engineering could have. Some believe there are lines that should not be crossed, especially attempts to create genetically modified human beings (sometimes called "designer babies"), and suggest that the risks to individuals and to society will never be worth any supposed benefit. Others argue that if it's "safe," anything goes. A few even hypothesize that humanity will have a moral duty to genetically "enhance" our children if the technology and underpinning genetics progress.

No matter which opinion one holds, everyone needs to be aware of these new technologies and be able to engage in decisions about what is safe, ethical and beneficial.

There is a dearth of oversight for the rapidly emerging frontier of this merger of engineering and biology. Historic precedent demonstrates that failure to ensure transparency, democratic input and practical regulatory oversight can give license to unethical research that manifests with unintended consequences resulting in harm. Only in retrospect have these transgressions been made public.

For example, over a period of 40 years between 1932 and 1972, the U.S. Public Health Service and the Tuskegee Institute engaged in unethical research, telling hundreds of black men that they were receiving treatment for syphilis, when in fact researchers were studying the impacts of the disease as it went untreated.[4] In the 1940s, U.S. government medical researchers infected people in Guatemala with gonorrhea and syphilis without consent.[5]

More recently, there have been instances where either self-regulation has failed or scientists have not cooperated with government regulators. For example, some fertility clinics have routinely failed to follow existing professional guidelines regarding payment for women's eggs, social sex selection and the number of embryos transferred.[6] Cases of fraud and abuse have been documented from unregulated, unlicensed stem cell clinics that continue to proliferate, particularly off-shore.[7] In the late 1990s and early 2000s, several patients died as a result of unexpected reactions in gene therapy experiments.[8] In the follow-up to that tragedy, the National Institutes of Health discovered that "only 35 to 37 of 970 serious adverse events" in one kind of gene therapy trial were reported as required.[9]

The implications and potential impacts of gene editing are vast and in many cases, irreversible.

## Executive Summary (continued)

We need broad-ranging, inclusive discussions that expand beyond the ivory towers of academia or corporate-funded experts in the field, and that actively involve and integrate the perspectives of the public, including civil society organizations, labor unions, the faith community and others. The Center for Genetics and Society and Friends of the Earth-U.S. advocate that everyone should have a voice in such monumental decisions about the future direction of humanity. Open, meaningful and full public participation at every level is essential and must include consideration of the wide-ranging ethical, social and economic impacts of these technologies alongside currently uncertain predictions around safety.

We are already seeing attempts to pave the way for genetically engineered humans. Consider this sequence of recent events:

- In April 2015, researchers from Sun Yat-sen University reported that they had used gene editing techniques to alter human embryos,[10] the first time in history this is known to have occurred.[11]
- In April and May 2015, many U.S. scientists, as well as the White House, National Institutes of Health and other agencies, called for a moratorium on experimenting with human embryos, and the National Academies of Sciences announced plans for a meeting to discuss the implications of this research in December 2015.[12]
- In September 2015, a group of six major UK research funders and the Hinxton Group, an international consortium on stem cells and ethics, both released statements advocating for gene editing research in human embryos.[13]
- Also in September 2015, a team of researchers affiliated with the Francis Crick Institute applied to the UK's Human Fertilisation and Embryology Authority for a license to begin genome editing research in human embryos.[14]

Together, these developments suggest that researchers may be much closer to heritable human applications of gene editing than previously thought, and that addressing the related social, environmental, health and ethical concerns is now critical.

Recent genetic engineering discussions have focused on CRISPR/Cas9, a molecular complex intended to "edit" a genome by cutting out and/or splicing in parts of DNA sequences. This technique (which is not yet perfected, but is rapidly being refined) is promoted as a promising tool to prevent genetic diseases.

Using gene editing at the request of health-impacted patients with specific diseases, often referred to as "somatic" gene therapy, may be a worthwhile goal, if it is in fact feasible, and if the implications of such procedures are fully understood and accepted. But using the same techniques to modify embryos in order to make permanent, irreversible changes to future generations and to our common genetic heritage — the human germline, as it is known — is far more problematic.

Even the developers of the CRISPR/Cas9 tool are concerned about how others may use it. One of the discoverers, University of California, Berkeley researcher Jennifer Doudna, said:

> *"Once the discovery is made, it's out there. Anybody with basic molecular biology training can use it for genome editing. That's a bit scary."*[15]

In order to fully understand the implications of these technologies, there are essential questions that must be addressed:

- What might be the unforeseen consequences of editing DNA, about which scientists still understand very little?
- What if something goes wrong? With gene "editing" there is no simple "undo" button.
- Which of the proposed human engineering applications could address important problems?
- How can we avoid harms caused by a rush for new opportunities for profit?

## Executive Summary (continued)

- What are the risks of intervening in a patient's genome?
- Who has access and will benefit from these proposed applications?
- How do we evaluate assumptions about disease prevention, disabilities or the social creation of genetically modified humans?
- What is ethical, and who decides?

The potential human applications of synthetic biology tools, such as gene editing, put big questions on the table. It is important to look at the assumptions we are making and to quickly raise awareness about how these technologies may impact our own DNA and health, and that of future generations.

### Findings and Key Concerns

- There are significant scientific, environmental, health and ethical challenges to the human applications of synthetic biology, which currently include reengineering the human microbiome, gene drives, xenotransplantation and gene editing.
- Science and biotechnology developed in the context of private funding, public investment, intellectual property and commercial pharmaceuticals is subject to systemic incentives to rush newly discovered technologies to market, regardless of their social utility and ahead of appropriate, transparent assessment and oversight.
- Heritable genetic modification in humans, also known as human germline intervention, is exceedingly difficult to justify on medical grounds, and carries enormous risks, both for individuals and society.
- Some of those who are advocating for moratoria on editing the human germline nonetheless limit discussions of "ethics" to questions of scientific risk (safety), and fail to significantly consider social, ethical and legal risks.
- The advent of human germline intervention could lead to the development of new forms of social inequality, discrimination and conflict. Among the risks of heritable genetic modification is the possibility of a modern version of eugenics, with human society being divided into genetic "haves" and "have-nots."
- Dozens of countries, including many of those with highly developed biotechnology sectors, have explicitly banned heritable human genetic modification, as has the Council of Europe's binding 1997 Convention on Human Rights and Biomedicine.

### A Call to Action

***We call for:***

- National and international prohibitions on the use of gene editing and synthetic biology to alter the human germline for reproductive purposes. This call is especially relevant in those countries, like the U.S., that have not already enacted such a prohibition.
- Explicit and expansive public engagement on the human applications of synthetic biology, including consideration of not just safety thresholds, but also of social and ethical concerns.
- An ongoing, transparent, democratic process with which to evaluate and appropriately regulate new, emerging and proposed human applications of synthetic biology. This broad public oversight will hold scientists and entrepreneurs accountable to responsible regulation of these potentially hazardous technologies.
- Increased investment in more socially just and less risky solutions to environmental, health and social problems.

# **Executive Summary** Endnotes


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## Prologue: A Pivotal Moment in Human Applications of Synthetic Biology

Biotechnology is at a crossroads. A set of converging technologies may make possible what has, until now, existed only in works of science fiction: making permanent genetic modifications to people and their descendants, and rapidly altering the genetic makeup of other species and the world in which we live.

Synthetic biology — which public interest advocates have termed extreme genetic engineering[1] — designates a group of tools and techniques that are capable of redesigning life forms, from microbes to entire ecosystems and even human beings. Synthetic biology technologies include digital design tools for synthesizing DNA, 3-D biological printing, biobricks, gene drives and gene editing. These techniques are already being applied to cells, microbes, plants, insects and animals. They are rapidly being refined, and are already more powerful and simpler to use than they were just a few years ago.[2]

Here are just a few examples. Already, scientists are experimenting with synthetic biology and similar techniques to:

- "reprogram" existing organisms like algae to convert sugars or biomass into substances these organisms wouldn't produce naturally (such as industrial chemicals, fuels, flavors and fragrances)
- grow food in petri dishes or via 3-D biological printers[3]
- "edit" dairy cows' DNA so that they no longer grow horns.[4]

Synthetic biologists are working to "humanize" animal organs for the purpose of transplantation into humans,[5] and on engineering near-replicas of formerly extinct animals.[6] Some plan to use synthetic DNA to create self-replicating organisms not previously found in nature, or to change existing organisms — even people — in previously unthinkable ways.

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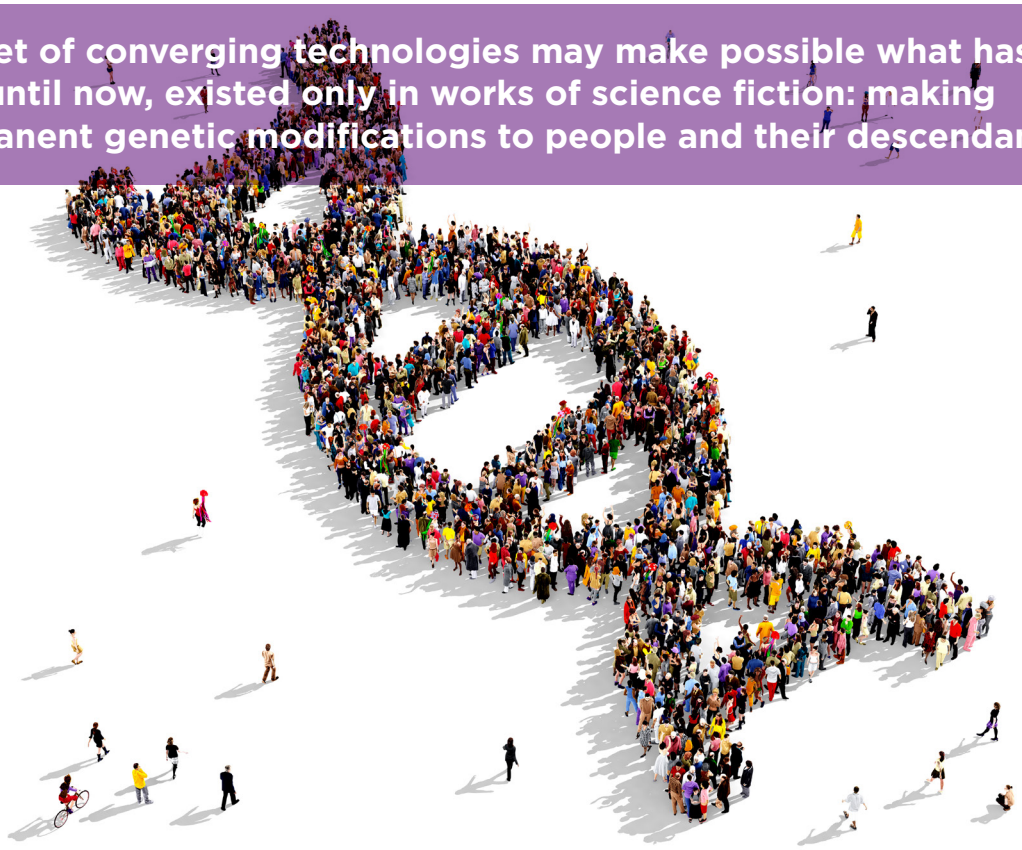

If they work, these approaches have the potential to dramatically change our lives, for better or worse. And indeed, concerns about risks to ecosystems, agricultural economies and human health are growing.

Despite promises of large benefits, some scientists developing synthetic biology applications have voiced concern about possible risks and the need for appropriate regulations.[7] At a larger level, there is concern about the new "bioeconomy," defined as a new economic system that relies on "biologically-based materials, technologies and 'services.'"[8] And this new economy is off to a big start — the synthetic biology market is "forecast to reach almost $39 billion by 2020."[9]

In practice, the bioeconomy has so far referred to an industry based on transforming biomass into fuels and other chemicals. But that's just the beginning. Synthetic biology advocates claim it will "tackle global challenges such as climate change, energy consumption, environmental protection and health care."[10] However, it remains to be seen if future outcomes will match the current enthusiasm of synthetic biology's proponents and whether its benefits will outweigh its risks.

The raw materials of synthetic biology may soon include our own human DNA. The processes being developed, which may lead to the reengineering of various life forms, including humans, are likely to be controlled and owned by corporations.

The scope of synthetic biology techniques is vast, as are concerns about both intended and unintended consequences and the current lack of safety assessment, transparency, regulation and oversight. This report focuses on emerging human applications of synthetic biology and the urgent need for a robust, informed and open society-wide discussion of how they may impact the human future and how we will manage them responsibly.

The powerful and relatively new gene-editing tool CRISPR/Cas9 (see page 21) is still unfamiliar to many people, yet CRISPR's relative ease of use and cost efficiency makes the prospect of editing human DNA more likely than ever before. The most controversial proposed human application is the use of gene editing in human germline or reproductive cells (ova, sperm and embryos). Scientists can already, although not yet perfectly, replace, add or delete all or part of one or more genes in an organism's genome. The replacement material can come from a different individual or a different species; it could also be modified and designed to order. Using these techniques to modify human germ cells

**Using these techniques to modify human germ cells (those that give rise to sperm and eggs and thus the human germline) would change the genes passed down to future children and generations. In other words, it would create genetically modified human beings.**

**More than 40 countries and a binding international treaty, the Council of Europe's Convention on Human Rights and Biomedicine, prohibit such procedures by law. The United States has no formal prohibition at present, but the National Institutes of Health (NIH) views the germline as "a line that should not be crossed."**

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Research is moving so fast that it is hard to say how much of this has currently been achieved, and what is widely anticipated. Debate about editing the human germline intensified in early 2015 after a report announced that scientists had experimented with editing the genes of human embryos.[11]

This is not the first time society has had this discussion: The rapid development of genetic technologies in the late twentieth century, including the first genetic tests and the prospects of sex selection, embryo research and medical gene transfer trials, prompted deliberations in many countries during the 1990s about what is often termed "human germline modification."[12] As a result, more than 40 countries and a binding international treaty, the Council of Europe's Convention on Human Rights and Biomedicine,[13] prohibit such procedures by law.[14] The United States has no formal prohibition at present, but the National Institutes of Health (NIH) views the germline as "a line that should not be crossed."[15]

At this point, conversations about concerns arising from synthetic biology have not been widely accessible outside biotech circles.

However, the complex but profoundly important technical, ethical and safety issues at hand will affect humanity writ large.

These issues deserve wide-ranging, careful, extensive and broadly inclusive public discussion. It is crucial that synthetic biology applications — of all kinds — are properly regulated so that they are not released onto the market or into the environment without thorough, accountable and independent assessment of their impacts on human health, the environment and society. Claims of benefits must be evaluated skeptically and compared carefully with possible costs of all kinds, including safety issues, both short- and long-term, and broader social implications. It is also important to analyze non-synthetic biology alternatives that address similar problems to those that synthetic biologists propose to resolve.

If synthetic biology applications do move forward, there must be robust, transparent, and precautionary regulation and oversight to address both foreseeable and unintended negative consequences, and to guarantee the use of these techniques for the broader public good.

## 1. Dreaming Big with Synthetic Biology

The term "synthetic biology" is a kind of shorthand for a basket of techniques that represent an engineering approach to biology. These techniques are used to design and construct novel biological parts, devices and systems, and to redesign existing biological systems and organisms.[16]

While conventional genetic engineering has involved mixing and matching pieces of DNA from different organisms, synthetic biology aims to use synthetic (human-made) DNA — "rewritten" genetic sequences — to create new forms of life or to reprogram existing organisms to produce chemicals or perform other tasks that they would not otherwise do. Synthetic biology techniques are potentially faster, more precise and broader in scope than earlier forms of genetic engineering. They straddle the life sciences, engineering and information technology.

*Bioreactor which contains live culture for chemical synthesis. (source: Shutterstock)*

Among the outputs of synthetic biology research are yeast cells equipped with synthetic gene sequences that cause the organism to secrete chemical compounds including vanillin, stevia or saffron flavorings; reengineered microbes that produce biofuels; and a synthetic self-replicating bacterium, whose creators claimed it to have been the first completely artificial life form.[17] The

production of biofuels as a "climate-friendly" replacement for fossil fuels was initially one of synthetic biology's grand promises and selling points. In 2010, maverick scientist-entrepreneur Craig Venter told the *New York Times*, "The goal is to replace the entire petrochemical industry."[18]

Only a few years later, however, synthetic biologists were forced to acknowledge that they could not make synthetic biofuels commercially viable. *Newsweek* tweeted, "Synbio was going to save the world. Now it's being used to make vanilla flavoring."[19] But that hasn't stopped synthetic biology proponents from dreaming big. Even after the biofuel debacle, a biotech entrepreneur who sits on the boards of the J. Craig Venter Institute and of Human Longevity, Inc., conjectured that "ultimately, climate change, infectious diseases and famine could meet their match with applied and synthetic biology. … Synthetic biology will be the future of manufacturing, engineering and medicine."[20] Whether this will turn out to be hype or reality remains to be seen.

Key scientists who are deeply involved in synthetic biology believe that it could dramatically change both the society and the natural world in which we live. According to

synthetic biology pioneer Drew Endy, Professor of Bioengineering at Stanford University, "We actually have a chance of reinventing civilization."[21] Endy and similar proponents seem eager to reinvent civilization by changing its technological parameters, but without any framework for considering ramifications for the environment, health or social justice.

Some think these transformations are imminent. Another central synthetic biology figure, George Church, is Professor of Health Sciences and Technology at Harvard University and MIT. He notes that "people talk themselves out of things very easily. Things that they think are a million years away or never, are actually four years away." [22]

What are the new techniques that underlie these visions? The following section lists some of the key tools and approaches in the synthetic biology kit.

## Synthetic Biology Tools and Approaches

Part of the impetus behind early approaches to synthetic biology was to reverse-engineer biological systems in order to understand how they work. This is a potentially productive line of basic research, as there is still a great deal of biology that is not well understood. For over a decade, however, there has been a push to make new living things — novel biological artifacts.

In service of these goals, synthetic biologists are experimenting with a variety of rapidly developing approaches, often in combination, including the following:

### *BioBricks*

BioBrick parts are small, interchangeable biological units: standardized sequences of DNA with a particular function that can be put together, like toy LEGO® building blocks.[23] They are used to design and assemble synthetic biological circuits, which can then be incorporated into living cells (for example, *E. coli*) to construct new biological systems. The standardized list of BioBrick parts was introduced in 2003.

### *Xeno DNA*

All natural DNA contains four chemical compounds called "bases," but researchers have invented artificial DNA varieties with six bases rather than four, which may have applications in research and perhaps medicine.[24] These have been touted as a "biosafety tool"[25] but the ethical, legal, economic and social effects could be enormous. This work is at a fairly early stage but xeno DNA has been shown to survive in a living cell.

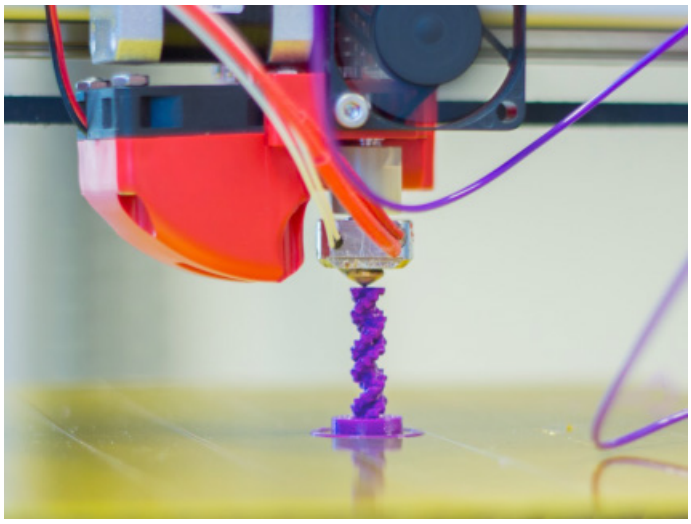
### *Digital DNA and Gene Synthesis*

Much of the work of constructing or changing genetic sequences is done on computers, and then converted to physical output as artificial DNA.[26] There is now an industry devoted to supplying customized genes on demand, and it is becoming increasingly capable of synthesizing viruses and eventually more complex organisms.[27]

Synthetic biologists speak of designing life from scratch. So far, this entails "mimicking" life by generating artificial DNA and then inserting it into an existing cell to replace (some of) the genetic material previously there.[28]

### *3-D Biological Printing*

What if we could create physical organisms that have been digitally designed? At a microscopic level, that is already plausible. Experimental 3-D



*3D printers are now capable of printing more than plastics which is depicted here, including 3D Printed human tissue and 3D printed food. Source:* creative commons via Wikimedia Commons

printing of cancerous cells was reported in April 2014.[29] Venter and others assume that remote 3-D printing of even more complex biological structures will eventually become standard practice.[30]

3-D printing would be of marginal use for vaccines, which can be flown anywhere in the world in a matter of hours, but would be almost essential for another of Venter's dreams. He wants to investigate life on Mars.[31] As he sees it, this implies sending a portable genome sequencer to the planet, beaming back its digitized results, and then analyzing and possibly even re-creating the findings on Earth.[32] Venter is of the opinion that this is a plausible, medium-term goal, "not a fantasy." [33]

### *Gene Editing*

For years, scientists have been able to delete very short segments of DNA in an organism, or turn off ("knock out") specific genes. To insert new DNA, they have harnessed viruses as transporters into the cell and the genome. But this method is highly inaccurate. Today, several new and more sophisticated techniques are being developed to delete or replace specific pieces of DNA, both in petri dishes and in organisms. At present, the biologically engineered system known as CRISPR/Cas9 is generating the most interest of several gene editing techniques (see page 21).[34]

### *Gene Drives*

One emerging application of synthetic biology and gene editing is known as a "gene drive."[35] This system would permit the genetic alteration of populations of organisms, and thus of entire ecosystems. It relies on the introduction of "selfish genetic elements that can increase the odds that they will be inherited," as noted by Harvard's Kevin Esvelt, combined with other genetic changes that might be thought desirable, for instance to block malaria transmission by mosquitoes.[36] Normally, the introduced gene would have a 50% chance of being passed on to the next generation, but a gene drive increases these odds dramatically.

Over subsequent generations, a modification made to a single individual can spread until it is present in all members of a population. Thus, the supposedly harmless genes would drive the undesired genes out of the population. Researchers have tested CRISPR-based gene drives in fruit flies[37] and in yeast,[38] as well as in mosquitoes. Some of the concerns with gene drives are discussed on pages 29-31.

## 2. Human Applications

Human applications, particularly in healthcare, are among the most prominent goals of synthetic biologists, investors and federal agencies. A 2013 Wilson Center report noted that almost half of the designers and manufacturers in the rapidly growing synthetic biology field listed "medicine" as their principal or sole focus.[39] A headline from a publication of the Biotechnology Industry Organization takes a typically optimistic — even mythological — view: *Synthetic Biology: The Sword in the Stone to Defeat Devastating Diseases.*[40]

This is not about "designer babies," which is an imprecise but popular term for heritable human genetic modification, discussed in the next section. These applications are focused on curing or preventing disease.

There is a widespread assumption that some of these processes will become valuable, although the exact routes that entrepreneurs think will lead to clinical success remain obscure. Part of this obscurity is because of a commercial culture of confidentiality.[41]

### Medical Diagnostics

Scientists at Stanford University and the University of Montpellier, France, reported in 2015 that they had modified bacteria to recognize glucose levels in urine and change color, thus potentially providing a test for diabetes.[42] So far, it is not quite as reliable as the standard dipstick, but it is seen as a proof of principle.

The next step in using synthetic biology to create a diabetes detection system is one that works internally, checking blood levels. Stanford's Drew Endy, co-author of the glucose paper, is optimistic:[43]

> *"Why not make our medicines from biology directly? We foresee that global health can be practically and affordably realized using biology. If you need more medicine somewhere, people can simply grow it where and when it is needed."*

Researchers are also focusing on cancer detection. In 2015, a team from the University of California at San Diego and the Massachusetts Institute of Technology announced that they had modified *E. coli* so that it could detect cancer in urine. The engineered bacteria are swallowed and then generate what MIT synthetic biologist Tal Danino calls a "high-contrast urine signal."[44] The research is important, but the technology is still largely hypothetical and certainly not ready for prime time before the unanswered questions about the safety of the engineered bacteria and unforeseen impacts are more thoroughly assessed.

### Vaccine Production

Synthetic biologists are currently testing how to produce vaccines more rapidly. The vision, as described by Craig Venter, involves automated "sequencing from biological samples, gene synthesis and assembly, and virus rescue."[45] He envisages mobile units that can sequence strain samples from around the world and automatically upload that data into a database, allowing scientists anywhere to access the information and create or re-create vaccines without needing the physical strain sample.

Venter's Synthetic Genomics Vaccines, Inc., together with the U.S. Centers for Disease

Control and Prevention (CDC) and Novartis, are collaborating "to speed up influenza vaccine production."[46] In May 2013, they published a description of a test case in which they had designed a vaccine in less than a week after receiving the genetic code.[47] The goal is mass production of the vaccine without requiring the hundreds of thousands of chicken eggs currently used in the standard manufacturing process.[48] Venter promoted this as "the first real-world product from synthetic biology" and "...just a tiny hint of the future of what's to come."[49]

Development of this technique is accompanied by serious safety risks. As more and more labs have the capability to create living viruses from genetic sequence data, the risks of an accident increase. The viruses that Venter and Novartis have used, deadly H7N9 isolates from Chinese victims, are capable of causing a public health crisis if accidentally released, as would a number of other influenza strains and other viruses (including Ebola) that can be created using synthetic biology and similar techniques.

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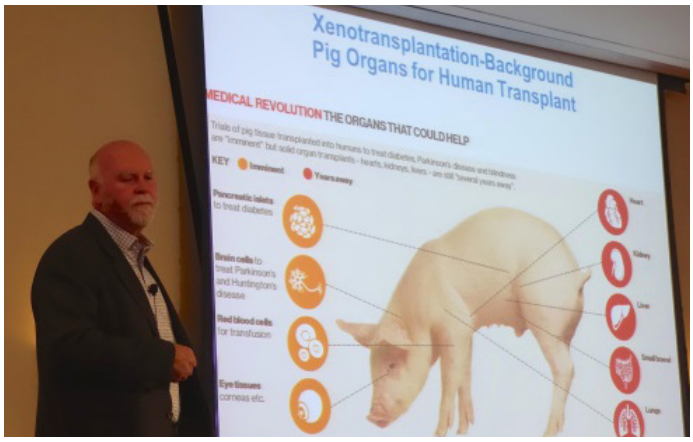
So far, Venter and Novartis' technique merely speeds up the process of sharing some kinds of viruses across the globe — exclusively between labs that are highly technologically equipped. This research suggests that scientists might be able to use synthetic methods to produce vaccines against novel influenza strains more quickly and to send the virus by e-mail rather than physical delivery, saving a few days. However, Philip Dormitzer of Novartis, the lead author of the paper describing this, admitted that "the process still isn't fast enough for viruses such as HIV that mutate quickly, nor is it necessary for those that evolve slowly, such as rabies."[50] Thus, rather than being a new vaccine technology, this kind of synthetic biology is a new way to send a virus from one place to another — an evolution rather than a revolution.

## Xenotransplantation

Xenotransplantation refers to the use of organs from other animal species to replace faulty ones in humans. Efforts are being made to genetically modify pigs, and possibly other animals, to create organs that are at least partly "humanized" and thus available for research (Intrexon is already selling custom transgenic swine models[51]) or even for clinical use. Among others, Craig Venter's Synthetic Genomics is working on this project with Lung Biotechnology




*Craig Venter of Synthetic Genomics presenting on xenotransplantation. Source: Steve Jurvetson* creative commons via flickr.com

Inc., a subsidiary of United Therapeutics. Venter optimistically stated, "We are re-engineering the pig, changing its genetic code. If we succeed with rewriting the pig genome, we will have replacement organs for those who need them."[52]

Synthetic Genomics is trying to modify cells that Lung Biotechnology plans to use in order to generate genetically altered pig embryos. Still in a very early step in the process, another team has created pig hearts that survived in baboons for a year, albeit not working as hearts but "grafted into the abdomen of an otherwise healthy baboon."[53]

One of the substantial risks is that the organs may be rejected by the human body. In addition, pigs can suffer from over 25 known diseases that can infect humans, and new pig viruses are still being discovered.[54] Demonstrating adequate safety is likely to be challenging, if not impossible.

## Genomics

The genome is the entire set of DNA in a person (or any other organism). Genomics is the analysis of the genome, partly in the hope of figuring out which genes have what effects. Understanding what will happen when a particular gene is inserted or removed is vital to gene editing, synthetic biology and effective gene therapy (as well as to proposals for genetic "enhancement"). Scientist-entrepreneurs have deep interests and influence in efforts to reduce the cost of genomic sequencing and increase technological capability. The rapid development in sequencing techniques has lowered the costs of gene sequencing to the point where routine clinical use is being seriously considered for future use.

Researchers suggest that genome analysis could have applications such as identifying patients who are likely to have a bad reaction to particular medications.[55] Similarly, analyzing the genomics of cancer tumors could help researchers develop more precise drugs that are specific to certain variants.

However, technical success in gene sequencing seems to be outstripping the identification of genes that can reliably be said to cause certain effects. There have been notable successes in identifying the rare single-gene diseases, but they are the exception. Pharmacogenomics and cancer genomics may eventually turn out to be medically useful, but that day is some ways off. A 2014 survey article in *Science Translational Medicine* noted, "Unlike rare Mendelian disorders, the genetic dissection of common, complex diseases such as cancer, cardiovascular disease and diabetes has proven to be more difficult."[56]

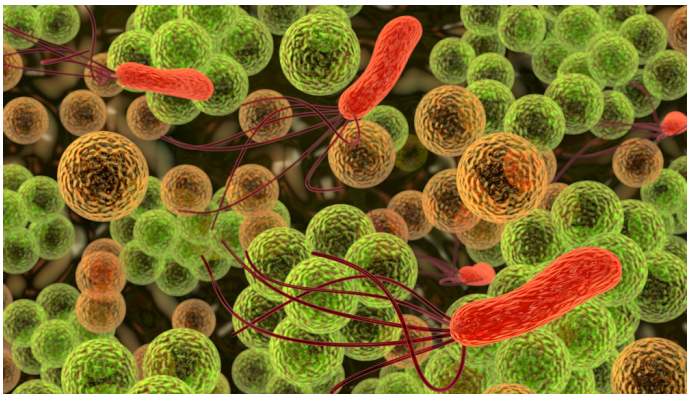
This is partly the result of complex interactions between genes and the environment. Health is often affected by many environmental and socio-economic factors in addition to genetic influences.[57] In short, researchers have not yet technically figured out how to achieve the goals of complex disease prediction — let alone prevention — as they had hoped.

Genomics has become increasingly reliant on genome-wide association studies (GWAS), which need very large numbers of patients in order to identify relatively rare genetic variations that may have cumulative effects. Ideally, DNA sequences should be fully representative of populations from around the world, and patients' medical history and physical data — not just of disease but of levels of normal functioning — should be part of the analysis. Efforts are underway to coordinate enormous databases with global reach.[58]

There are problems with this: If your genomic data is on file, then samples of your genome can be used to identify you, though not quite

as infallibly as television and prosecutors often suggest.[59] Moreover, the same data can be used in an attempt to make predictions about your future health or even behavior — and those predictions may be false. In almost all cases, they indicate at best a statistically significant correlation between your genes and an increased or decreased likelihood of some outcome. There really are not "genes for" most traits, though the claims do persist.[60]

Not surprisingly, many members of the public remain skeptical about trusting their genetic data to strangers, and there is a widely, though not universally, desired need for privacy protections. The U.S. Genetic Information Nondiscrimination Act (GINA), signed into law in 2008,[61] provides important but limited legal protections. Employers are not permitted to discriminate on the basis of genetic data, but they are allowed access to employees' medical and genetic information, and there have been a few legal cases in which employers tried to use genetic information against employees.[62] Given the large DNA databases that already exist, it is critical to have robust federal and state oversight and regulations to adequately address people's privacy concerns.



## Human Microbiome

All humans, healthy or not, are hosts to an enormous number of microorganisms, some of which are known to be essential and many of which have unknown roles, if any. They have different genes than we do, and are collectively known as the human microbiome. The National Institutes of Health (NIH) has a major project underway to investigate this fascinating aspect of biology.[63]

Though study of the human microbiome is in an early stage, several researchers are pursuing the prospect of engineering it. A group of French students won a medal at the 2014 International Genetically Engineered Machine competition (iGEM) for, what the Paris Bettencourt team called "a BioBrick smell library for mixing genetic perfumes and a CRISPR-mediated technology for isolating naturally odorless bacterial strains," in order to "target common odors of the armpit and foot, as well as odors specific to old age or genetic disease."[64] The group's analysis mentioned the project's bioethical dimensions, but the discussion was minimal. For example, while it touched on informed consent, it noted that this minimal standard should be supplemented, if at all, by internal peer review.[65]

At this point, scientists have little understanding of what the impacts of engineering the microbiome might be, particularly in vulnerable populations like infants, whose microbiomes are just being established. Scientists are exploring and just beginning to understand the microbiome's interactions with the human body's immunological, metabolic and neurological systems.

The NIH project includes an element on the ethical, legal and social implications of microbiome research. In addition to questions about informed consent, privacy, risks, products and possible regulations, they note "broader societal implications," including "what it means to be 'human.'"[66] This deserves further funding and consideration.

But at this point, we barely know what questions to ask. What happens if (or when) novel microorganisms mutate further or spread to other individuals? What applications might be useful enough to evaluate? What might be the unintended side effects? Without a deeper understanding of the microbiome, how it functions and what it impacts, reengineering the human microbiome could have vast unforeseen consequences.

## Gene Therapy

Gene therapy — treating or curing serious genetic conditions by replacing atypical genes that are thought to be in some way "flawed" — has been one of the most alluring goals of genomic research for several decades. In practice, gene therapy has encountered several stubborn problems.

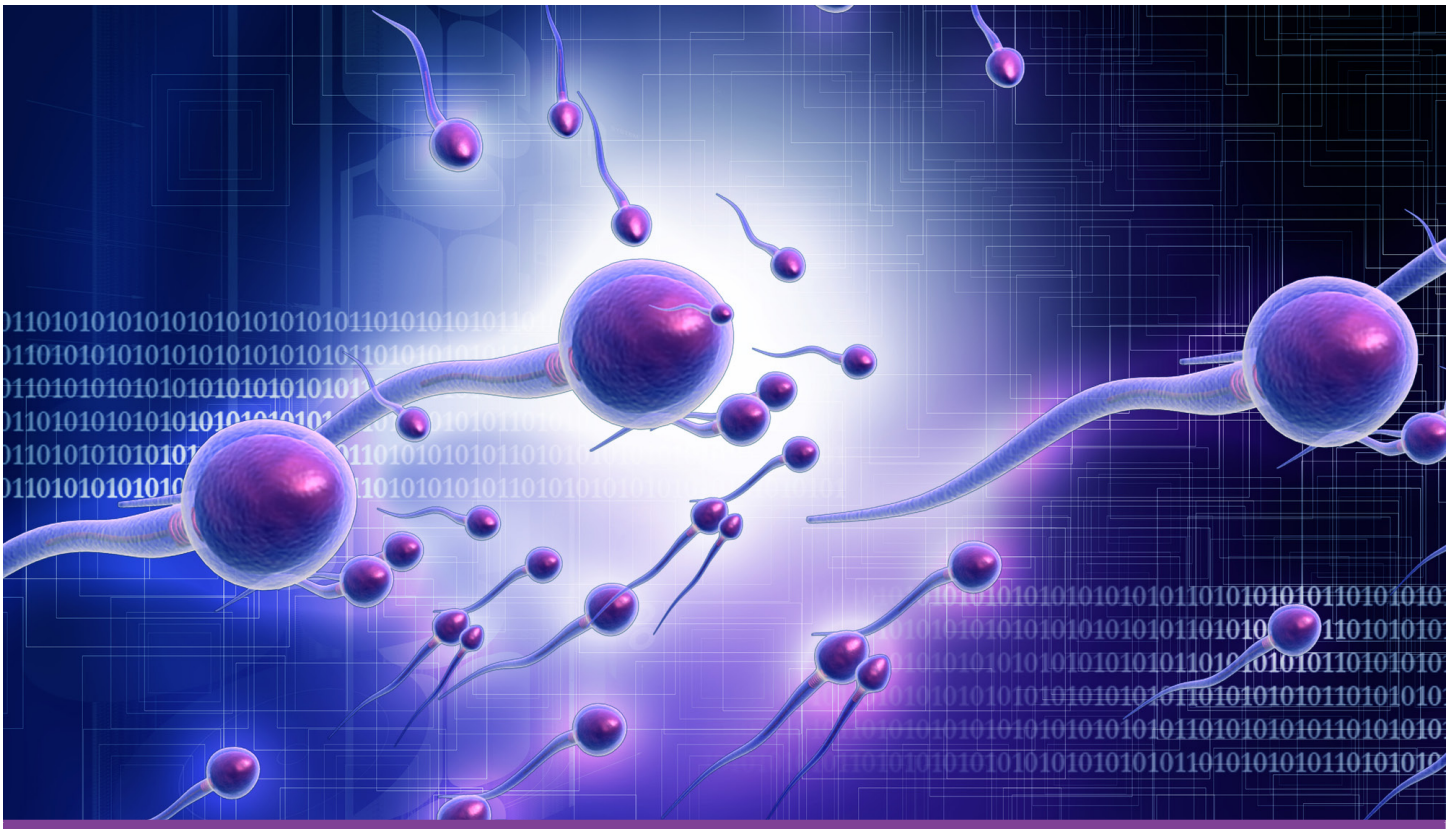
First, genetic mutations, in many cases, do not function predictably. The same genetic variants may or may not be associated with a particular expression in any individual. This may be due to varying interactions among genes, interactions between genes and the environment and/or the different ways genes can be expressed.

Additionally, the genetic replacement delivery mechanism developed in the 1980s and 1990s, which relied on viruses to carry DNA into cells, was not accurate, so genes were frequently not inserted where they were needed. Tragically, in the late 1990s and early 2000s, several patients died as a result of unexpected reactions in gene therapy experiments.[67]

However, researchers have gradually begun to overcome these obstacles for some conditions. Gene therapy clinical trials started in 2014–15 may show promise for treating some eye diseases (though results are mixed),[68] some kinds of hemophilia[69] and even some cancers.[70] As a result, investment money and big pharmaceutical companies are moving into the field of gene therapy.[71] Scientists have recently published research using CRISPR/Cas9 gene editing in T cells for autoimmune diseases,[72] and others are seeking to use synthetic biology and gene editing in further research.[73]

Gene therapy serves to treat existing conditions in only the individual. It is distinct from germline genetic modification which is heritable, passing on changes to all future generations. Some scientists working on these techniques are eager to consider not just "therapeutic" alterations but also novel attributes that they believe would make people "better than well."[74] Both heritable modifications and the idea of human enhancement are dimensions of genetic interventions that raise important ethical and social justice questions.

**Some scientists working on these techniques are eager to consider not just "therapeutic" alterations but also novel attributes that they believe would make people "better than well."**



## *Box A*: What Do *Germline* and *Somatic* Mean?

*Germ cells* are eggs and sperm and the cells that make them. These reproductive cells pass particular versions of genes to offspring, and the line from parent to child is known as the *germline*. So, germline changes are heritable modifications to genes that affect the descendants of a family or, more broadly, of a species. (In the popular press, these are sometimes called "designer babies.") Germline alterations would be made to sperm, eggs or early-stage embryos.

The prospect of modifying the human germline has been discussed for years. Only very recently, however, have such deliberate changes seemed even close to being possible.

*Somatic* comes from the Greek word *soma,* or body. Somatic genetic modification alters cells in the body *except* egg and sperm cells. These changes would affect an individual but not that person's descendants, just as working out may make you stronger but will not make your children athletes. However, recent research into epigenetics suggests that some somatic changes may affect the expression of some inherited genes, although little is known about how this occurs.[74] There remains a lot to learn.

Somatic genetic modification for medical purposes, or gene therapy, can be dangerous if something goes wrong, but it will probably never affect anyone directly other than the patient. Errors involving germline interventions, however, would affect all future descendants, potentially in very unpredictable ways.

Some advocates use the term "germline gene therapy" which may be confusing and is actually inaccurate. Patients receive therapy in order to heal; altering germ cells or embryos may perhaps be seen as a form of prevention but cannot by definition be healing.

## 3. Human Germline Modification

A round of policy debate about human germline modification (also known as heritable genetic modification) took place in many countries in the 1990s. More than 40 countries decided to put laws in place prohibiting attempts to alter the human genome in ways that would be heritable. The Council of Europe's 1997 Convention on Human Rights and Biomedicine, a binding treaty, also proscribed it.[76] No country that undertook a policy consideration during that period decided to permit human germline modification. But the prospect of what are often called "designer babies" is now being raised again by synthetic biology researchers and entrepreneurs, especially in response to the development of gene editing techniques like CRISPR. (See next page).

**The prospect of creating genetically modified humans is now an immediate, pressing issue.**

### CRISPR Developments in 2015

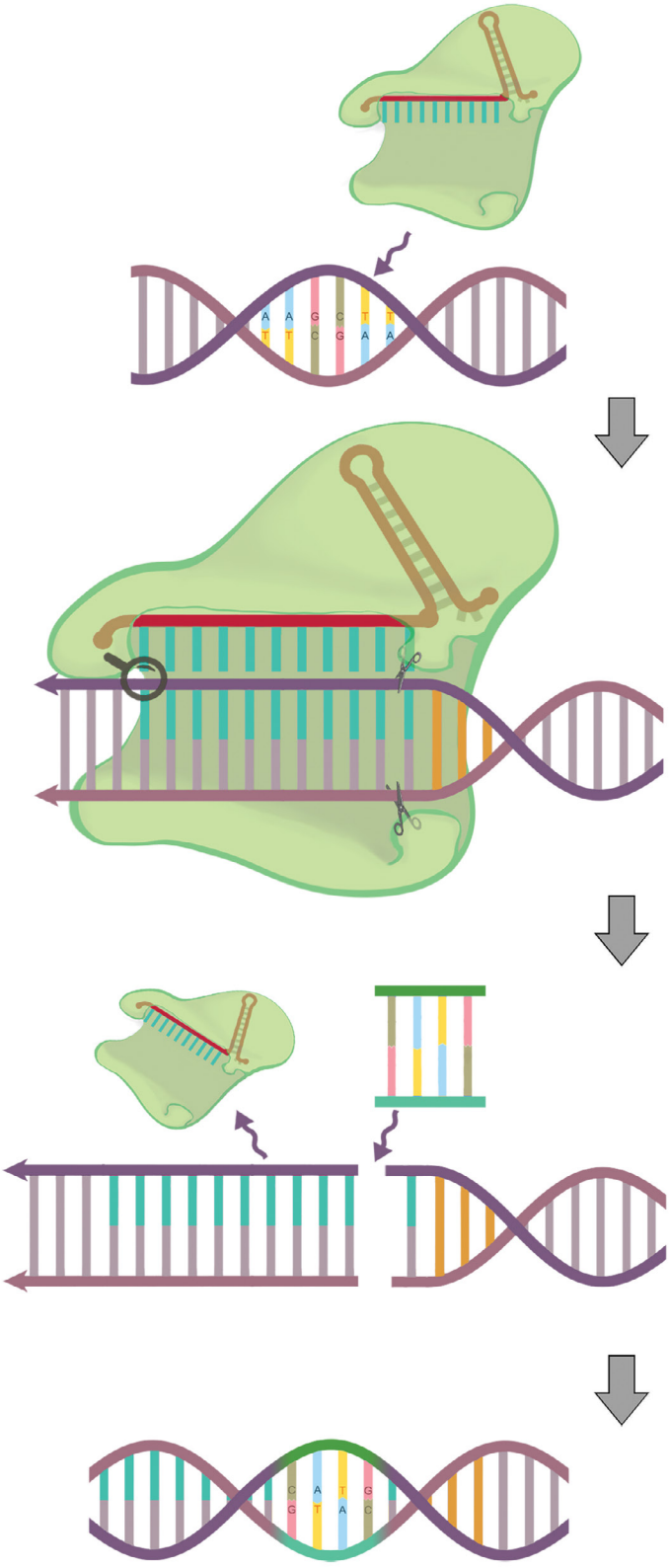
The prospect of creating genetically modified humans is now an immediate, pressing issue. It has been developing for some time, but the discovery of the much more efficient gene-editing process known as the CRISPR/Cas9 system brought it to the forefront.

CRISPR, or Clustered Regularly Interspersed Short Palindromic Repeats, was originally discovered by scientists researching anti-viral defense mechanisms in bacteria. The CRISPR/Cas9 system relies on RNA-DNA base pairing to identify a targeted location in a genome, and produce a double-strand break at this locus in the existing DNA — gene editors have been called molecular scissors — allowing researchers to insert new sequences and other modifications.

By early 2015, the technical possibility of using CRISPR to create genetically modified humans had become alarmingly close. Even the developers of the CRISPR/Cas9 tool are concerned about how it might be used. One of them, Jennifer Doudna, said, "Once the discovery is made, it's out there. Anybody with basic molecular biology training can use it for genome editing. That's a bit scary." [77]

Doudna is Professor of Biochemistry and Molecular Biology at the University of California, Berkeley, and Executive Director of the Innovative Genomics Initiative.[78] In spring of 2015, she and other prominent scientists took the unusual step of writing articles and speaking to reporters about their concerns. Two different groups of scientists and biotech figures published articles in *Nature* and *Science* calling for at least a temporary moratorium on such experiments.

The group including Doudna and 17 others (headed by David Baltimore and Paul Berg), writing in the journal *Science*, proposed a limited moratorium on using gene editing for reproductive purposes, but also actively encouraged research to determine whether it can be made "safe enough" to consider using it to produce genetically modified human beings.[79] Another group of five scientists, headed by president and CEO of Sangamo BioSciences Edward Lanphier, writing in *Nature,* argued that there is no scientific justification for using these



**CRISPR/cas9** is a protein complex that carries **RNA 'programmed'** by researchers to find a specific target sequence of **DNA**.

CRISPR finds this target by matching its RNA sequence to the **corresponding sequence of DNA**.

While matching sequences, CRISPR also looks for the presence of a specific signal sequence [called **PAM sequence**].[1]

If this **PAM sequence** is present, CRISPR will bind to the site and use two nucleases (molecular scissors) to perform a double-strand cut of the DNA at the end of the target sequence.

*Note: If CRISPR matches its RNA with a sequence of DNA with no PAM present, it will not make a cut.*

CRISPR releases from the site and moves away. The cut DNA may now be modified in a number of ways.

Here we show CRISPR used to insert **novel DNA**.

The DNA to be inserted needs to be bordered on both sides by DNA sequences that are homologous (the same) to the DNA to the left and right of the cut (not shown).

(An engineered DNA segment may be introduced that is tailored to fit into the area that was cut.)

After CRISPR cuts and releases, the cell's own repair enzymes are activated, seeking out the damaged areas to bring the cut strand back together.

The cell's enzymes will move in and repair each break, attaching the engineered DNA to the original cut ends. The cell's DNA now includes the new sequence. (This is called "HDR", homology directed repair).

[1] Protospacer adjacent motif (PAM)-distal sequences engage CRISPR Cas9 DNA target cleavage. http://www.ncbi.nlm.nih.gov/pubmed/25275497

technologies to modify human sperm, eggs and embryos.[80] Under the title "Don't edit the human germline," they recommended forgoing this use altogether.

**"Once the discovery is made, it's out there. Anybody with basic molecular biology training can use it for genome editing. That's a bit scary."**

—CRISPR co-discoverer Jennifer Doudna

In April 2015, almost immediately after the publication of these two articles, the first published scientific paper emerged describing attempts to use CRISPR/Cas9 gene editing to modify human embryos by researchers at Sun Yat-sen University.[81]

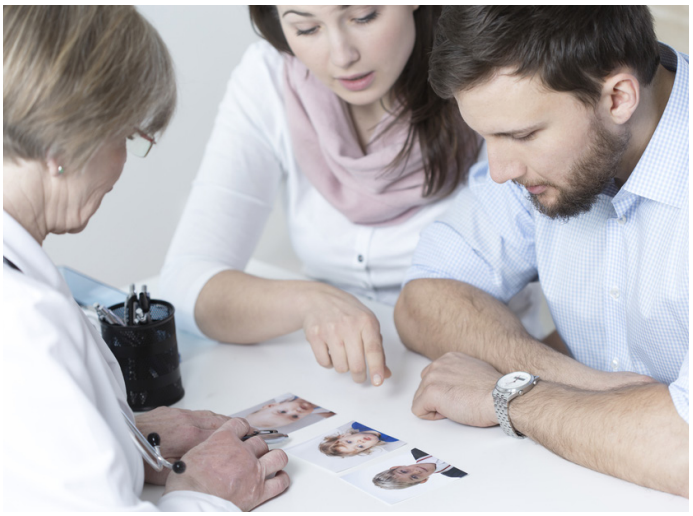
The Chinese researchers worked with 86 non-viable embryos from In Vitro Fertilization (IVF) procedures. Of these, they were able to study the results in 71. The outcome was far from a resounding success. They found that CRISPR frequently missed its target and inserted the new version of the gene in the wrong place. This result, known as an off-target mutation, could easily create a new kind of disorder or malfunction. In addition, CRISPR managed to cut the DNA only in some of the embryos, and insert the new version of the gene in only a fraction of those. Further, some of the embryos they examined wound up with a mix of accurately and inaccurately modified cells.

Nonetheless, the point was clearly made: If those embryos had been viable, had been implanted in a woman, and had been brought to term, they would have been genetically modified humans.

**The advent of germline gene editing could all too easily lead to the development of new forms of social inequality, discrimination and conflict.**

This attempt was made before any broad societal discussions about a new procedure that would enable the creation of genetically redesigned human beings. According to the lead author, their paper was rejected by two major journals, *Science* and *Nature,* on ethical grounds before being published in *Protein and Cell*.[82]

In response to the published study, even those who advocate moving forward with developing germline gene editing acknowledged that the technology is not yet ready to be used for "clinical applications" — that is, to initiate a pregnancy.[83] But while safety is universally cited as a prerequisite for applying gene editing and synthetic biology to humans, there are significant differences about what would constitute proof of safety. How many experiments would be needed? How many generations of animals would be required before use in humans should be contemplated? And what level of risk on the immediate targeted organism or person is acceptable?



Moreover, technical safety is by no means the only concern. Creating genetically modified humans raises profoundly important questions about medical assumptions made to justify manipulation, and the consequences of irreversibly altering future generations. If these genetically modified humans were to be perceived, or to perceive themselves, as superior to the "unenhanced," the advent of germline gene editing could all too easily lead to the development of new forms of social inequality,

discrimination and conflict. Questions about ethical implications, oversight and regulation are as critical as those about short- and long-term safety, and will require an essentially political forum in which to resolve these concerns. As Daniel Sarewitz wrote in *Nature*, "Science can't solve it."[84]

The prominence and new urgency of these developments led to an announcement in May that the National Academy of Sciences and the National Academy of Medicine were launching an initiative on human gene editing, including an "international summit," scheduled for December 1–3, 2015.[85]

## A Bright Line and Some Blurry Lines

In evaluating and differentiating human genetic technologies, several categorical distinctions are helpful. One concerns the purpose of a prospective genetic intervention; it distinguishes procedures undertaken for therapy from those aimed at enhancement. This distinction, however, is an inherently blurry one. When does a medical treatment become a procedure aimed at making someone "better than well"? One example is the use of synthetic human growth hormone. Should it be used only in children who suffer from a hormonal deficiency that limits their height, or can it also be used in children who are simply short?

Some advocates of human germline engineering say they want to limit prospective uses to changes in what are considered medical conditions. Others are focused on making children smarter or more athletic. Claims that future generations can be engineered to be "virus-free" represent another example of the blurry distinction between medical and non-medical.[86]

A second line, between somatic and germline genetic interventions, is much clearer. As noted in Box A on page 19, somatic genetic procedures modify the genes of an existing person, while germline modifications are made to gametes or early embryos and would change the genes of future generations.

A third technical distinction separates two

types of interventions, both of which affect future children and generations. One type can be thought of as "selection" technologies, such as embryo screening via pre-implantation genetic diagnosis (PGD) or prenatal testing followed by pregnancy termination. The other type of intervention consists of "manipulation" technologies that actually alter the genes, and thus the traits, of future humans.

There is wide agreement that human germline modification is on the off-limits side of an ethical and policy "bright line." However, this does not ensure that the technologies and procedures on the near side of that line are ethically or socially unproblematic.

Prenatal and pre-implantation procedures are viewed by some as a way to avoid transmitting heritable conditions. Their availability makes the medical argument for modifying the human germline tenuous, as some scientists involved in developing gene editing have noted.[87]

However, when selection technologies are used to prevent the birth of children that express particular traits, they suggest a distinction between "good" and "bad" genes, which may devalue the bodies and lives of people with different abilities or disabilities. This distinction works to change our assumptions about normality, acceptability, self-worth, human value and diversity. While most disability rights advocates and scholars who have articulated this critique, support the right to terminate a

pregnancy for any reason, they also point out that selection technologies do stigmatize people with disabilities — effectively reducing human beings to one characteristic: a "flawed" gene.[88]

In contrast to the blurred distinction between selection and manipulation technologies, as well as between therapy and enhancement, the distinction between germline and somatic is sharply focused. This has led to the development of a globally widespread policy framework that puts human germline modification in a prohibited category.


## Policies and Perspectives

The prospect of making permanent changes to the human gene pool has been regarded for many years as dangerously unacceptable. Dozens of countries have explicitly forbidden it, as does a binding treaty of the Council of Europe.[89] No country or intergovernmental organization has formally or informally supported either human reproductive cloning or germline interventions that affect DNA in the nuclei of human cells. These prohibitions against modifying human descendants constitute a "bright line" that is simple to define, allowing a ban to be written into law without fear of misinterpretation.[90]

The U.S., unlike most other countries with an active biotech sector, has no formal, legal prohibition of human heritable genetic modification. Rather, the Food and Drug Administration (FDA) has made clear its view that it has the power to prevent human germline engineering.[91] In April 2015, Francis S. Collins, Director of the National Institutes of Health, reiterated NIH policy not to fund "any use of gene-editing technologies in human embryos," since NIH views the germline as "a line that should not be crossed."[92] In May, John Holdren, Director of the White House Office of Science and Technology Policy, issued a statement that "the Administration believes that altering the human germline for clinical purposes is a line that should not be crossed at this time."[93]

Writing in the *New England Journal of Medicine*, Eric Lander, Director of the Broad Institute of Harvard and MIT, which holds patents on CRISPR gene editing technologies, urged "great caution" and saw "much wisdom" in at least a limited ban on germline interventions. He wrote, "It has been only about a decade since we first read the human genome. We should exercise great caution before we begin to rewrite it."[94]

The "bright line" that puts human germline modification off limits has been widely considered an internationally settled position for safety, social and ethical reasons. However, even before the recent controversy about using CRISPR on human embryos erupted, some had already begun to question it.[95]

In early 2015 the U.K. decided in principle to allow mitochondrial interventions ("3-person babies") that would be heritable, and thus would constitute a limited form of human germline engineering. In addition, a small number of academics, notably including Julian Savulescu of Oxford and John Harris of the University of Manchester, have begun to argue that human germline genetic modification will soon be an ethical obligation.[96]

Those supporting such interventions often make dubious assumptions about their short- and long-term safety. Some claim that new gene editing techniques will offer unprecedented precision and predictable accuracy, but many scientists contest that expectation. Lander

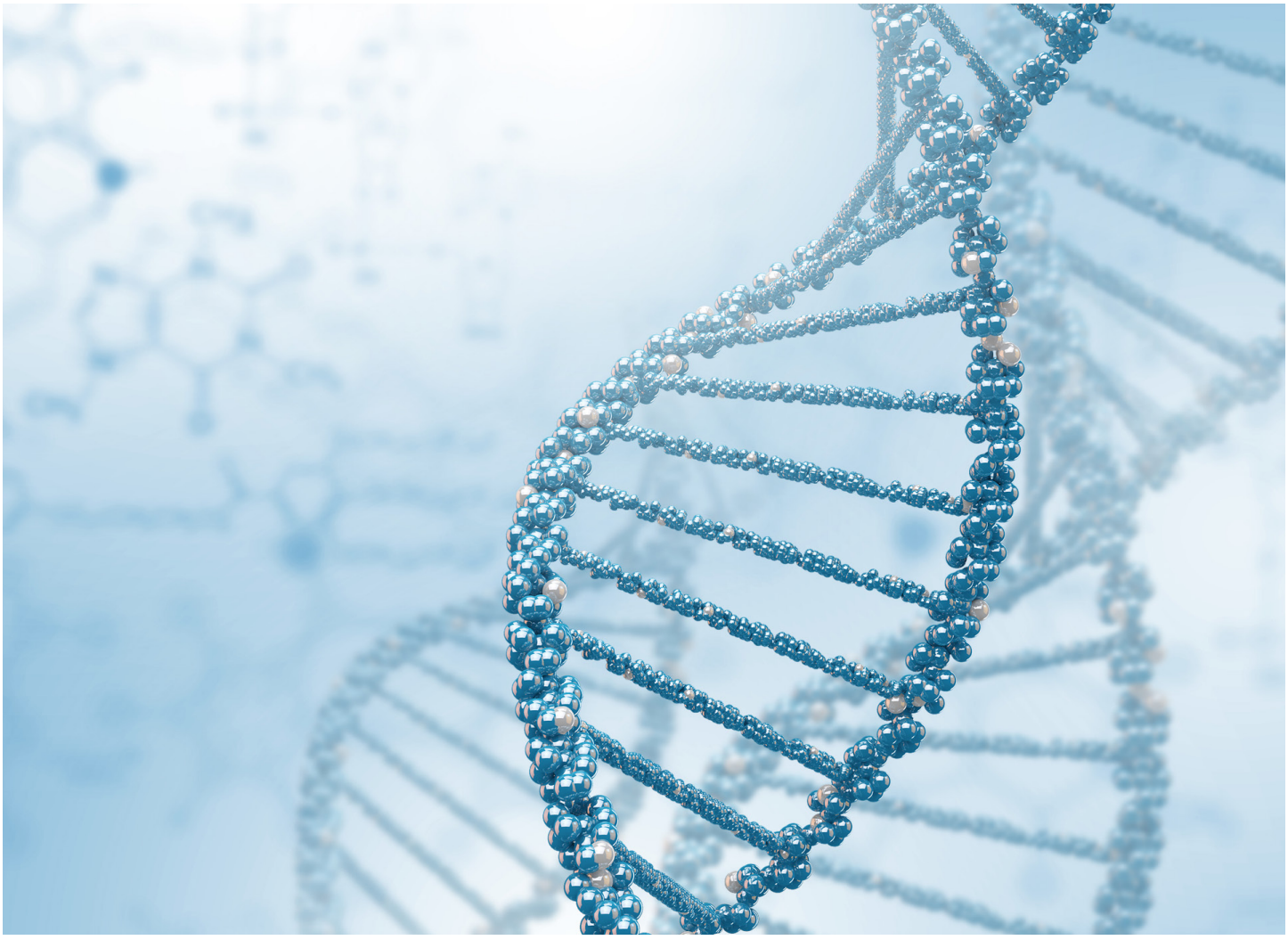
believes that "[e]ven with improved accuracy, the process [of germline gene editing] is unlikely to be risk-free."[97] In any case, testing assertions of safety would require performing experiments on humans that have historically been considered unethical.

A relatively small number of vocal advocates unequivocally favor human germline intervention and "enhancement."[98] Some of these enthusiasts are "transhumanists,"[99] and believe in "seizing control of our evolutionary future"[100] so that at least some members of our species become "more than human."[101]

It is also clear that some of those who call for public discussion about the immediate risks of gene-editing technologies would be delighted if their work is deemed safe enough to proceed. George Church is a prominent example: he signed the paper in *Science* calling for a moratorium on human germline intervention; he has actively called for discussion and regulation of gene drive technology; and he is also the co-author of *Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves*.[102]

But most people, including most scientists, have more nuanced views and are in the process of developing their opinions on the social and ethical implications of human germline modification.

**It has been only about a decade since we first read the human genome. We should exercise great caution before we begin to rewrite it.**



# 4. Challenges and Concerns in Human Applications of Synthetic Biology

When it comes to technology, enthusiasm is an easy sell. Caution is less appealing. Facebook's original motto, "Move Fast and Break Things," became globally famous, but it's a precarious approach.[103] The science of synthetic biology has been moving fast, and we currently have no adequate democratic process for holding biotech companies accountable when there are accidents or errors that impact the public or the environment. As human and other applications for synthetic biology develop, it is urgent that we have a broad public discussion of the challenges and concerns these technologies raise and how to address them.

Concerns about biological engineering technologies are by no means limited to short-term safety issues. Technologies need to be evaluated holistically, with skepticism, taking into account that there may be long-term and/or unforeseen consequences. Claims of 99% or greater certainty that a technology is safe must be evaluated against the risks of failure. For some ecology-changing or species-changing events, a 1% risk could be far too large to take.

Some current and proposed applications of synthetic biology raise health, safety, environmental, political and ethical issues that are roughly comparable with those that previous generations of disruptive technologies posed, and the actual consequences may be familiar. For example, new medical treatments available only at great expense would perpetuate already alarming global health and economic disparities.

Other projected synthetic biology applications hold the potential of changing humans and societies on a more fundamental level. Technologies that could dramatically reshape entire ecosystems and cultures, and that enable us to turn genetic manipulation on ourselves, confront us with novel and difficult challenges.

All of these prospects are taking shape in a context of huge ambitions, incomplete science, big money, self-regulation, relentless promotional activity, little or no public debate and unstudied impacts on human health and safety. They also hearken back to an era of history that many people seem to have forgotten.

## Understanding Modern Eugenics

It is important to understand both the similarities and the differences between efforts to create genetically modified human beings and the historical experiences of eugenics. While many proponents of human germline modification reject the idea that their vision has anything to do with eugenics, others have embraced the term "liberal eugenics."[104] From this perspective, using genetic technology to "improve" future children is a matter of individual parental choice, and should be ethically allowable. In fact, some have elevated this to a principle of "procreative liberty,"[105] and others believe it will become ethically obligatory.[106]

From the time the term was coined by Francis Galton in 1883, eugenics was about "improving" future generations. This was neither an exclusively right-wing nor a particularly left-wing political movement; in the early twentieth century it was supported by a wide cross-section of society's leaders, especially in the United States.[107] Indeed, American experts helped the German Nazi regime construct the legal and ideological edifice that later provided the support for their murderous eugenics program.[108]

The horrors revealed in World War II led directly to the Nuremberg Code and the development of modern bioethics.[109] Its emphasis on individual

autonomy derives from revulsion at state-mandated eugenics. But eugenics was and is much more than state coercion. The "better babies" and "fitter families" contests of the early twentieth century, for example, were voluntary but certainly eugenic affairs.[110]

In today's fertility industry, some practices veer close to a new eugenics. Numerous clinics promote sex selection to satisfy parents' desires. One physician-entrepreneur offered a program that claimed to select embryos for hair, eye and skin color.[118] Eggs and sperm sold online are advertised according to providers' appearance, test scores, educational achievement, musical talent and the like. The genetic testing company 23andMe filed for a patent for "gamete [i.e., egg or sperm] donor selection based on genetic calculations" that might include "height, eye color, gender, personality characteristics and risk of developing certain types of cancer," though the company now claims that it won't use the patent.[119]

In a 2009 *New Yorker* profile, Drew Endy asked, "What if we could liberate ourselves from the tyranny of evolution by being able to design our own offspring?"[120]

If synthetic biology and gene-editing techniques are allowed to take this trend of trait selection further, by making interventions easier, and without questioning the underlying assumptions and motives of the technologies, we could see the emergence of a society in which eugenic aspirations are widely accepted. This point has been stressed by the biologist Robert Pollack in

## *Box B*: Failures of Regulation and Self-Regulation

History has shown us that science and technology used in an ethical vacuum, without adequate oversight, can lead to unintended irreversible consequences. Examples include:

- In the late 1990s and early 2000s, several patients died as a result of unexpected reactions in gene therapy experiments.[111] The most publicized case was that of Jesse Gelsinger but in the follow-up to that tragedy, the NIH discovered that "only 35 to 37 of 970 serious adverse events" in one kind of gene therapy trial were reported as required.[112]
- Between 1946 and 1948, U.S. government medical researchers infected people in Guatemala with gonorrhea and syphilis without consent.[113]
- From 1932 to 1972, the U.S. Public Health Service and the Tuskegee Institute deceived hundreds of black men about whether they were receiving syphilis treatment.[114]

Even short of such tragedies, there are numerous instances where either self-regulation has failed or overworked authorities have struggled to overcome lack of cooperation:

- Many fertility clinics have routinely failed to follow guidelines developed by their professional bodies regarding payment for women's eggs, social sex selection and the number of embryos transferred.[115]
- FDA has struggled for years to regulate the Direct-to-Consumer (DTC) gene testing industry, which continues to attract enormous investments.[116]
- FDA has had even less success stemming the growth of unlicensed stem cell clinics, partly because some of them operate abroad. According to UC Davis stem cell scientist, Paul Knoepfler, these "potentially dangerous, unproven treatments" they offer are not usually covered by insurance, can run up to $100,000 and rarely rise to the level of clinical trial.[117] Fraud and abuse have been documented, and the potential for more is enormous.

Regulation requires resources and enforcement. The precedents of ethical failure under self-regulation by professional bodies demonstrate the failure of this approach, and underscore the need for a democratic, transparent and multidisciplinary approach to governing this industry.

a letter to *Science*,[121] and in great detail by the historian Nathaniel Comfort in *The Nation*.[122]

If the technology were to facilitate trait selection, it could lead to greater inequality as the wealthy spend large sums in hopes of making their children "superior" to those of normal people.

But what would be the social implications for children "designed" by parents and biotech engineers? What would it mean to divide people into groups of genetic "haves" and "have nots," whose differences were based on genetic manipulations? Who would decide the "desirable" standards? These are critical questions.

## Germline Modification and Human Health

Any technological intervention in fertility, be it hormones, egg extraction, embryo implantation, prenatal testing or any other part of the assisted-reproduction process, carries some risk for the woman or women involved. What special, increased risks may be involved in a process involving deliberately modified embryos remains unknown.

The experience of reproductive cloning in animals offers justification for caution, notably because a significant number of pregnancies result in Large Offspring Syndrome, with potentially lethal consequences for the mother.[123] This is one reason why human reproductive cloning is widely prohibited.

Safe outcomes for genetic interventions in future children cannot be guaranteed. Predicting the precise effects that might emerge in an adult some twenty years after genetic interventions made at the embryonic stage is effectively impossible. This in itself is enough for many people to rule out such interventions. There are also other, slightly more subtle, ethical and philosophical concerns.

One concern is that in almost all cases it is virtually impossible to confirm that a very early-stage embryo actually has the harmful mutation about which those who wish to intervene are concerned. As MIT Biology Professor Rudolf Jaenisch has explained, generally speaking half the embryos that might be edited would have been normal, even if the other half carried a mutation. He concluded that "it is unacceptable to mutate normal embryos. For me, that means there is no application."[124]

There also remain difficult questions about social divides, consent and expectations. The children cannot consent ahead of time, and may not agree with the parental decisions when and if they become adults. A parent might have intended to make their child "better," but what does that mean? Would the parents then expect the child to be exceptional, to be smarter or stronger or better looking or more capable in some other way — and how would the parents react if the child turned out differently than specified? What does this mean for people who have not been modified? How will we decide what is an acceptable application and who will participate in these decisions?

## Huge Ambitions

As noted, synthetic biology pioneers have voiced ambitious visions for the techniques they are developing. Another example is Endy's argument, which he has made explicitly for more than a decade, that synthetic biology can "rebuild the living world."[125]

Of course, reality may fall short of such ambitions, and certainly major technical problems remain. But what if "reinventing civilization" and "rebuilding the living world"

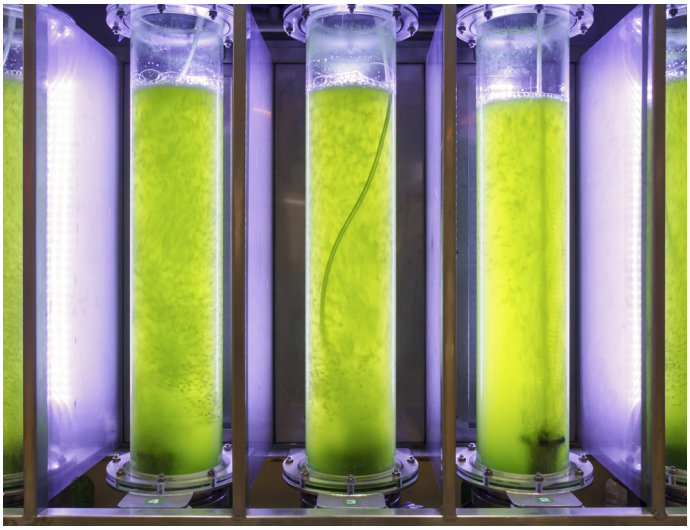
**But what if "reinventing civilization" and "rebuilding the living world" come to pass, even partially? What kind of world should be designed?**

come to pass, even partially? What kind of world should be designed? How should we reshape our relationships with nature and each other? What would be the impacts on equity? How would we as a society decide what is acceptable; oversee the experiments and the inevitable failures along the way; and manage the results? Can we, collectively, choose whether or not to go down this path?

Deliberatively and decisively altering the planet and humanity is not a new idea. Indeed, C. S. Lewis critiqued it in 1943, noting that:

> *What we call Man's power over Nature turns out to be a power exercised by some men over other men with Nature as its instrument.*[126]

It is important to see the politics of power and impacts to democracy with a set of technologies like synthetic biology, and to carefully choose when and if it is possible to use them wisely.



*Photobioreacter in lab with algae for biofuel research.* Source: shutterstock

## Incomplete Science

There is an enormous amount still to be learned about human (and other) biology, especially in areas such as early organism development and the progression of diseases like cancer. Researchers are exploring the potential applications that gene-editing and synthetic biology techniques could have in vitro. But the path to using these technologies in a clinic is not predictable, and will almost certainly be a long one.

The issue is urgent precisely because the science is developing so fast. Several gene-editing techniques exist now, and could soon provide a level of precision in both deleting and inserting genes. The original breakthrough paper on the CRISPR gene-editing process by Jinek, Doudna, Charpentier and colleagues (see page 20) was only published in 2012, and has been cited in over 500 scientific papers in less than three years.[127] In 2014, gene editing was hailed by *MIT Technology Review* as one of the Top Ten Breakthrough Technologies of the year.[128] The field is moving so fast that no one can be sure they are entirely on top of it.

Combined with the continuing development of genomics — the analysis of which genes contribute to producing which traits — new possibilities for manipulating genes in people are now plausible. But who decides if they are acceptable?

## Additional Specific Applications

### *Gene Drives*

As described above (page 13), scientists are exploring the gene drive as a way to (for example) eliminate malaria, by replacing a population of wild mosquitoes with genetically engineered mosquitoes that would not transmit the disease. But the questions remain: What might be the environmental side effects of thousands of genetically altered insects released into natural ecosystems? Might the new species disrupt local ecosystems in harmful ways, for instance, or even turn out to be a carrier of a different disease?

## *Box C*: Expert Concerns about Human Germline Intervention

Many experts, including scientists credited with the discovery of the CRISPR gene-editing tool, have publically expressed concerns about the heritable modification of humans, for reasons including its grave safety risks, the lack of medical justification and a range of unacceptable social and ethical consequences.

**Emmanuelle Charpentier**, co-discoverer of CRISPR: "Personally, I don't think it is acceptable to manipulate the human germline for the purpose of changing some genetic traits that will be transmitted over generations."[129]

**Jennifer Doudna,** co-discoverer of CRISPR: "I think in principle it [heritable human gene editing] could be done, but I think personally I'd be uncomfortable with that. Certainly, at this stage, I don't think we understand it well enough. Would you be correcting one problem but introducing others?"[130]

**Edward Lanphier**, Sangamo Biosciences: "Many oppose germline modification on the grounds that permitting even unambiguously therapeutic interventions could start us down a path towards non-therapeutic genetic enhancement. We share these concerns."[131]

**Eric Lander**, Director of The Broad Institute: "[A]uthorizing scientists to make permanent changes to the DNA of our species is a decision that should require broad societal understanding and consent. It has been only about a decade since we first read the human genome. We should exercise great caution before we begin to rewrite it."[132]

**Francis S. Collins**, Director of the National Institutes of Health: "The concept of altering the human germline in embryos for clinical purposes has been debated over many years from many different perspectives, and has been viewed almost universally as a line that should not be crossed."[133]

**Vivek Wadhwa**, Fellow at Stanford University: "No one is prepared for an era when editing DNA is as easy as editing a Microsoft Word document. … Rarely do I argue that a moratorium on technological progress is the prudent course. But the stakes in the case of CRISPR are so high that I believe a blanket moratorium is the only course."[134]

**Rudolf Jaenisch**, Professor of Biology, MIT: "We must ask ourselves and others tough questions. … Until we have addressed [them], a moratorium on any clinical application of gene editing in human embryos is critical."[13]

**George Annas**, Professor and Chair of Department of Health Law, Bioethics and Human Rights, Boston University: "[T]here is both a public and scientific consensus that it is unsafe and unwise to attempt to make a "better baby" by altering the genetics of a human embryo. … If we want to avoid turning babies into manufactured products, changing the nature of what it means to be human, and perhaps developing a superior race that could see us as subhuman, we need to outlaw the use of genetic editing technology on human embryos."[136]

**Daniel Sarewitz**, Senior Sustainability Scientist, Arizona State University: "The idea that the risks, benefits and ethical challenges of these emerging technologies are something to be decided by experts is wrong-headed, futile and self-defeating."[137]

**While presently the capability of creating synthetic versions of diseases is limited to a few hundred labs worldwide, if synthetic biologists' visions of widespread use of "3D vaccine printers" and similar technologies become reality, the risks of synthetic biology being put to criminal purposes are set to dramatically increase.**

The ecological and other consequences of an unintended or faulty release could be disastrous. Some of the leading scientists in the field, notably Kevin Esvelt and George Church of Harvard's Wyss Institute, have repeatedly called for public discussion of how to regulate this technology.[138] The National Academies of Sciences have begun an evaluation process of how to conduct gene drive research in non-human organisms.[139] If applications were expanded to other organisms, what would we eliminate? What would be the implications for what is "normal" and accepted in a population? Much further discussion is urgently required.

### *Bioweapons*

Applications of synthetic biology for bioweapons are a concern, although how significant a threat they pose is controversial. For example, researchers Filippa Lentzos, Catherine Jefferson and Claire Marris evaluated what they called the "the myths (and realities) of synthetic bioweapons" in 2014 and suggested that any such efforts would likely be small-scale and could be countered with standard medical responses.[140] Security expert Kathleen Vogel suggests that replicating results from synthetic biology is complex and difficult, and that amateur synthetic biologists working out of garage-style labs are unlikely to produce new bioweapons.[141] However, George Dvorsky, a generally pro-technology futurist, noted that:

> *Access to this information, along with the tools required to construct such WMDs [Weapons of Mass Destruction] (like bio-3D printers), can only get easier as time passes. Given the dire consequences, it's not too early to start worrying.*[142]

Meanwhile, the Defense Advanced Research Projects Agency (DARPA) is ramping up its expenditure on synthetic biology, as well as on neuroscience and infectious diseases.[143] According to the Wilson Center, "DARPA is by far the most significant source of synthetic biology funding within the U.S. government, with nearly $110 million in funding for 2014." The report notes that less than one percent of federal funding is allocated for research on risks.[144] The Army, Navy and Office of the Secretary of Defense, among others, also finance synthetic biology research. Total U.S. public investment since 2008 is approaching a billion dollars. Details on many of these initiatives are limited essentially to public-relations pronouncements, presumably for reasons of national security.

While presently the capability of creating synthetic versions of diseases is limited to a few hundred labs worldwide, if synthetic biologists' visions of widespread use of "3D vaccine printers" and similar technologies become reality, the risks of synthetic biology being put to criminal purposes are set to dramatically increase.

### *Other Applications*

Gene editing, synthetic biology and related technologies are developing so fast that it is increasingly hard to distinguish blue-sky fantasies from real-world applications. Somewhere between the two line scientific experiments such as xeno DNA (see page 15) that will undoubtedly produce information but may or may not have practical applications.

The medical diagnostics, vaccine production, xenotransplantation and microbiome research discussed in Section 2 all need careful and appropriate oversight. Some of the potential issues are mentioned there, but it is highly likely that others will arise that are as yet unseen.

When the federal government reorganizes the structure of regulation, as noted below, it will be vital to make it flexible enough to respond to concerns we cannot necessarily yet specify.

## Worker Safety Concerns

It is critical to ensure the safety of workers in manufacturing plants and biotech labs, and there is extensive evidence that existing regulations for workers in the biotech industry are inadequate, particularly for rapidly emerging technologies like synthetic biology.

Problems with workplace safety have been seen both in the private sector and in government labs. For instance, genetics research whistleblower Becky McClain successfully sued Pfizer for lax safety practices that exposed her to novel engineered viruses,[145] and the Centers for Disease Control have reported a series of escapes of anthrax from high-security labs.[146] Containment is never 100%, so it is critical to have strong standards, oversight and regulations in place.

## Funding and Profit-Driven Research

The political and industrial emphasis on results-driven funding over the last 35 years has had questionable effects on biotech and biomedical research.[147] In that context, it's worth noting that the CRISPR gene-editing tool was discovered and initially developed as part of a basic research effort, not as part of a market-driven research project; Jennifer Doudna described it as, "probably the most obscure thing I ever worked on."[148]

Some scientific, therapeutic and more general technological breakthroughs may indeed come from focused attention on particular research goals. But important breakthroughs, like CRISPR, can also come from work driven by scientific curiosity — and therefore are much less likely to be funded by profit-oriented or simply results-driven organizations.

This is an important argument in favor of government funding of basic research. Equally significant is the fact that federal funding carries with it some regulatory constraints and oversight, which can be publicly addressed, debated and if necessary amended in the political sphere, more so than with private funding.

We have already seen significant changes in the commercial aims of synthetic biology. Early investment was focused largely on projects to develop biofuels, industrial chemicals and pharmaceuticals. However, by about 2012 it had become clear that synthetic biology start-ups and others in this industry were not able to scale up their biofuel production in a cost-effective manner.[149] Several companies shifted their focus to high-value, low-volume products like flavors and fragrances, some of which are beginning to reach the market in food and consumer products ahead of adequate safety assessment and oversight.[150]

Gene editing has attracted large investments in the few years it has been around: at least $300 million has poured into gene-editing firms since 2012. The principal inventors of gene-editing techniques have all set up companies — Editas, Caribou, Intellia and CRISPR Therapeutics — to profit from the process. Editas was founded with $43 million from four major venture capital firms, and has since raised another $120 million; CRISPR Therapeutics raised $25 million; and Caribou and its spin-off Intellia, which raised $70 million in its Series B round of funding, have signed agreements with pharma giant Novartis.[151]

Overall, biotech venture capital funding hit a recent high in 2014, led by the "biotech human subsegment."[152] The incentives for venture

speculation may be significant; in the U.S. alone, spending on healthcare is around three trillion dollars a year.[153] Even a modest proportion of that turnover could make the field a goldmine.

The medical applications these companies are thought to be pursuing (the details are often vague) do not explicitly involve heritable genetic modifications. But the technologies under development are the same or very closely related to the ones that would enable the permanent modification of future people.

## Relentless Promotional Activity

Similarly to biofuels, the pharmaceutical industry has promoted potential medical applications with optimistic claims, but these remain hypothetical and absent of thorough analysis. Some scientists and biotech leaders involved with the development of synthetic biology and gene editing say that they are on the verge of providing quick, cheap and effective breakthroughs for a range of conditions.[154] Treating people who are sick and suffering is a widely supported goal. But too often, enthusiastic promises of treatments and cures are simplistic and unrealistic, and downplay the significant risks that experimental genetic interventions will entail for the foreseeable future. At times the promotion is also misleading, in that it suggests a far more predictable relationship between genes and health outcomes than is known to exist.

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We also need to question whether everything that counts as a medical condition always needs to be fixed. That assumption buys into what many disability rights advocates and scholars call the "medicalization of difference."[155] Some conditions, even those that may be limiting, are best addressed by non-medical accommodations. The mobility of people who use wheelchairs, for example, can be improved today by putting curb cuts in streets and ramps in more buildings. From a disability rights perspective, attending to social policies and the built environment is often a more effective way to improve the lives of people with disabilities than focusing on speculative procedures to change some aspect of their bodies.[156]

Some promises about medical treatments to help sick people may be realized, but others are unlikely to come to pass. And hyperbolic claims about imminent cures clearly function as promotional tools that encourage unquestioning public support for a technology platform and generous public and private funding for the entire field of synthetic biology. In addition to private investments, total U.S. federal spending on synthetic biology from 2008 to 2014, much of it defense-related as noted on page 31, has been estimated at $820 million and increasing exponentially.[157]

Many of the individual scientists, research groups and commercial organizations involved in gene editing and synthetic biology are trying to move quickly through the stages of basic research, technical feasibility and commercial application.

As with any new technology, we should beware of exaggerated marketing and attempts to downplay profit motives.

Opinion polls show considerable public skepticism about synthetic biology and gene editing technologies. A poll conducted in May 2015 for the Synthetic Biology Project at the Woodrow Wilson International Center showed broad support for a moratorium on their use in humans — 72% "favor or lean towards favoring a temporary research ban."[158] In general, opinion about gene editing was mixed: 18% considered gene editing a positive development, 12% a negative one, and 43% thought it was "both a positive and a negative development." (When undecideds were pressed to choose, 62% said it was both.)

In response, proponents frequently lean upon the idea that public education will overcome any opposition. Bioethicist and social scientist Claire Marris has discussed this in her article, "The Construction of Imaginaries of the Public as a Threat to Synthetic Biology":

> *Fear of the public's fear of synthetic biology, which I characterize as 'synbiophobia-phobia,' has been the driving force behind the promotion of public engagement and other activities to address 'ethical, legal and social issues' (ELSI). These activities have been problematic in two ways. Firstly, they are based on the discredited 'deficit-model' understanding of public responses to science, in which negative public attitudes towards science are thought to result from a lack of scientific knowledge. Secondly, they have taken for granted sociotechnical expectations put forward by scientific institutions.*[159]

Support for scientific research is essential; but scientists alone should not be authorized to make social and political decisions about how technologies are used. Accurate and ethical reporting is essential to check the promotional temptations of scientists operating within the incentives of professional reputation and funding for research.

## Attempts to Avoid Regulation

There has been a concerted effort over the past 35 years from scientists working with recombinant DNA, and now with synthetic biology, to advocate for minimal external regulation and instead to self-regulate.[160] There has also been considerable criticism of this approach.[161] In the extreme case, one prominent advocate of editing human genes, Steven Pinker, recently called for bioethicists to "get out of the way."[162] This too has been widely, and appropriately, criticized.[163]

It is essential that the independent assessments and third-party regulators (government agencies) draw from multi-stakeholder expertise, with advice from those with ethical, social, legal and political backgrounds in addition to those with purely scientific backgrounds. In the case of human applications of synthetic biology, that really means all of us.

## *Box D*: Synthetic Biology's Indirect Impacts on People

Commercial products derived from synthetic biology may have unintended social consequences. Many of the currently commercialized products of synthetic biology appear to be threatening the livelihoods of small-scale farmers in developing countries, while increasing the profits of elite investors and entrepreneurs. This new economic model for synthetic biology could have serious impacts on the health of people and ecosystems, on our planet's biodiversity and on communities around the world. **For example:**

**Artemisinin**: The French pharmaceutical company Sanofi announced in 2013 its commercial production of a "semi-synthetic" (synthetic biology derived) version of artemisinin, an important anti-malarial ingredient extracted from the wormwood plant.[164] Sanofi publicly announced that its goal was to completely replace the natural source, grown by an estimated 100,000 small farmers in East Africa, India and Southeast Asia, despite the fact that these farmers were able to meet global demand.

**Vanillin**: Evolva recently commercialized vanilla flavoring (vanillin), produced in a vat by synthetically engineered yeast that feed on sugar but marketed as "natural." The livelihoods of 200,000 farmers who produce truly natural plant-based vanilla in Madagascar, Mexico and elsewhere, along with the semi-intact rainforests where the vanilla orchid is cultivated, may be threatened.[165]

**Perfumes**: Amyris' synthetic yeast-grown version of patchouli, a plant-based fragrance ingredient currently produced by small farmers across Indonesia, Malaysia and China, could soon displace the economic system of these farmers.[166] Allylix, now owned by Evolva, has developed a synthetic biology-derived product to replace vetiver, a plant-based perfume ingredient currently produced by 27,000 Haitian farming families, which has important conservation benefits, preventing soil erosion and helping maintain water quality.[167]

**More to come**: Small farmers who produce other plant-based commodities targeted for replacement by synthetic biology companies, including stevia, rubber, coconut oil and saffron, could be threatened by similar environmental, social and economic consequences.

**Assessing safety**: There have been virtually no transparent, independent health or environmental assessments done for synthetic biology ingredients or the full lifecycle of production. Synthetic biology-derived vanillin was allowed onto the market with voluntary certification as "Generally Regarded As Safe."[168] This may set a precedent for other synthetic biology flavors and fragrances currently in development — as well as sweeteners, coconut oil, animal feed additives and even animals genetically engineered with synthetic genes — to be commercialized without adequate safety assessment or oversight.

**Environmental risks**: Currently commercialized synthetic biology organisms such as algae and yeast require large amounts of sugar and other feedstocks produced via chemical-intensive industrial agriculture which requires large amounts of water, fertilizers, pesticides and fuel and has major impacts on water, soil, biodiversity and broader ecosystems. The release of artificial organisms, whether plants or microbes, could have serious and unforeseeable consequences, including genetic contamination of wild species, disruption of natural ecosystems and spread of chemical and biological pollutants. See also the discussion of gene drives, above.

**Intentional releases**: A small company called Glowing Plants intends to exploit a loophole in the USDA's regulatory system to sell fluorescent plants with no oversight.[169] Impacts are difficult to predict but once released into the environment, like other synthetic organisms, these plants will be impossible to recall.

The expectation of governments, investors and many scientists is that gene editing and synthetic biology technologies will bring about an economic and social revolution. Even if these predictions are overstated, and even if the direct modification of people is prohibited, we have already seen enough to know that improved regulation is absolutely essential.

## 5. Regulating Synthetic Human Biology for the Common Good

The modern tools of biological engineering are extremely powerful. None of them are fully understood, but if released or applied, many could significantly change the world in which we live.

Among the central questions at hand: If synthetic biology and gene-editing technologies are developed for human applications, who would regulate and assess them, how would they be used and who would benefit from them? In a democratic society, the answers should be determined by an inclusive political process. The least responsible approach would be to "leave it to the market." Not far behind would be "leave it to the experts." And a refusal to decide — a refusal to make an explicit, collective, social series of decisions — is itself a political decision.

Some technological enthusiasts argue that decisions about creating genetically modified people should be left to parents who have the right to "engineer" the traits of their children. But, as the United Nations Educational, Scientific and Cultural Organization states, the human genome is the common heritage of humanity,[170] and of our grandparents and grandchildren as well. It represents who we are, collectively, and we have a collective stake in what happens to it. Are we really ready to decide to change the permanent genetic heritage of our species?

Ethicists and professional bodies are still working through their ideas about when and to what extent the results of genetic analysis should be explained to patients — and to their relatives. If you have an increased chance of illness, not a certainty and not necessarily something you can easily avert with medicine or diet or other lifestyle changes, do you want to know? Should your doctor tell you? Should you or your physician tell your siblings? These are tricky questions that we have not finished exploring.

As responsible people who value protecting children and respect a diversity of people with different traits and abilities, we need to understand the societal limits of what is acceptable to do to our children and future generations.

On a more immediately practical level, there are technological enthusiasts who assert that, "ethics is quite simple: life is better than death, and health is better than disease. That's it."[171] They then use this principle to claim that high-tech germline interventions are unquestionably ethical or even mandatory. Yet they say little or nothing about the ways that society could — with currently available technology — reduce infant mortality or improve the lives and prospects of all citizens as well as the environments we all share.

Furthermore, current arguments in favor of genetic engineering of people don't address the underlying assumptions about disease or deficiencies as static across time and different cultures, nor what the boundaries of these definitions are.

We need, collectively, to establish limits on the application of biotechnology on people.

### A Window of Opportunity

Currently, there are few regulations or provisions for careful oversight of these powerful new technologies in the U.S. or internationally, beyond the aforementioned prohibitions on human germline modification. Despite the multiple agencies that have some authority over synthetic biology applications for food, biofuels or human engineering, unregulated synthetic biology products have already reached the market without any oversight or labeling, a

worrying precedent for human applications.

Among the relevant agencies are the Food and Drug Administration (FDA), National Institutes of Health (NIH), National Science Foundation (NSF), Department of Energy (DOE), National Institute of Standards and Technology (NIST), Department of Defense (DOD), Environmental Protection Agency (EPA), Centers for Disease Control and Prevention (CDC), Commerce Department, Occupational Safety and Health Administration (OSHA) and the Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA). Not all will be involved in regulating human applications, but, as a 2015 National Academies report recommended, they should "work together to broadly assess, and regularly reassess, the adequacy of existing governance."[172]

Clinical trials of anything produced with synthetic biology or gene editing will require FDA approval. But it's not clear how far the agency's authority would extend. Though it has claimed jurisdiction over human reproductive cloning, for example, that practice is not explicitly illegal at the federal level in the United States, as it is in dozens of other countries and some U.S. states.[173]

The fundamental mandate of the FDA is to ensure that the products it regulates are safe and effective.[174] Although the FDA is well aware of "ethical and social policy issues," it regularly frames discussions as "technical" in order to stay clearly within its mandate.[175] Regulations must be scientifically appropriate and reasonably practical, but it is also vital to consider the wider social and ethical implications ahead of time. In the U.S., there is no clear process for doing that.

How will the multiple federal agencies that will need to address synthetic biology applications be overseen? Theoretically, Congress has the power to restructure the scope of the NIH, USDA and other regulatory bodies, but governmental inertia and industry influence make Congressional effectiveness challenging. While many observers of existing biotechnology governance agree on the need for improvement, what new regulations and oversight would look like, both at national and international levels, has been a topic of debate.

In the U.S., many scientists and biotechnology companies, as well as public interest groups and others, are now calling for clarification of policies and laws. In 2012, 111 civil society groups from around the world signed onto the *Principles for the Oversight of Synthetic Biology*.[176] In brief, the principles include protecting health and worker safety, requiring corporate accountability, protecting environmental and social justice and employing the precautionary principle. The declaration also calls for a "ban on using synthetic biology to manipulate the human genome in any form, including the human microbiome."

In July 2015, the White House issued a memorandum directing the three Federal agencies that have primary oversight responsibilities for existing synthetic biology products — the EPA, the FDA and the USDA — to "develop a long-term strategy to ensure that the system is prepared for the future products of biotechnology, and commission an expert analysis of the future landscape of biotechnology products to support this effort."[177] This overdue initiative will take some years to complete, and it will be critical that the strategic development engage a strong mix of stakeholders.

The White House initiative, and the high-stakes issues that have been put on the table by recent developments, provide an opportunity for discussion, negotiation and formulation. We need to establish ground rules. How do we — as a society — sort through what, if anything, may be useful about synthetic biology and what might be harmful? What criteria should we use? How should our government assess these synthetic biology organisms and techniques? What should we support, what should we regulate and which applications may be just too risky?

## 6. Recommendations

General principles governing policies to regulate novel biological techniques must include the following precautionary elements, while the details should be worked out in comprehensive, public discussion that involves all stakeholders.

### A Ban on Human Germline Gene-Editing

We reiterate the call in *Principles for the Oversight of Synthetic Biology* for a prohibition on the use of gene editing and synthetic biology to manipulate the human germline. Countries that have not already adopted laws prohibiting the creation of genetically modified human beings, especially including the United States, should do so as soon as possible.

A binding international treaty that prohibits human germline modification, the Council of Europe's Convention on Human Rights and Biomedicine (also known as the Oviedo Convention),[178] has been in force since 1998. Countries that are not part of the European Union are also encouraged to sign this treaty. Non-member countries that are eligible to sign and ratify the Oviedo Convention should do so.

Other institutional efforts should also be brought to bear to strengthen the widespread agreement that puts human germline modification off limits. National and international agencies, professional organizations and scientific organizations should issue statements endorsing prohibitions on human germline modification.

Gene-editing research, especially any research that involves gametes or embryos, should be tightly limited. Institutional review boards and funding agencies should ensure that research on germ cells aimed at refining techniques specifically for reproductive purposes should be rejected.

Public and private funders should announce that they will not consider supporting any efforts that would violate these prohibitions, and institutional review boards should make it clear that any proposed experiments involving human germline modification will be rejected. Scientific journals should not accept for publication any studies involving efforts to modify the human germline. Finally, scientists around the world should observe the widespread agreement to forgo experiments that would modify the human germline, whether or not their home countries or the countries in which they are working have adopted such prohibitions. Any effort to create genetically modified humans should be publicly condemned.

### Prioritizing Ethical and Social Considerations

The regulation of biotechnology needs to be updated to take into account the novel safety *and* social risks of gene-editing, synthetic biology and other emerging biotechnologies. We support increased public and philanthropic funding to support independent and thorough investigation of the ethical, legal, social and economic risks that other synthetic biology applications may pose to patients, workers and the general public.

Funding scientific research is vitally important, and basic research in particular deserves higher levels of public funding. Where appropriate, we must also invest in simpler, more affordable, more socially just and less risky solutions to environmental, health and social problems. Public health initiatives can improve infant mortality rates and childhood health in the short run far more certainly than costly and risky high-tech inventions.

### Reimagining Public Engagement in the Regulatory Debate

Issues of such large dimensions demand not only public involvement but novel methods of assessing, informing and learning from public opinion. Bodies such as the National Academies of Sciences, with their ability to

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collate expert opinion, can make important contributions. But it would be a serious mistake to hand over deliberations or decisions about powerful new technologies to a single sector of society, especially one dominated by scientists competing for research grants and control of a burgeoning industry. Scientists and especially regulators should listen and respond to the public, community and civil society organizations, labor unions, faith communities and others.

Several possible models exist, and doubtless more can be devised. One area that may offer useful lessons is the question of access to human genomic databanks.[179] Relatively few people seem to be willing to have their genetic data publicly available, so institutions such as Kaiser Permanente and several academic bioethicists have developed ways to work with clients in order to allow researchers specific access.[180] These may involve, for example, discussion groups that report back to larger bodies in a feedback loop that encourages communication and validation. Adapting this process could be challenging but worthwhile.

There is always a risk of "regulatory capture." Some official attempts to assess public opinion have seemed to be designed to create a particular opinion, and some have even distorted their own findings.[181] Nevertheless, the effort is necessary, and organizations such as the Consortium for Science, Policy and Outcomes at Arizona State University are working on improving the process.[182] So too are many others, including the Organization for Economic Co-operation and Development (OECD).[183]

Open, meaningful and full public participation at every level is essential and must include consideration of the wide-ranging effects, including ethical, social and economic consequences, of these technologies. Discussion about the applications of gene editing and synthetic biology is urgent but must not be rushed. It is important that it be broad-based, which will require active encouragement. Achieving anything close to an informed social consensus will take an extended period of time.

While modern social media may offer alternative views and opinions to those presented in mainstream media, they cannot and should not be seen as acceptable substitutes for a multi-stakeholder process with many opportunities to provide public input to develop a robust system of oversight and safety assessment.

Governments must take the initiative to provide meaningful involvement for the public throughout the entire decision-making process related to the development of gene editing, synthetic biology and the products of these technologies. That includes decisions about setting the research agenda, the context and scope of risk assessment, and later evaluation of the effects of such decisions.

## 7. Conclusion

While technical safety is a widely acknowledged concern, conversations regarding the democratic limits on genetically engineering humans, which are as yet barely beginning, should address a great deal more. This applies not only to human germline interventions but more generally to applications of gene-editing and synthetic biology techniques that would affect us all, directly or indirectly.

We need to take into account the social, ethical and economic consequences of applying these techniques. As applied directly to people, they could exacerbate inequality, possibly to the point of generating a genetic caste system that would undermine our democracy itself.

We do not know how to increase the intelligence of people by manipulating their genes. We do not know how to "enhance" future people to make them more athletic, musical, good looking or even healthy, and we may never know how to make such interventions with certainty. And yet there are those who encourage experimenting on our children, and propose genetic alterations that could change our species forever.

Much of the basic science of genetics is still far from well understood, yet researchers and funders are remarkably eager to proceed with risky technologies, bolstered by media coverage that often uncritically celebrates promises of disease elimination and genetic solutions to human suffering. Many of the problems researchers seek to fix are either problems of construction — simplistic definitions of disability as undesirable suffering, for instance — or the result of environmental and social factors, rather than problems determined by genetics.

Changing human genes in a way that is inherited by future descendants has been off-limits for years, and indeed in 2015 the NIH reiterated its opposition. We should support that position with a permanent ban.

These new genetic technologies are powerful and complex; before they are developed any further, we *all* need to be part of a conversation — ethical, moral and scientific — to ensure that they won't do more harm than good.

| Timeline | |
|---|---|
| 1953 | James Watson and Francis Crick publish the double-helix structure of DNA |
| 1970 | First unsuccessful and theoretically flawed attempt at gene therapy |
| 1971 | James Watson tentatively proposes a global ban on human reproductive cloning |
| 1973–4 | Paul Berg et al. call for a moratorium on combining DNA from different sources |
| 1975 | Asilomar Conference on Recombinant DNA recommends research guidelines |
| 1977 | Frederick Sanger develops a technique for rapidly sequencing DNA |
| 1982 | Humulin, synthetic insulin developed by Genentech, approved for sale |
| 1985 | Robert Sinsheimer proposes what eventually becomes the Human Genome Project |
| 1990 | Human Genome Project launched |
| 1990 | First officially approved gene therapy trial |
| 1997 | EU Convention on Human Rights and Biomedicine bans human germline modification |
| 1997 | First mammal successfully cloned from an adult cell, Dolly the sheep |
| 1998 | UCLA symposium on Engineering the Human Germline |
| 1998 | EU Additional Protocol bans human reproductive cloning |
| 1999 | First known death in gene therapy trial; others were subsequently revealed |
| 2000 | Working draft of human genome announced; officially completed 2003 |
| 2001 | President Bush bans federal funding for newly created human embryonic stem cells |
| 2001–4 | Several eccentrics win global headlines by claiming (falsely) to be cloning people |
| 2002–3 | Gene therapy in trouble because supposedly cured patients developed leukemia |
| 2003 | *E. coli* engineered to make synthetic precursors to artemisinin, an anti-malaria drug |
| 2003–5 | UN efforts to ban human reproductive cloning stopped by disputes over research cloning |
| 2003–7 | Zinc-finger nucleases (ZFNs) gene-editing technique developed |
| 2004 | First international synthetic biology conference held at MIT |
| 2009 | President Obama restores funding for stem cells, condemns reproductive cloning |
| 2009–11 | Transcription activator-like effector nucleases (TALENs) gene-editing technique developed |
| 2012 | First papers describing CRISPR gene-editing technology published |
| 2012–14 | Gene therapy attracts major investments as clinical trials start |
| 2012–5 | UK moves to allow heritable changes in human mitochondrial DNA |
| 2013 | Commercial production of semi-synthetic artemisin |
| 2013 | First reports of genome engineering in human stem cells using CRISPR |
| 2013–4 | Several large companies founded to exploit CRISPR technology (Editas, Caribou, etc.) |
| 2014 | First gene therapy drug on sale in Germany for $1.4 million per treatment |
| 2014 | The U.S. patent for CRISPR is awarded but disputed, presaging a long legal battle |
| 2015 | Papers in *Science* and *Nature* call for a moratorium or ban on germline gene editing |
| 2015 | First publication of attempt to edit the genomes of human embryos |
| 2015 | NIH reiterates policy not to fund gene-editing of human embryos |
| 2015 | White House officially opposes altering the human germline for clinical purposes |
| 2015 | Congressional hearing on the science and ethics of genetically engineered human DNA |
| 2015 | National Academies begin a major, multi-faceted initiative on human gene editing |

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