FRONTIER TECHNOLOGY QUARTERLY

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Playing with genes: The good, the bad and the ugly

Genetic technologies[1]—the ability to manipulate and transform the properties of cells, seeds, microbes, insects, plants, animals and even humans—are pushing the frontiers of science and offers us new hope for disease control and cure. This field has come a long way since Gregor Mendel, the father of genetics, first postulated the rule of heredity in the 1850s. Genetic technologies are changing the way we produce food, improving crop yield and preventing catastrophic losses from droughts, floods and pests. They also are offering new solutions for fighting cancer and many hereditary diseases, improving quality of life and life expectancy. In addition, genetic technologies are increasingly used in criminal justice systems to exonerate the innocent and convict the guilty. Such technologies, moreover, have given rise to genetic genealogy, allowing people to find their ethnic roots.

While the upsides of genetic technologies are promising, we also need to consider their downside risks. Access to gene therapies to combat diseases, for example, may be limited to those who can afford them, potentially increasing inequality in health outcomes within and across countries. Genomic research that serves to identify pre-existing conditions can potentially deprive patients from health insurance and medical care. Genetic technologies may exacerbate productivity gaps in agriculture, disadvantaging small farmers, especially in developing countries, who cannot access or afford genetically modified seeds. Moreover, there can be unintended health consequences of genetically modified crop production, including increased risks of contamination and loss of biodiversity.

The downside risks can be even uglier. Genetic modifications can potentially lead to the production of "designer babies" and super-humans and fundamentally alter the human species. Genomic research can be weaponized to target and harm specific population groups. The legal, ethical and moral boundaries of using genetic technologies are increasingly unclear, creating opportunities for their misuse and abuse. Weighing potential benefits against risks thus remains an urgent challenge. This *Frontier Technology Quarterly* discusses the potential of genetic technologies for improving health and agricultural productivity, two important goals of the 2030 Agenda for Sustainable Development, the risks posed by these technologies for increasing inequities in health outcomes and their potential misuse and abuse.

1 The term broadly encompasses both genetics—the study of genes and their role passing traits or conditions from one generation to another, and genomics—the study of all of a person's genes (the genome), including interactions of those genes with each other and with the person's environment. Genomics includes the scientific study of complex diseases such as heart disease, asthma, diabetes, and cancer because these diseases are typically caused more by a combination of genetic and environmental factors than by individual genes. Genomics is offering new possibilities for therapies and treatments for some complex diseases, as well as new diagnostic methods (source: www.genome.gov).

I. The good

Genetic technologies are offering new solutions for disease control, prevention and cure. They are now being used to diagnose and treat complex diseases such as heart disease, asthma, diabetes and cancer. Genetic technologies may also soon allow us to eradicate malaria, a major health menace in many developing countries.

Eradicating malaria

Malaria is one of the most severe public health epidemics in sub-Saharan Africa and large swaths of Asia and Latin America (*Figure 1*). It is a leading cause of death, especially in Africa, where a quarter of the population remains at risk of contracting the disease. According to the World Health Organization (WHO), one child dies from malaria every two minutes. In 2017, there were an estimated 219 million malaria cases worldwide and 435,000 deaths.[2] The social

2 https://www.who.int/news-room/fact-sheets/detail/malaria

World Economic and Social Survey 2018: Frontier Technology for Sustainable Development—a flagship publication of the United Nations Department of Economic and Social Affairs (DESA)—generated considerable interest in new technologies and their development impacts. Inspired by this strong interest, the Economic Analysis and Policy Division has undertaken to produce quarterly reviews on frontier technologies, delving deeper into specific aspects of a new technology. The series will identify challenges and raise many questions—and answer a few—while motivating policy research in DESA and beyond. This second edition of the series discusses genetic technologies. The quarterly reviews will be shared and discussed in development policy seminars and social media platforms to enrich policy discourse on frontier technologies.

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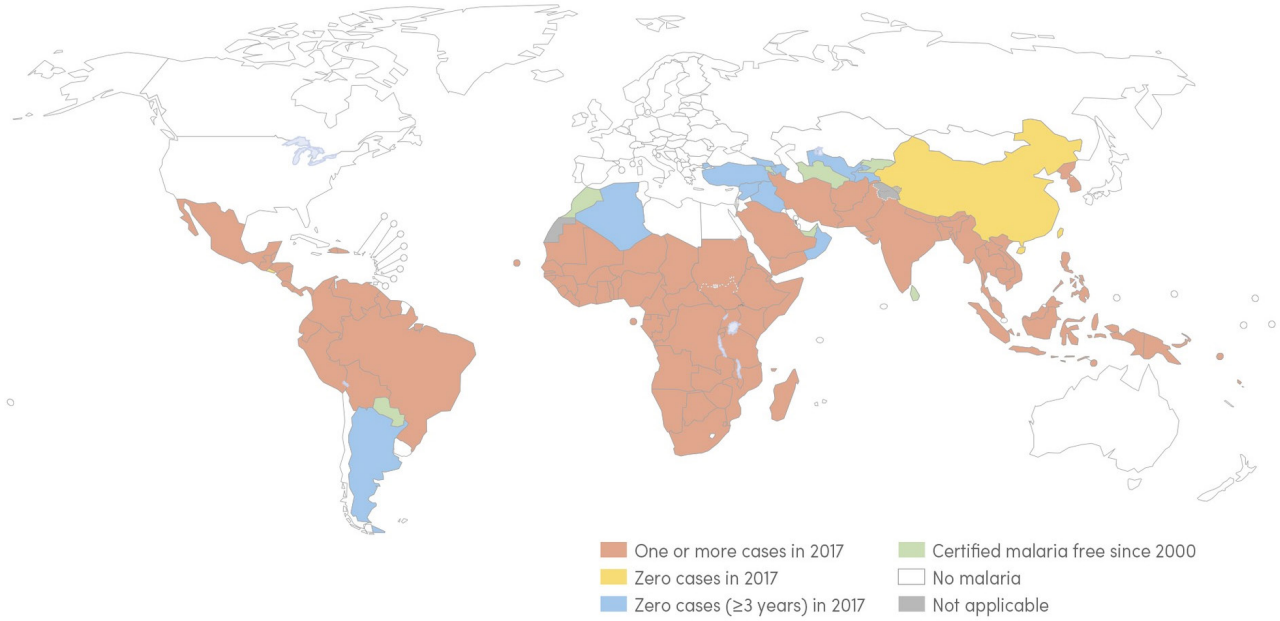
Figure 1
Countries with indiginous cases of malaria in 2000 and their status by 2017

Source: World Health Organization



and economic costs of malaria are significant. Governments and societies bear the cost burden of health facilities, personnel, drugs, public health campaigns and interventions to fight and contain malaria, diverting scarce resources away from productive economic activities.

Gene drives[3] to combat malaria promise large improvement in health outcomes in many developing countries, particularly for young children and pregnant women who are most vulnerable to the disease. They can alter the life cycle of the parasite or eradicate it completely. Computer models—simulating the gene drive and other interventions—estimate that malaria could be eliminated from large regions within two decades. The speed and effectiveness of gene drives also make the technique potentially dangerous, as it may trigger unforeseen mutations or affect other insect species.

Developing resilient food crops

Food production is often susceptible to adverse weather, ecological and soil conditions. Genetically engineered (GE) or genetically modified organisms (GMO)[4] are allowing the production of more resilient crop varieties. A new cost effective and easy-to-use technique, known by its acronym CRISPR, has revolutionized the process of decoding and precisely editing genetic information of organisms.[5] The International Rice Research Institute (IRRI), for example, has genetically engineered the Stress-Tolerant Rice for Africa and South Asia (STRASA), which maintains normal yield even when submerged in flood water. By 2017, more than 8 million farmers in South Asia were using the STRASA rice variety.

Adoption of genetically modified crops has been rapid, especially in the United States (*Figure 2*) where GMO crops account for more than 80% of planted acres. Brazil, China and India are also leading producers of GMO crops. While GMO crops have made food production more resilient to pesticide, infestation, drought or flooding, they have also raised concerns about direct and indirect costs of production, including cost of seeds, land degradation, environmental sustainability and safety.

Large farms in developed economies can usually afford the scale and intensity of GMO crop production, potentially disadvantaging small farmers in developing countries. Not surprisingly, GMO crop production remains concentrated in a handful of countries, with the United States accounting for 40% of the planted crop land (*Figure 3*).[6] This raises additional concerns regarding competition, global supply chain, crop prices, and food security for millions in many developing countries. Large-scale GMO crops are increasingly disadvantaging small farmers in developing countries, who are unable to compete in the market place on either price or quantity. The GMO seed production is also concentrated among few large firms who enjoy enormous market power to control price and supply of seeds, making small farmers vulnerable to market manipulation.

3 A gene drive is a genetic engineering technology—adding, deleting, disrupting, or modifying genes—to rapidly spread a particular genetic trait to an entire offspring population. A gene drive can alter or eliminate an entire species.

4 A genetically modified organism (GMO) is an organism in which one or more genes (called transgenes) have been introduced into its genetic material from another organism using recombinant DNA technology. For example, the genes may be from a different kingdom (such as from a bacterium to a plant) or a different species within the same kingdom (e.g. from one plant species to another).

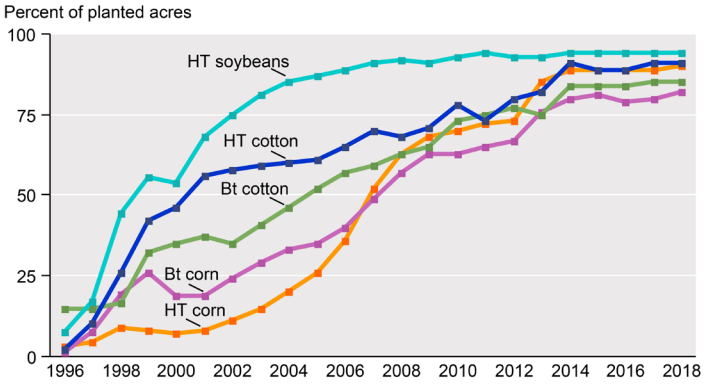
5 http://www.fao.org/3/MX160en/mx160en.pdf

6 Author's compilation from http://www.isaaa.org/resources/publications/briefs/53/download/isaaa-brief-53-2017.pdf

Figure 2

Adoption of genetically engineered crops in the United States, 1996-2018

Source: US Department of Agriculture, https://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us.aspx



Note: HT indicates herbicide-tolerant varieties; Bt indicates insect-resistant varieties (containing genes from the soil bacterium Bacillus thuringiensis). Data for each crop category include varieties with both HT and Bt (stacked) traits.

Advancing human genome research

Technological breakthroughs are lowering the cost of gene sequencing and editing, but gene therapies are still too expensive for most people. The cost of sequencing genes has declined dramatically—from nearly $9 million in 2007 to just $1,100 per genome in 2017—due to a revolutionary technology called Next Generation Sequencing.[7] This drastic reduction in cost, though still prohibitively expensive for average income-earners in many developing countries, has made sequencing and studying genes feasible for many countries. It has encouraged competition among countries to establish themselves as leaders in genomics, pursuing a range of objectives (*Table 1*).[8] While countries are prioritizing genomic research, international cooperation is also playing a critical role. The Human Heredity and Health in Africa (H3Africa) initiative, an example of successful collaboration in genetic research, directs funding from the National Institutes of Health (NIH) and the Wellcome Trust to research sites across Africa that study genomics, environmental determinants of common illnesses, disease susceptibility and drug responses in African populations.

II. The bad

The high price tag of many genetic technologies means that not everyone will benefit. The cost of gene therapies for rare diseases as approved in the United States and Europe can range from $373,000 to $1 million per patient per year. While genomics is shaping the future of medicine, the research is often targeted for certain population groups in mind, especially wealthy people who possess the ability to pay.

7 https://www.genome.gov/sequencingcostsdata/

8 Authors compilation from https://www.clinicalomics.com/topics/biomarkers-topic/biobanking/10-countries-in-100k-genome-club/

A widening genomics-divide in healthcare

According to the WHO, only 10 per cent of the US$70 billion health research spending worldwide is focused on the health needs of 90 per cent of the world's population. Large pharmaceutical companies primarily focus their efforts on profitable markets and as a result, only 13 of the 1,223 new drugs introduced between 1975 and 1996 targeted tropical diseases.

This reflects not only the entrenched divide in research and development (R&D) expenditures between developed and developing countries but also differential priorities in medical research.

Pharmaceutical firms in developed countries dominate genomic innovations, raising concerns of a "genomics divide" that can further exacerbate existing inequality in health outcomes between rich and poor nations. The Food and Drug Administration in the United States, for example, has received over 100 applications for new gene therapies in 2017. The 721 on-going gene therapy trials will treat 1,000 rare diseases, which means only a small number of patients will benefit from such gene therapies, keeping the price of treatment out of reach for most people. It will nevertheless remain important to establish clear guidelines for genetic research and access to genomic information, to ensure that the beneficiaries of various genomic research represent the diversity of the entire population.

The market demand for finding cures for rare diseases explain the rapid proliferation of gene therapies in the United States and other developed economies. There are, however, positive spillover effects of the high cost of—and the high pay-off from—gene therapies. As researchers look for cure for one rare disease, they will invariably expand our understanding of gene level behavior and

Figure 3

Global Share (%) of GMO-planted Croplands in 2017

Source: UN DESA

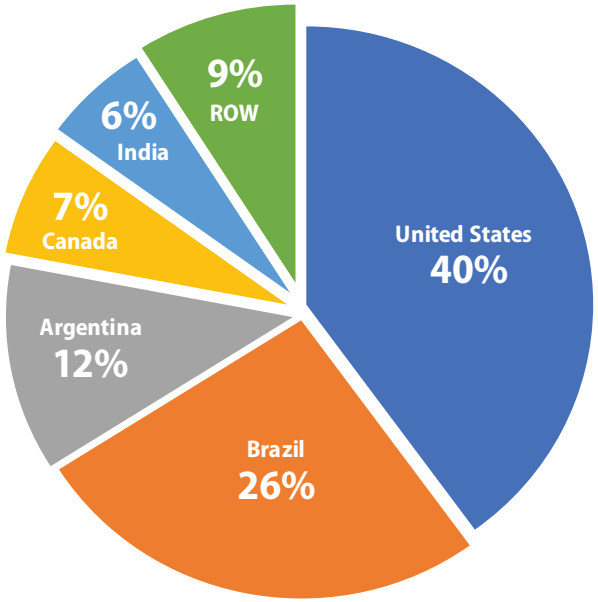


Table 1
Countries establishing themselves as leaders in genomics: select projects and their objectives

Country	Initiative	Objective
Australia	Australian Genomics Health Futures Mission	Develop national standards and protocols to enhance data gathering and analysis; promote the value of genomics to the broader community; and encourage government partnerships with philanthropists and businesses
China	100,000 Genome Project	Study how Chinese population transform from health to disease, environmental impacts, and the interactions between environmental factors and genes, and its influence on people's health
Estonia	Personalized Medicine Programme	Develop genotypes that will enable personalized reports for use in everyday medical practice through the national e-health portal
France	France Génomique 2025	Integrate genomic medicine into routine patient care and establish a genomic medicine industry to fuel economic growth. By 2020, France aims to have increased its annual sequencing capacity to 235,000 genomes, of which 175,000 are to come from cancer patients, and the remaining 60,000 from rare disease patients
Japan	Initiative on Rare and Undiagnosed Diseases	Develop innovative drug candidates by targeting novel, single pathological mutations, apply new NGS-based genome analyses to cases that remain unsolved, and facilitate international data sharing
Saudi Arabia	Saudi Human Genome Program	Study more than 5,000 inherited diseases using more than 10,000 samples from Saudi patients with inherited diseases that resulted in identification of more than 2,000 variants underlying the diseases
Turkey	Turkish Genome Project	Sequence the genomes of 100,000 Turkish nationals and increase that number to 1 million genomes by 2023
United Arab Emirates	United Arab Emirates—Dubai Genomics	Sequence all of its 3 million residents. Dubai Genomics is one of numerous projects within the Dubai Future Foundation's "Dubai 10X Initiative," launched to catapult the UAE 10 years ahead of the rest of the world
United Kingdom	100,000 Genome Project	Incorporate genome sequencing in routine healthcare through the Genomic Medicine Service (GMS). Sequenced 71,095 whole genomes
United States	All of Us Research Program	Glean health and wellness data from 1 million or more Americans

potentially lead us to cures for other intractable diseases. While each life matters, societies will need to make tough choices, considering the opportunity costs of spending millions, if not billions of private and public money, to treat rare diseases that affect very small population groups. Making a few better off, while ignoring the medical needs of millions, will only exacerbate inequities in health outcomes, even in the most developed countries. The rich living longer and healthier, while the poor lack basic healthcare, will further entrench alienation and societal discontent.

III. The ugly

Gene editing has opened a Pandora's Box. While it presents great hopes for curing disease and eliminating hunger, gene editing is still imprecise, which could lead to inadvertent and undesirable changes to a genome. There are also concerns regarding the unknown, long-term safety of gene editing.

Ethical concerns

There are growing concerns about how to govern the use of germline editing technologies in the health sector. Germline editing refers to genetic modifications that can be inherited by an offspring. This process raises many ethical questions, especially if gene editing is used to address a genetic diagnosis of an unborn child, where any off-target edits can evolve quickly. The discussion around the usefulness and the risks of germline editing came to the spotlight after a Chinese scientist announced he had edited the genetic material of two babies prior to their birth. The changes were meant to be benign, making the unborn babies less susceptible to HIV infection. There are, however, concerns that the genetic sequence targeted in this procedure may also affect brain development. It also raises questions about what constitutes "informed consent". How can a future person have a voice on genetic changes that will affect them throughout their lives, and perhaps passed on to their offspring? Regulation of gene editing research involving human embryos has gained added urgency in recent months as news broke out that the first genetically edited children have been born in China. Some 30 countries already have in place legislation that directly or indirectly bars the use of germline editing technologies.

Introducing genetic changes in a population, even if successful, can also lead to unforeseen ecological impact. Delivering a genetic mutation for combating malaria—using a gene drive into the wild—is risky and the harm caused by a disease such as malaria must be balanced against the possible ecological side-effects of the proposed solution. Once released, the mutation will spread as

Select country approaches to regulate genetic technologies

Canada, strongly influenced by public outcry over the production by British scientists of a cloned sheep called "Dolly", decided to ban and criminalize human cloning research in 2004. In **Germany**, the creation, use, and harvesting of embryonic cells for basic research are also prohibited. In **France**, the modification of the human genome may be undertaken for preventive, diagnostic or therapeutic purposes only. The **United Kingdom**, on the other hand, allowed in 2016 the application of genetic technology in research on human embryos. In the **Republic of Korea**, laws prohibit genetic experimentation with and modification of human embryos, including any product that alters genes. The concerns about "off-target effects" of genetic technologies, meaning that not all copies of the target gene are edited, have also further complicated the regulatory process in a number of countries.

Because of deep-rooted concerns that developments in the field of genetic technologies may outpace ethical guidelines, there is strong public support across countries in all regions for subjecting regulation in this area to extensive stakeholder consultations. In **Germany**, for example, the National Academy of Sciences convened a gene editing debate in 2017 that included members of the public as well as officials from various federal ministries. In **Australia**, the Office of the Gene Technology Regulator, in 2017, invited the public to provide comments during a review of the country's gene technology regulation. In **Qatar** has adopted a consultative approach to policymaking on issues relating to bioethics of new genetic technologies. The Qatar consultations have involved scientists, industry experts, government representatives and scholars in Islamic jurisprudence.

designed and may not be recalled or easily disabled. There is also the possibility that eliminating a species may unleash unforeseen consequences. The genetic mutation itself may somehow affect a benign insect species, such as bees, causing untold harm to the ecosystem that supports farming and other plant life.

There are also social and national sovereignty considerations as mutations will not be confined to certain geographical regions or national borders. As genetic technologies continue to advance and as the technical barriers to solving many challenges fall, social and sovereignty concerns remain and are accentuated. Genetic drives to combat malaria, for example, will likely need a regional, and possibly a global, agreement among countries.

IV. Finding appropriate balance

Countries will need to find appropriate balance between incentivizing advances in genetic technologies and managing their intended benefits and unintended consequences. The balance will rest on three pillars: (1) consent and privacy; (2) information sharing and intellectual property rights; and, (3) ethical boundaries. First and foremost, genetic research involving humans must require informed consent. The privacy and safety of a research subject or beneficiary must be protected to facilitate further progress in genetic research. The immortal Hela cells of Henrietta Lacks, an African American cancer patient who died in 1951, have been a major source of genetic research worldwide for more than 60 years. Since the 1950s, scientists have grown as much as 50 million metric tons of her cells, and there are almost 11,000 patents involving HeLa cells. Yet neither Henrietta nor her family members ever consented to the research, raising concerns for her privacy. There was a public outcry when a group of scientists published the HeLa genome in 2013 without the consent of her descendants. By the time the researchers removed the genome from public view it had been downloaded at least 15 times.

The privacy concerns of individuals must be balanced against the need for sharing genetic data broadly to facilitate research collaboration. Achieving this balance is particularly difficult in genomics given that DNA sequence is unique to each person, making it impossible to fully anonymize the data. There is, however, broad consensus in the research community that DNA sequencing data should be made public within 24 hours of being generated, as agreed in the Bermuda Declaration. The open access policy largely explains the rapid advances in human genome research during the past 15 years.

The privacy concern and open access policy, however, can come into conflict with intellectual property protection typically afforded to innovation. Patents encourage innovation and incentivizes investments in research and yet it can also stifle further innovation, limiting access to critical genetic information stored behind patent protection. The future of genomic research will also hinge on intellectual property rights information and sharing of information. The earliest genetic patents were issued in 1982, which opened the debate whether DNA sequencing was a mere discovery or met the definition of invention. In 2013, the US Supreme Court concluded that DNA in its natural form cannot be patented. However, gene therapies and other genetic interventions typically enjoy patent protection, explaining the high price tag. International cooperation in genomic research will need to address patent protection issues to make gene therapies more accessible and affordable.

Ethical concerns will remain the most critical challenge for managing the risks in genetic research. Genetic research is becoming more commonplace and yet most genetic tests are not regulated, even in the United States. The claims of many genetic results are not independently verified, making them susceptible to fraud and manipulation. More importantly, there is no internationally agreed guidelines for human genome research. Informed consent, privacy protection and patent rights can still be insufficient to prevent unethical genetic research. The genetic research community generally adheres to the Declaration of Helsinki that the World Medical Association adopted in 1964 to guide medical research with human subjects. The code of ethics embodied in the Declaration protects individual subjects from potential harm but does not necessarily spell out the responsibility of the researcher to take into account the risks on third parties and other spillover effects.

International cooperation

A number of prominent scientists have called on governments to adopt more specific standards and principles at the intergovernmental level to guide the regulation of genetic technologies. This includes a group of eighteen scientists and ethicists from seven countries, who in a 13 March 2019 article in the Nature magazine called on governments to declare a 5-year global moratorium on all clinical uses of germline editing until the technical, scientific, medical, societal, ethical and moral implications have been more thoroughly discussed and understood.

Earlier this year, the Director-General of WHO established a new advisory committee on developing global standards for governance and oversight of human genome editing. The committee agreed that it would be irresponsible at this time for anyone to proceed with the clinical application of human germline editing. It has also requested WHO to immediately begin working on a central registry on human genome editing research. Over the next two years, the committee will conduct a series of meetings and consultations with all relevant stakeholders with a view to providing recommendations for a governance framework that is scalable, sustainable and appropriate for use at the international, regional, national and local levels.

An effective global governance framework is an imperative for ensuring safe and sound application of genetic technologies and making them accessible to all. The stakes are high when it comes to the unsafe and unethical application of genetic technologies as discussed in this FTQ. The World Health Organization and the Food and Agriculture Organization of the United Nations will need to continue playing a pivotal role in promoting greater understanding of the risks and benefits of genetic technologies and developing internationally agreed norms and standards for their safe and ethical use. The quest for reaching a global consensus on ethical use of genetic technologies should not encourage the Member States to look for the least common denominator solutions and *de minimis* standards. The standards should be sufficiently aspirational and forward-looking—guided by the principles of the UN Charter and the Universal Declaration of Human Rights—given that they will affect not only this current generation but also our future generations. A misstep will be too costly for humanity.

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