On gene technology and the role of the scientific community

STOCKHOLM SCIENCE CITY FOUNDATION

Authors: Anna Frejd, Andreas Namslauer and Johan Gómez de la Torre, Stockholm Science City
Publisher: Stockholm Science City
Published: November 2018
Cover photo: Johan Gómez de la Torre

The cabbage shown on the cover page has been gene edited using CRISPR/Cas9. In the plant, a gene has been deleted. The cabbage is used to demonstrate one of the challenges associated with the European legislation on genetically modified crops, since; no analysis method can tell whether it has been gene edited as nothing has been added to its DNA. It was grown in Umeå, Sweden, by professor Stefan Jansson who brought it to the conference at Engelsbergs bruk.

Introduction

Gene technology is a perfect example of a scientific field where advances provide radically new opportunities for society and challenge accustomed perceptions of the world we live in. A sound policy should be based on scientific knowledge, but history shows that scientific facts can be neglected when opinions are strong. This has, for instance, led to a set of paradoxical laws that regulate the use of gene technology in Europe; the same technology that is accepted for the development and production of drug-producing microorganisms is widely banned for the development of new crops. The European legislation on genetically modified crops is based on misconceptions and resistance to new technology rather than on current scientific data. This situation causes Europe to miss out on a more sustainable agricultural industry and many business opportunities. Meanwhile, regulatory agencies allow genetic tests for various health-related examinations to be sold directly to consumers, tests with limited ability to provide scientifically sound and clinically relevant conclusions.

When science and new technology have a large impact on society, what can be expected from the scientific community when it comes to spreading new knowledge to society and taking cautious measures about the use of new technology? Can the scientific community help public to understand benefits and risks and to help form sound policies and nuance the expectations about new technology?

This is a report partly based on a number of presentations and discussions at the conference *Where is Life Science Heading in the Future: Genes, Technology and Society* arranged by Stockholm Science City and the Axel and Margaret Ax:son Johnson Foundation at Engelsbergs Bruk, May 14-15, 2018. The conference aimed to bring together representatives of different organisations and fields of interest to discuss the present status and future development of the life sciences with a special focus on gene technology. This report aims to emphasise the importance of, and the challenges associated with, public outreach and sound scientific communication. Hopefully it can inspire discussion and new trains of thought on the role of the scientific community.

The report provides a short introduction to gene technology before highlighting two areas in more detail: gene technology in plant breeding and gene technology in medicine.

Presenters at the conference

Stefan Ståhl – KTH Royal Institute of Technology
Jennifer Kahn – New York Times Magazine & Princeton University
Karin Dahlman-Wright – Karolinska Institutet
Sara Sjöling – Södertörn University
Per Farholt – Per Farholt Global R&D Advisory Service
Stefan Jansson – Umeå University
Audrun Utskarpen – Ecolabelling Norway
Marju Orho-Melander – Lund University
Anna Wedell – Karolinska Institutet & Karolinska University Hospital
Douglas Hanahan – Swiss Federal Institute of Technology Lausanne & Swiss Institute for Experimental Cancer Research
Saar Gill – University of Pennsylvania
Torbjörn Tännsjö – Stockholm University & Karolinska Institutet

Gene technology and its applications

Genes are the basic physical and functional units of heredity. They are made up of segments of deoxyribonucleic acid (DNA) and are found in all living organisms. Genes are transferred from one generation to the next and the genetic setup determines most of the characteristics of an organism. Thanks to advances in genetics and biotechnology, we now know that humans share genes with all other organisms on Earth. For example, we share about half of our genes with bananas, but that does not make us "half bananas", nor does it make those shared genes "banana genes". They are just genes, useful to bananas and humans in different ways. Hence, the term "foreign genes" that sometimes occurs in public debates about gene technology is challenged by scientists. The word *genome* refers to the total genetic material of an organism, i.e. including all genes.

Even though most people may first associate gene technology with the use of genetic modification (GM), giving rise to a genetically modified organism (GMO), only some gene technologies produce GMOs. The term *gene technology* covers technologies used both to study and to modify the genetic setup of organisms. We can describe gene technology as the application of knowledge in the field of *genetics*, which is the study of genes, genetic variation and heredity in living organisms.

Humans have used methods of genetic manipulation in organisms for more than 10 000 years.[1] For example, ancient farmers in what is now Mexico developed maize from the wild grass Teosinte through what is called selective breeding; when only the kernels from plants with desirable traits were planted, the cobs grew larger over time and had an increasing number of kernels, and eventually maize as we know it today took form.[2] Selective breeding has also given us wheat with seeds that do not fall to the ground, bananas with nearly unnoticeable seeds, and apples that are sweet and juicy. Another method of genetic manipulation is deliberate interbreeding to transfer genes from one variety to another in order to introduce new traits. In the 1930s, breeders started using radiation and chemicals to alter the DNA of plants to generate new traits, a process called mutagenesis. Up to today, more than 3 200 mutagenic plant varieties from 214 plant species have been released for commercial use.[3]

In 1973, Stanley Cohen et al. published a paper describing a method for selectively cutting out genes from organisms and pasting them into the DNA of others,[4] so-called recombinant DNA technology. Soon after, Rudolf Jaenisch created the first genetically engineered animal when he inserted foreign DNA into a mouse in 1974.[5] Suddenly, specific genes could be transferred between organisms from different kingdoms, enabling researchers to engineer organisms in an unprecedented manner. Direct manipulation of DNA using biotechnological methods, such as recombinant DNA technology, is often referred to as *genetic engineering*. The term was actually first coined by the fiction author Jack Williamson, who was slightly ahead of the scientists, in his science fiction novel *Dragon's Island* involving a battle be-

---

[1] Larson G, Piperno DR, Allaby RG, et al. Current perspectives and the future of domestication studies. *Proceedings of the National Academy of Sciences of the United States of America* **111**, 6139-6146 (2014).

[2] Wang H, Nussbaum-Wagler T, Li B, et al. The origin of the naked grains of maize. *Nature* **436**, 714-719 (2005).

[3] Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture. Plant Breeding and Genetics. Available at: http://www-naweb.iaea.org/nafa/pbg [accessed on June 29, 2018].

[4] Cohen SN, Chang ACY, Boyer HW, Helling RB. Construction of Biologically Functional Bacterial Plasmids *In Vitro*. *Proceedings of the National Academy of Sciences of the United States of America*. **70**, 3240-3244 (1973).

[5] Jaenisch R, Mintz B. Simian Virus 40 DNA Sequences in DNA of Healthy Adult Mice Derived from Preimplantation Blastocysts Injected with Viral DNA. *Proceedings of the National Academy of Sciences of the United States of America* **71**, 1250-1254 (1974).

tween humans and mutants. It was published in 1951, one year before DNA's role in heredity was confirmed by Alfred Hershey and Martha Chase, and two years before James Watson, Francis Crick and Rosalind Franklin showed that the DNA molecule has a double-helix structure. And even earlier, the general concept of direct genetic manipulation was explored in rudimentary form in Stanley G. Weinbaum's 1936 science fiction story *Proteus Island*, where the main character finds himself exploring an island used as a laboratory for genetic manipulation. Hence, long before genetic modification was a reality, it has appeared in horrific scenarios in literature.

The first methods for DNA sequencing were developed in the 1970s. DNA sequencing is the process of determining the precise order of building blocks in a DNA molecule; hence, it can be used to determine the DNA sequence in individual genes, larger genetic regions or the entire genomes of any organism. The first method for DNA sequencing was described in 1970 by Ray Wu[6] and adopted by Frederick Sanger, who developed it further into a much faster process that was presented in 1977.[7] The method is based on the selective incorporation of chain-terminating molecules during DNA replication using the enzyme *DNA polymerase*. Frederick Sanger was later awarded the Nobel prize in chemistry for his work on DNA sequencing, a prize he shared with Walter Gilbert, who developed another method for DNA sequencing, and Paul Berg for his studies of nucleic acids. Since then, a large number of new techniques for DNA sequencing have been developed, offering increasingly faster and cheaper analyses. One example is the so-called pyrosequencing method, developed by the Swedish scientist Pål Nyrén and colleagues, which had a significant effect on the costs of DNA sequencing. The method, which was first described in 1993, relies on the generation of light during enzymatic synthesis of a complementary DNA strand to the sample consisting of a single-stranded piece of DNA.[8] Other examples of DNA sequencing techniques are illumina-dye sequencing, SOLiD sequencing and single-molecule-real-time (SMRT) sequencing. Today these techniques are fundamental to basic biological research and have applications in fields such as medicine and medical diagnosis, forensics, evolutionary genetics and more. Image 1 shows how the cost of sequencing a human-sized genome has plummeted to about a millionth of its value in 2001.

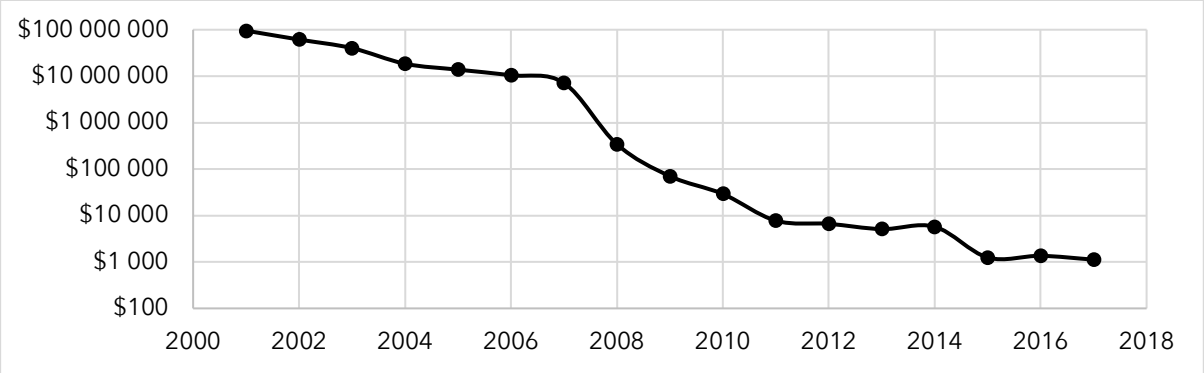

Image 1. Cost of sequencing a human-sized genome. Data from the NHGRI Genome Sequencing Program.[9]

[6] Wu R. Nucleotide sequence analysis of DNA. I. Partial sequence of the cohesive ends of bacteriophage lambda and 186 DNA. *Journal of Molecular Biology* **51**, 501–521 (1970).

[7] Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. *Proceedings of the National Academy of Sciences of the United States of America*. **74**, 5463-5467 (1977).

[8] Nyren P, Petersson B, Uhlen M. Solid Phase DNA Minisequencing by an Enzymatic Luminometric Inorganic Pyrophosphate Detection Assay. *Analytical Biochemistry* **208**, 171-175 (1993).

[9] Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP). Available at: www.genome.gov/sequencingcostsdata [accessed on October 12, 2018].

In 2012, a new method for genetic engineering known as CRISPR-Cas9 was presented by Emmanuelle Charpentier and Jennifer Doudna and colleagues;[10] this allowed, for example, direct deletion of genes in plant DNA.[11] The technique was further developed by Feng Zhang and George Church and colleagues for use in mouse and human cells.[12,13] This has been described as a game-changer in the field of biotechnology. CRISPR-Cas9 (short for clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9) was adapted from a naturally occurring genome editing system used by bacteria in their defence against viruses. The CRISPR-Cas9 method has generated a lot of excitement in the scientific community because it is faster, cheaper, more accurate, and more efficient than other existing genome editing methods. Some researchers have compared the method to a word processor, capable of effortlessly editing a gene down to the level of a single letter. Work that earlier took months can now be done in a couple of days. The method is also much easier to use and experiments can, with the right tools, easily be performed even by non-scientists. CRISPR-Cas9 do-it-yourself (DIY) kits including "everything you need to make precision genome edits in bacteria at home" are for example available online for anyone to buy.[14]

The introduction of easy-to-use DIY kits for genetic engineering may be seen as a democratisation of science, giving people the tools to understand and use technology that is used all around them. However, at the same time this releases powerful and potentially dangerous tools that could, for example, be used to quite efficiently and quickly manipulate living organisms that could spread in nature.

Modern gene technology has a wide range of applications. How it is used for plant breeding and in medicine, and public opinion about its use, will be discussed in the following chapters but to illustrate the diversity of applications, some others are listed below.

Basic biology, medical research and understanding the world of microorganisms

Basic research in biology, biochemistry and medicine relies heavily on gene technology today. Genetically engineered microorganisms and animals (also called transgenic animals) are everyday tools used by both academic and industrial scientists to understand biological mechanisms (e. g. signalling in cells and metabolism) as well as diseases (when biological mechanisms are malfunctioning). For example, by knocking out the genes responsible for certain conditions, it is possible to create animal models of human diseases. Also, gene technologies such as DNA sequencing have been used, and are crucial, for the progress of the entire medical field, enabling scientists to study for example genetic causes of and risks for diseases. The ever-increasing speed and capacity of the DNA sequencers and the development in the field of bioinformatics (computational tools and methods for analysis of biological data) have enabled new research fields such as metagenomics, which is the study of genetic material recovered directly from environmental samples. Metagenomics has opened the door to the study of diversity in the

[10] Jinek M, Chylinski K, Fonfara I, et al. A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity. *Science* **337**, 816-821 (2012)

[11] Woo Woo J, Kim J, Kwon S, et al., DNA-free genome editing in plants with preassembled CRISPR-Cas9 ribonucleoproteins. *Nature Biotechnology* **33**, 1162–1164 (2015)

[12] Cong L, Ran FA, Cox D, et al. Multiplex Genome Engineering Using CRISPR/Cas Systems. *Science* **339**, 819-823 (2013).

[13] Mali P, Yang L, Esvelt KM, et al. RNA-Guided Human Genome Engineering via Cas9. *Science* **339**, 823-826 (2013).

[14] The ODIN. DIY Bacterial Gene Engineering CRISPR Kit. Available at: http://www.the-odin.com/diy-crispr-kit [accessed on September 21, 2018].

microbial worlds, both large and small. It is, for example, used to understand the environmental adaptation of microorganisms in the oceans and to understand the impact of our gut microbiome on our health.

Molecular anthropology and evolutionary genetics

DNA sequencing is a key tool in the study of the evolution of humans, historic migrations and development of societies around the globe. Genetic data provide linkages between ancient and todays human populations,. This type of research, and the techniques it employs, is the foundation for the commercially available, DNA-based ancestry tests.

Environmental research and application of biomolecules

Gene technology is used to study biodiversity and track variations in genetic material, for example in microorganisms, to better understand environmental changes. Gene technology is also used to study the biomass of microorganisms, which represent the majority of life forms on Earth and can be found all over the globe. These life forms have unparalleled ways of adapting to various conditions and, with their enormously diverse metabolic capacity, are a great source for discovery and production of biomolecules. Biomolecules are used in various applications such as waste management, medicine, biofuels, food and beverages, detergents, biopolymers, biocatalysts and more. They have already provided ecologically sustainable solutions to various challenges, since they developed in symbiosis with the natural surroundings of the microorganisms.

When producing biomolecules, such as enzymes for detergents or paper pulp production, the actual production is carried out by cells kept in a bioreactor. When the biomolecules of interest have been produced, they are harvested and purified. The microorganisms used as cell factories are often genetically engineered in order to produce high yields of the desired molecule.

Forensics

Humans share about 99.9 % of their DNA with everyone else; however, the small differences that exist are as unique as fingerprints and can be used to distinguish individuals from each other. This is used in criminal investigations where DNA from suspects is compared to DNA found on the crime scene. In DNA profiling, a specific part of the genome, called the *variable number tandem repeat* is studied. DNA profiling is not based on DNA sequencing but uses other techniques, such as polymerase chain reaction (PCR) and short tandem repeat (STR) analysis, to study the specific DNA area. The process for DNA profiling was developed by Alec Jeffrey at the University of Leicester and was commercialised in 1987. The process can also be used to establish relationships between individuals and was first put to test in an immigration case to confirm the identity of a British boy whose family was originally from Ghana.

Agriculture and fear of the genetically modified plant

Gene modification of organisms has a long history in agriculture and is of the uttermost importance for our global food supply. Today, gene technology is transforming agriculture as we know it and society is struggling with how to handle these changes.

In the rear mirror

The development of recombinant DNA technology in the 1970s opened up countless new research possibilities, but also raised concerns about possible dangers to human health and the ecosystem. To evaluate the state of the technology and the possible associated risks, a conference held in 1975 gathered leading scientists from around the globe, as well as lawyers, members of the press and government officials.[15] The conference was held at the Asilomar Conference Center in California; hence the event has become known as the Asilomar conference. For three days, the attendees discussed the safety of recombinant DNA research based on the available scientific literature, which was limited at the time. It was concluded that experiments were to be allowed to continue, but only if a set of strict guidelines were adhered to. Recombinant DNA research was thus allowed to move forward and today, more than 40 years later, the scientific community agrees that the technology is safe when the guidelines are followed. No incidents or possible hazards to either public health or ecology related to the use of recombinant DNA research have been reported. Today, the term GMO is used when referring to organisms developed with recombinant DNA technology. In 2010, the European Commission stated in a report surveying 25 years of EU-funded research on the safety of GMOs that recombinant DNA technology is "not *per se* more risky than e.g. conventional plant breeding technologies".[16]

Since the introduction of recombinant DNA technology into plant breeding, crops with for example better resistance to diseases and higher yields have been developed. Today's scientific knowledge base was built on decades of research, and large-scale field production of GM crops have proven GMOs to be not only safe but also beneficial for ecosystems, farmers and consumers. In a comprehensive meta-analysis from 2014[17] which included 147 original studies, it was concluded that GM crops, in the countries where they are allowed, have on average:

- reduced chemical pesticide use by 37 %
- increased crop yields by 22 %
- increased farmer profits by 68 %.

However, in some parts of the world, especially in Europe, GM crops for human consumption are frowned upon and to a large extent banned for cultivation. How can that be? In addition, GM crops

[15] Fredrickson D.S. Asilomar and recombinant DNA: the end of the beginning. In *Biomedical Politics* (Ed. Hanna KE), *National Academy Press*, Washington, DC (1991).

[16] Directorate-General for Research and Innovation, European Commission. A decade of EU-funded GMO research (2001-2010), *Publications Office of the European Union*, Luxembourg (2010).

[17] Klümper W, Qaim M. A Meta-Analysis of the Impacts of Genetically Modified Crops. *PLoS ONE* **9**, e111629 (2014).

are not allowed to be used in organic farming, even though they can reduce the need for pesticides (which is also used in organic farming[18,19]) and increase crop yields.

The first GM crop was approved for commercial production in 1992. This was in the U.S. and the crop was a tomato called Flavr Savr that had a gene that increased the shelf life of the product. In 1998, a maize called MON810 with resistance to the European corn borer was the first GM crop approved for commercial cultivation by the European authorities. The authorisation came just before a moratorium was posed on any new approvals of GMOs in the EU ahead of new regulatory laws that were passed in 2003. Authorisation for cultivation and import of GM crops is given by EU authorities dependent on precautionary principles based on the safety of human health and the environment. Since 2015, member states can also opt out from GM cultivation for reasons other than food safety, including e.g. public policy.[20] By 2018, 17 member states have imposed a total ban on GM cultivation in their respective territories and MON810 is still the only GM crop cultivated anywhere in Europe. Meanwhile, more than 50 GM crops have been approved for import into Europe; however, while these have been approved for human consumption, they are in practice only used as animal feed. In fact, the European animal feed industry is totally dependent on imported protein crops and, for example, 92 % of all imported soybean is estimated to be GM soybean.[21]

The import rules for crops shipped into the EU are very strict. Since 2007, any shipment of food or feed must, in practice, be completely free from even trace amounts of GM crops that have not been approved. This has already resulted in a trade war with the U.S. because of the difficulties of ensuring GMO-free deliveries. In fact, Europe could run short of imported crops if countries elsewhere approve and grow increasing numbers of GM crop varieties, making it harder to avoid GMO contamination during transport.[22]

The European legislation was built on the perceptions and limited knowledge about GMOs from the early days of recombinant DNA and has not been updated according to current scientific understanding since. EU regulators have adopted a "process-based" approach that discriminates against GMOs simply because they are GMOs, not based on the safety of the products themselves. This approach was challenged by the scientific community as early as the 1980s, when the European Molecular Biology Organization (EMBO) positioned themselves by stating:[23]

> "EMBO strongly believes that there is no scientific justification for additional, special legislation regulating recombinant DNA research *per se*. Any rules or legislation should only apply to the safety of products according to their properties, rather than according to the methods used to generate them"
>
> October 1988, 40th meeting of the EMBO Council

---

[18] Bahlai C, Xue Y, McCreary C, et al. Choosing Organic Pesticides over Synthetic Pesticides May Not Effectively Mitigate Environmental Risk in Soybeans. *PLoS ONE* **5**, e11250 (2010).

[19] Avery AA. Organic pesticide use: What we know and don't know about use, toxicity, and environmental impacts. Crop Protection Products for Organic Agriculture. In *Crop Protection Products for Organic Agriculture* (Eds. Felsot AS, Racke KD). *American Chemical Society,* Washington, DC, 58–77 (2006).

[20] Directive (EU) 2015/412 of the European Parliament and of the Council.

[21] USDA Foreign Agricultural Service. EU-28 Agricultural Biotechnology Annual 2017, *USDA GAIN reports*, Washington, DC (2017).

[22] Wager R, McHughen A. Zero sense in European approach to GM. *EMBO Reports* **11**, 258-262 (2010).

[23] Cantley M. The Regulation of Modern Biotechnology: A Historical and European Perspective: A Case Study in How Societies Cope with New Knowledge in the Last Quarter of the Twentieth Century. In *Biotechnology: Legal and Ethical Dimensions* (Eds. Rehm HJ, Reed G). *Wiley-VCH Verlag*, Weinheim, 508-681(1995).

However, this scientific standpoint was overshadowed in the legislation process by opposition against GMOs from the general public based on the preconception that GM crops are "unnatural" and basically different from other crops.[24,25] However, in nature DNA is transferred between organisms and species; viruses can infect cells by injecting DNA into them and, to fight off such infections, bacteria and other prokaryotes have developed the ability to cut and reattach parts of their DNA. Recombinant DNA techniques used in the laboratories are based on the same principles, using the same genes and enzymes that exist in nature. Examples of this type of gene transfer occurring in nature and resulting in organisms with new traits include butterflies with wasp genes[26] and sweet potato with genes from bacteria.[27] It has also recently been demonstrated that humans, without knowing it, might have been producing GMOs for millennia by grafting plants. In the grafting process where, for example, a tree with sweet fruits is grafted onto a tree with greater disease resistance, mitochondria[28] and cell nuclei[29] can be transferred across the graft, fusing genomes and potentially creating a new species.

Early on, the concept of GMOs also challenged the perception of the "natural" agriculture sector dominated by small family farms using traditional methods. In the eyes of many, GM crops represented a large scale and highly industrialised form of agriculture associated with extensive use of pesticides, ground water pollution and water depletion. Public opposition in the EU was also fuelled by the fact that Monsanto, a U.S. company, was the first mover on the market, rather than one of its European counterparts. Monsanto did not GMO-label their products, which led consumer groups in Europe to claim that they deprived consumers of freedom of choice. At the same time, Monsanto bought a large number of seed companies and rumours started to spread about Monsanto's introduction of a "terminator gene" (a gene causing second generation seeds to be sterile) in their products. It should be noted that no such products have been introduced onto the market by any seed company. However, this made European farmers suspect that Monsanto's marketing of GMO seeds was part of an American strategy to control European agriculture.[30]

Public concern about food safety and agriculture was also high at the time due to the recent outbreak of bovine spongiform encephalopathy (mad cow disease) in the UK, resulting in the death of several infected humans. This added to the scepticism against new technology and methods in agriculture, as well as distrust for the European regulatory system that had failed to protect European citizens.[30] In the UK, GM crops were referred to as "Frankenstein foods" and food producers and retailers in Europe adapted to public opinion by excluding GM crops in their products. In 1995, a survey showed

---

[24] Davison J, Ammann K. New GMO regulations for old: Determining a new future for EU crop biotechnology. *GM Crops & Food* **8**, 13-34 (2017).

[25] Tagliabue G. The EU legislation on "GMOs" between nonsense and protectionism: An ongoing Schumpeterian chain of public choices. *GM Crops & Food* **8**, 57-73 (2017)

[26] Gasmi L, Boulain H, Gauthier J, et al. Recurrent Domestication by Lepidoptera of Genes from Their Parasites Mediated by Bracoviruses. *PLOS Genetics* **11**, e1005470 (2015)

[27] Kyndt T, Quispe D, Zhai H, et al. The genome of cultivated sweet potato contains *Agrobacterium* T-DNAs with expressed genes: An example of a naturally transgenic food crop. *Proceedings of the National Academy of Sciences of the United States of America* **112**, 5844-5849 (2015).

[28] Gurdon C, Svab Z, Feng Y, et al. Cell-to-cell movement of mitochondria in plants. *Proceedings of the National Academy of Sciences of the United States of America* **113**, 3395-3400 (2016).

[29] Fuentes I, Stegemann S, Golzyk H, et al. Horizontal genome transfer as an asexual path to the formation of new species. *Nature* **511**, 232-235 (2014)

[30] Lynch D, Vogel D. The Regulation of GMOs in Europe and the United States: A Case-Study of Contemporary European Regulatory Politics, *Council on Foreign Relations,* New York (2001). Available at: https://www.cfr.org/report/regulation-gmos-europe-and-united-states

that 85 percent of Swedish consumers regarded genetic engineering as a "serious health hazard".[31] Many environmental NGOs oppose the use of GM crops and, for example, Greenpeace often has an anti-corporate agenda.[32] Violent attacks have been directed towards scientific personnel dealing with GMO-related matters at the European Food Safety Authority (EFSA). Because of these repeated attacks, 56 science organisations wrote an open letter to the president of the European Parliament in 2016 urging them to condemn physical attacks on scientists.[33]

Current status

Today, industrial organisations such as the Federation of Swedish Farmers (LRF) favour the use of GMOs in order to promote a sustainable, competitive agricultural industry.[34] Despite this, GM crops remain banned in organic farming because GMOs are still considered "unnatural". Hence, GM crops pose an economic threat to premium, prized organic products since GM crops can compete with lower prices. Cross contamination in the production and handling of crops can result in products that cannot be labelled as organic. The prevailing fear of GMO food among European consumers makes it economically unfeasible for eco-labelling organisations to support the acceptance of GMOs in organic farming, even though the scientific arguments show that they should. While there are individuals within the organic farming community who do advocate that GM crops should be allowed, since it would benefit both the soil and the ecosystem,[35] strong opposition from consumers, NGOs and organic farmers in Europe continues to support the political stance of strict GMO regulations in the EU. Meanwhile, the science community is not sitting silent and, for example, in 2016 107 Nobel laureates signed a letter urging Greenpeace to end its efforts to block introduction of a GM strain of vitamin-A rich rice (golden rice) which could potentially reduce the vitamin A deficiency that is causing blindness and death in children in the developing world.[36]

The scientific community and other advocates of plant biotechnology in Europe are now putting their hopes onto new gene-editing techniques that might not fall within the scope of European GMO legislation. One important example is the CRISPR/Cas9 method. In 2016, the Swedish Board of Agriculture confirmed that plants in which genes have been deleted using CRISPR/Cas9 and which have no added genes do not fall under the European GMO definition.[37] Later the same year, Stefan Jansson, professor at Umeå University, ate what was probably the first legally produced CRISPR meal ever

---

[31] Hoban TJ. Consumer Acceptance of Biotechnology: An International Perspective, *Nature Biotechnology* **15**, 232-234 (1997).

[32] Greenpeace. What's wrong with genetic engineering (GE)? Available at: https://www.greenpeace.org/archive-international/en/campaigns/agriculture/problem/genetic-engineering [accessed on July 6, 2018].

[33] Beltran JP. Open letter to the President of the European Parliament to encourage society to respect independent science advice and to condemn physical attacks on scientists (July 7, 2016). Available at: http://www.epsoweb.org/respect-science-advice [accessed on July 5, 2018].

[34] Lantbrukarnas Riksförbund (LRF). GMO-reglerna, GMO i foder och mer svenskt protein. Available at: https://www.lrf.se/politikochpaverkan/aganderatt-och-miljo/gmo [accessed on July 5, 2018]

[35] Jabr F, Organic GMOs could be future of food – if we let them. WIRED (Oct 7, 2015). Available at: https://www.wired.com/2015/10/organic-gmos-could-be-the-future-of-food-if-we-let-them

[36] Achenbach J. 107 Nobel laureates sign letter blasting Greenpeace over GMOs. *The Washington Post* (June 30, 2016). Available at: https://www.washingtonpost.com/news/speaking-of-science/wp/2016/06/29/more-than-100-nobel-laureates-take-on-greenpeace-over-gmo-stance

[37] Umeå Plant Science Centre. "Green light in the tunnel"! Swedish Board of Agriculture: a CRISPR-Cas9-mutant but not a GMO (December, 2016). Available at: https://www.upsc.se/about-upsc/news/4815-green-light-in-the-tunnel-swedish-board-of-agriculture-a-crispr-cas9-mutant-but-not-a-gmo.html [accessed on July 6, 2018].

served in the world.[38] However, on July 25 2018, the European Court of Justice ruled that crops edited using CRISPR should be subject to the same stringent regulations as other GMOs.[39] Hence, an opportunity for the EU to adopt a more science-based, innovation-friendly food policy was missed and there is great risk that both research and business will move elsewhere.

GM crops in Sweden

There is something of a paradox in Sweden concerning the attitude towards GM crops since, on the one hand, trust in science and scientists is generally high but, on the other hand, opposition to GMOs is also high, even from a European perspective. Most citizens have limited insight into the conditions of food production and are used to finding whatever they want, whenever they want, on the shelves at the local grocery store. The fear of GMOs from the 1990s still prevails in people's minds, making it difficult to change attitudes when alternatives to GMO food are abundant in the stores. It is difficult to argue that the benefits of GMOs outweigh the potential risks and there are no incentives for consumers to choose GMO food. In other words, it might be hard to get people interested in the matter as long as food is available at an affordable level. When the benefits of using GMOs are not clear, it is easier to maintain an anti-GMO attitude rather than updating oneself on the latest scientific understanding, especially when NGOs and eco-labelling organisations, which have economic interest in keeping their messages aligned with the general attitude, continue to preserve the concept of GMOs as "unnatural". Is it possible for organic farmers and their interest organisations to change positions and embrace GMOs as a way to increase yields and avoid pesticides? It may be a difficult market-communication project, but it should not be impossible. Using new technology to generate more environment friendly and sustainable agriculture could be a selling point.

In Sweden, a government agency called the Swedish Gene Technology Advisory Board was set up in 1994 to give advice and foster the responsible and safe use of gene technology. The agency also has the task of spreading knowledge on developments within the field to politicians and the public. The board has 15 members and includes both political representatives and experts on ethics, ecology and molecular biology.[40] The board acts as a bridge between the political sphere and the scientific community and provides a platform for scientists to influence political decision makers directly. Still, less than one third of the population consider themselves to have sufficient knowledge suggesting that more resources could probably be put on education about gene technology.[41]

Looking ahead

So, what can be done by the scientific community in terms of increasing the current understanding of GM among politicians and other policy makers, as well as consumers and people in general? Maybe the message could be tuned to be more in line with current trends and topics, with focus on innovation, sustainability and food supply in a world subjected to climate change. Maybe the message could be tuned to resonate better with people's feelings by not just presenting facts and figures but also adding a personal dimension to the story that people could relate to. Describing the process of scientific work, the amount of effort it takes and the conditions under which it is carried out could add to the

[38] Cohen J. Did a Swedish researcher eat the first CRISPR meal ever served? *Science* (Sep 7, 2016). Available at: http://www.sciencemag.org/news/2016/09/did-swedish-researcher-eat-first-crispr-meal-ever-served

[39] Callaway E. CRISPR plants now subject to tough GM laws in European Union, *Nature* **560**, 16 (2018).

[40] Gentekniknämnden. Om nämnden. Available at: https://www.genteknik.se/om-gentekniknamnden [accessed on July 6, 2018].

[41] Konsumentföreningen Stockholm. Svenskarnas attityder kring GMO och genteknik, *KFS Rapport*, Stockholm (2018).

transparency of the communications and hopefully increase trust both in the facts and in science as a whole.

Stepping out of our comfort zones and engaging with people outside the academic realm using social media and other means of communication is one way to reach a broader audience. The potential here is profound, given that many academics prefer more traditional ways of communication and have not yet fully embraced social media. To boost this idea among young scientists, communication might deserve a more prominent role in PhD programmes.

It is important to keep representatives of the education system updated on new science. Teachers, text book authors and education agencies should be included in activities where they can, to take part in the latest scientific understandings; this would be especially relevant in the continuing training of professional science teachers. All of this would fit into the scope of *public outreach*. However, given the risk of threats and physical attacks from anti-GMO activists, it is easy to understand why some academics choose not to engage in public debate.

Gene technology in medicine – a different story

Gene technology in all its forms is central to today's medicine, including analysis of genetic material for tailoring therapies or gaining understanding of the mechanism of diseases, genetically engineering microorganisms to produce e.g. protein drugs and gene therapies.

DNA analysis

DNA sequencing and other types of techniques for DNA analysis are important in medical research where the causes and mechanisms of diseases are studied. For instance, these techniques are used to study gene mutations associated with different types of cancer, and gene expression associated with the progression of a disease. In healthcare, DNA analysis can be used to understand the genetic setup of a disease in an individual patient in order to tailor efficient treatments. This is part of so-called *precision medicine* where the individual pre-requisites of each patient are considered in the treatment. This differs from traditional medicine where everyone with the same type of disease or symptom is treated similarly. Precision medicine has gained attention especially in the field of oncology but is also attractive in other areas, for example in the field of metabolic diseases where the conditions are caused by mutated genes. For instance, at Karolinska University Hospital and the Centre for Inherited Metabolic Diseases, whole genome sequencing is carried out for new-borns with rare metabolic diseases to find out whether, for example, dietary changes could stop the disease progression in these babies. Precision medicine is seen by many as the future for healthcare, and gene technology is the foundation for it.

The use of DNA analysis in individuals for medical and health-related reasons is often non-controversial and has been used, for example, to provide tools for predicting drug response in patients. This provides an opportunity to improve the equality, accuracy and cost effectiveness of healthcare. As an example, geographical ancestry has a large impact on people's specific genetic set-up and genotypes, and this in turn has a large impact on their reaction to drugs. Making a correct assessment of someone's ancestry without using DNA analysis is, in most cases, impossible. In the U.S., the social construct of (self-reported) "race" is sometimes used to establish the ancestry of patients when prescribing and administering medications, which has led to controversies because of the poor coupling between "race", genetic setup and drug response.[42] This highlights the importance of broad representation, including individuals from different ancestral, social and cultural backgrounds, in clinical trials when developing new precision medicines.[43] Unfortunately, this is currently far from the reality, as regulating authorities do not encourage drug-developing companies to enroll patients from minorities and the companies themselves fail to do it voluntarily.[44]

One application of DNA analysis that would probably benefit from more public discussion is direct-to-consumer genetic health tests. The low cost of genetic sequencing has led to the emergence of a consumer market and genetic tests are now offered directly to anyone who is interested in knowing if they carry any predisposition for genetic diseases. The tests are often based on analysis of only one or a few genes, which is one of the reasons for concern since most genetic diseases cannot be traced back to a

[42] Bonham VL, Callier SL, Royal CD. Will Precision Medicine Move Us beyond Race? *The New England Journal of Medicine* **374**, 2003-2005 (2016).

[43] Newkirk II VR. Precision Medicine's Post-Racial Promise. *The Atlantic* (June 8, 2016) Available at: https://www.theatlantic.com/politics/archive/2016/06/precision-medicine-race-future/486143

[44] Chen C, Wong R. Black Patients Miss Out on Promising Cancer Drugs. *ProPublica* (Sep 19, 2018). Available at: https://www.propublica.org/article/black-patients-miss-out-on-promising-cancer-drugs

single mutation or allele (variant form of a gene). The genetics involved in the development of a specific disease are often extremely complex and associated with variations in several genes; new details on the connections between different genes and gene functions are constantly being revealed. Environment, lifestyle and other factors also come into play in the development of many diseases, which moves the genetic setup into the realms of probability only. Therefore, some scientific communities oppose access to some of these tests, arguing that they fail to deliver meaningful results[45,46,] and that consumers face challenges in understanding the results.[47,48] The market is still partly unregulated but, in 2010, the FDA established that genetic tests claiming to predict inheritable diseases should be considered as medical devices and treated accordingly. In 2017, 23andMe was the first company to get market approval for such tests in the U.S. and, when granting the market authorisation, the FDA clarified that the tests were only approved for genetic risk testing, not for diagnostic tests. In Europe, the regulatory situation is unclear and differs between countries since there is a lack of common EU legislation addressing the issue.[49] All existing European guidelines on direct-to-consumer genetic tests in 2015 were reviewed in an overview published by Boccia et al.[50] In the discussion, the authors concluded that the general opinion among professional societies and associations is that there are disadvantages associated with the direct-to-consumer genetic tests, more research as well as education of both consumers and healthcare professionals are needed, and more research efforts are needed to integrate public health genomics into the healthcare system.

Strong market forces drive the development of this area; tests are also sold to give information on, for example, how to eat or how to reveal one's fitness potential, tests that deliver highly questionable results due to poor coupling to the scientific understanding of genetics.[51] It is suggested that the scientific community could raise general awareness about what a genetic test can actually reveal, based on the current scientific understanding of genetics, and what is still unchartered territory where available genetic tests fail to deliver scientifically sound conclusions. This could help to nuance the expectations that people in general have of genetic testing and help develop the field into a direction that really can be of benefit for individuals seeking knowledge about their genetic setup and its implications.

Protein drugs

Another application of gene technology in medicine is genetic engineering to produce drugs. The company Genentech was founded soon after the recombinant DNA technique was presented in the early 1970s. This was the first company that aimed to develop therapeutic proteins using genetic engineer-

---

[45] Hesman Saey T. What consumer DNA data can and can't tell you about your risk for certain diseases. *ScienceNews* (June 3, 2018). Available at: https://www.sciencenews.org/article/health-dna-genetic-testing-disease

[46] Evans JP, Green RC. Direct to consumer genetic testing: Avoiding a culture war. *Genetics in Medicine* **11**, 568-569 (2009).

[47] Moscarello T, Murray B, Chloe M, et. al. Direct-to-consumer raw genetic data and third-party interpretation services: more burden than bargain? *Genetics in Medicine,* published online ahead of print, doi:10.1038/s41436-018-0097-2 *(*2018).

[48] Wang C, Cahill TJ, Parlato A, et al. Consumer use and response to online third-party raw DNA interpretation services. *Molecular Genetics & Genomic Medicine* **6**, 35-43 (2018).

[49] Kalokairinou L, Howard HC, Slokenberga S, et al. Legislation of direct-to-consumer genetic testing in Europe: a fragmented regulatory landscape. *Journal of Community Genetics* **9**, 117-132(2018).

[50] Rafiq M, Ianuale C, Ricciardi W, Boccia S. Direct-to-consumer genetic testing: a systematic review of european guidelines, recommendations, and position statements. *Genetic Testing and Molecular Biomarkers* **19**, 535-547 (2015).

[51] Robbins R. Genetic tests promised to help me achieve peak fitness. What I got was a fiasco. *STAT* (Nov 3, 2016). Available at: https://www.statnews.com/2016/11/03/genetic-testing-fitness-nutrition

ing and in 1978 they took part in the pioneering work of producing insulin using genetically engineered *Escherichia coli*. Genentech partnered with Eli Lilly and company to commercialise their synthetic insulin, which was approved in 1982, making it the first-ever recombinantly produced therapeutic to be approved. Since then, protein drugs have become an increasingly growing and important class of drugs. The recombinant versions of natural proteins were soon followed by proteins purposefully modified to increase their clinical potential with enhanced effect, greater safety, reduced immunogenicity and improved methods of delivery.[52]

Today, protein drugs make up most of the so-called biological drugs or biologics - drugs containing an active substance that is produced in, or extracted from, biological sources. This contrasts with synthetic substances produced using traditional chemistry. Biologics are becoming increasingly important. In 2017, the FDA approved 46 new drugs in the U.S; of these, 12 were biologics.[53] The share of the total pharmaceutical market that biologics hold increased from 16 % in 2006 to 25 % in 2016, and last year four of the five top selling drugs were biologics.

In contrast to the public and often politicised debate on GM crops, there is no similar discussion on the development and use of genetically engineered organisms intended for drug production, even though the same tools and principles are used when developing a draught-resistant crop or an insulin-producing bacterium. There is also no similar legislation that bans the use of non-human genetically engineered organisms in a medical field.

One obvious reason for this difference is that GM crops are cultivated in open farmlands, with a greater potential for spreading through the environment, compared to protein-producing cells that are contained in bioreactors, i.e. the ability to control the genetically engineered organisms differs. However, other differences also come into play here, differences that are related to issues like access to alternative products and how people relate to different products. In the case of GM crops, they can be seen as improved versions of already existing crops, meaning that non-GM crops always exist as alternatives. In contrast, new drugs are developed as treatments for which there are no real alternatives. Perhaps as a result of that, the societal need for new drugs could appear to be more obvious, even though some of them prolong the life of cancer patients by only a couple of weeks, while GM crops holds potential to transform agriculture to a more sustainable industry that is better equipped to meet climate change on a global scale. From a legal perspective, another reason for the difference between how GMO crops versus medicine is perceived could be that there was already a regulatory system for drugs in place when protein drugs were introduced on the market. For crops, there was no similar system in place when products were ready for the market. These discrepancies seem to have had an effect on public opinion regarding where and when genetic engineering is acceptable.

Gene therapy

Gene therapy is yet another application of gene technology in medicine. Gene therapy refers to the modification of a patient's DNA in order to treat a disease-causing defect. The term gene therapy was first introduced in 1972[54] and, in 2003, China approved Gendicine (Shenzhen Sibiono GeneTech), the

[52] Carter PJ. Introduction to current and future protein therapeutics: A protein engineering perspective, *Experimental Cell Research* **317**, 1261-1269 (2011).

[53] FDA. CY 2017 CDER New Molecular Entity (NME) Drug & Original BLA Calendar Year Approvals. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM595049.pdf [accessed on Oct 16, 2018].

[54] Friedmann T, Roblin R. Gene therapy for human genetic disease? *Science* **175**, 949-955 (1972).

world's first commercially available gene therapy.[55] In 2012, Glybera (uniQure), used to treat the ultra-rare condition lipoprotein lipase deficiency, became the first gene therapy to be approved in the western world after its endorsement by the European Commission.[56] When introduced onto the market, it also became the world's most expensive drug in history with a price tag too high to let it fly,[57] and the product was later withdrawn from the market. In 2017, a gene therapy called Kymriah (Novartis) was the first to get approval on the U.S. market and is expected to soon get approval in the EU. It is an immunotherapy for leukaemia in which T cells, part of the immune system, are removed from the patient, genetically modified in a laboratory to allow them to recognise cancer cells, and then put back into the patient to attack the cancer cells. This form of therapy is called CAR T-cell therapy, where CAR stands for *chimeric antigen receptors,* the genetically engineered feature on the surface of the T-cells that recognises the cancer cells. In many cases the result is highly effective, and this type of gene therapy is believed to be a game changer for many other cancer forms. As always, therapies are associated with certain side effects and this type of immunotherapy has been shown to sometimes cause *cytokine release syndrome,* a type of systematic inflammatory response where the patient needs intensive care. CAR-T cell therapies are so far showing promising results, but because of both high development costs and the involvement of advanced hospital procedures, the costs are high compared to other treatments. Kymriah has been priced at $475 000 per treatment (patients are only treated once) and this does not cover the costs associated with the care of the patient, including the hospital stay and treatment for side effects.[58] The high costs associated with gene therapy indicate a need for new pricing models, such as pay-per-performance, where pharma companies are not paid up-front but are paid according to the clinical performance of their product in treated patients.

To date, almost 2 600 gene therapy clinical trials have been completed, are ongoing or have been approved worldwide. With the hundreds of new gene therapies now in clinical trials we can expect several new therapies on the market in the coming few years. This offers new possibilities to save lives, but at the same time will put high pressure on healthcare budgets. Healthcare systems need to be prepared to handle these new challenges and may face some tough prioritisation.

New gene therapies hold great promise for many patients suffering from cancer as well as various chronic diseases. The use of gene technology to alter human DNA may be controversial, especially since it may in the future come to be used for non-therapeutic human enhancement and the birth of so-called designer babies where human embryos are genetically edited for desired traits and capabilities.[59,60]. The consensus in the scientific community is that genome editing should be limited to so-called somatic cells, i.e. not egg and sperm cells. These changes would affect only certain tissues and are not passed from one generation to the next, while changes made to genes in egg or sperm cells (germline cells) or to genes in an embryo could be passed on to future generations. Concerns about

---

[55] Pearson S, Jia H, Kandachi K. China approves first gene therapy. *Nature Biotechnology* **22**, 3–4 (2004).

[56] Richards S. Gene Therapy Arrives in Europe. *The Scientist* (Nov 6, 2012). Available at: https://www.the-scientist.com/news-opinion/gene-therapy-arrives-in-europe-40230.

[57] Regalado A. The World's Most Expensive Medicine Is a Bust. *MIT Technology Review* (May 4, 2016). Available at: https://www.technologyreview.com/s/601165/the-worlds-most-expensive-medicine-is-a-bust.

[58] Hernandez I, Prasad V, Gellad WF. Total Costs of Chimeric Antigen Receptor T-Cell Immunotherapy. *JAMA Oncology.* 4, 994–996 (2018).

[59] Lanphier E, Urnov F, Haecker SE, et al. Don't edit the human germ line. *Nature* 519, 410-411 (2015).

[60] Ball P. Designer babies: an ethical horror waiting to happen? *The Observer* (Jan 8, 2017). Available at: https://www.theguardian.com/science/2017/jan/08/designer-babies-ethical-horror-waiting-to-happen

ethics and safety mean that germline cell and embryo genome editing are currently illegal in most countries.

Scientific opinions are in line with public opinions on this matter but, with the introduction of new technologies like CRISPR-Cas9, the means to perform alterations on genetic material has never been more accessible (kits is sold to anyone in webshops). This could be seen as a democratisation of technology, but it also means that people without a scientific background could do genetic modifications in different organisms, which could spread in nature, or could approach the area of gene editing in human DNA. People who might not adhere to the general consensus of restricted use of these technologies could already today experiment gene editing on human DNA. This has been raised as a concern, in both the DIY biohacking community[61] and the scientific community, and a new annual conference called CRISPERcon has recently been established to discuss these issues with representatives from academia, industry, government agencies, civil society and elsewhere.[62,63]

Looking ahead

Technology is developing at an extremely rapid and increasing pace. Gene technology is one example where the advancements have made it possible to fight deadly diseases in new ways. Scientific efforts such as the Human Genome Project (1990-2003), which mapped human DNA, and the Swedish-based research project Human Protein Atlas (ongoing), which aims to map all human proteins, have revealed connections between DNA composition, gene expression patterns and diseases, giving insight into areas such as how to better tailor gene therapy treatments. In order for this to reach its full potential and to let patients take advantage of the discoveries, the discussion on *what* should be done, *how* it should be done, and *what the cost* should be, should be held in public. The scientific community has an important role in explaining both possibilities and risks, and in helping to sort out which discussion topics are important and relevant. If the obvious benefits of using new gene technology to fight diseases get overshadowed by the discussion about e.g. designer babies, there is risk that we will get legislation that restricts research efforts to fight disease.

Technological breakthroughs precede legislation and, to take full advantage of new possibilities, the legislation process should be carried out in parallel with an open, transparent, public discussion. The scientific community can help to keep this discussion science-based and focused on issues that favour the sustainable development of our society. If scientists neglect to disseminate information through schools and in public debate, the chances are that the discussion of some aspects of new technologies will not be based on facts but on opinions, as occurred with the discussion of GM crops.

The future depends on our ability to understand and assess the benefits and risks of new technologies, to weigh them intelligently, and to discuss them transparently – and then to base our decisions and

---

[61] Brown KV. What Does an Infamous Biohacker's Death Mean for the Future of DIY Science? *The Atlantic* (May 5, 2018). Available at: https://www.theatlantic.com/science/archive/2018/05/aaron-traywick-death-ascendance-biomedical/559745

[62] Molteni M. CRISPR Fans Dream of a Populist Future for Gene Editing. *WIRED* (Aug 18, 2017). Available at: https://www.wired.com/story/crispr-fans-dream-of-a-populist-future-for-gene-editing/?intcid=inline_amp

[63] Molteni M. CRISPR Fans Fight for Egalitarian Access to Gene Editing. *WIRED* (June 6, 2018). Available at: https://www.wired.com/story/crispr-fans-fight-for-egalitarian-access-to-gene-editing/amp?__twitter_impression=true

regulations on the available facts. Thus, an important role for the scientific community is public outreach, where new scientific understandings are readily made available to the general public.