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Learning from other Domains to Advance AI Evaluation and Testing

We are grateful to the authors of the enclosed expert report, which forms part of a broader series commissioned by Microsoft.

These reports were commissioned as part of Microsoft's effort to draw lessons from other domains to strengthen testing and evaluation as a cornerstone of AI governance.

The insights contained in this report reflect the authors' independent analysis and expertise. The views expressed are those of the authors alone.

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GOVERNANCE OF GENOME EDITING IN HUMAN THERAPEUTICS AND AGRICULTURAL APPLICATIONS

January 2025

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Prepared for Microsoft

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1. INTRODUCTION: GENOME EDITING AND ITS GOVERNANCE IN CONTEXT

Genome editing in its current form burst upon the scientific scene most vividly with the 2012 publication of a landmark paper by Jennifer Doudna, Emmanuelle Charpentier and colleagues.[1] It was quickly apparent that this approach to genetic alteration *i.e.* controlled change to DNA sequences, which is more precise than earlier methods due to the use of a programmable, bacterial enzyme called Cas9, had tremendous potential across a wide variety of applications in multiple species, ranging from industrial processes to agricultural innovations to drug and gene therapy development.[2]

Responses to proposed uses of genome editing have been influenced by how genome editing is itself framed as a practice*, i.e.,* what genome editing is considered to *be*. Some saw its use in agriculture, for example, as continuous with pre-modern breeding techniques, which themselves exploited naturally occurring genetic variation in selective breeding for improved traits. Others focused on discontinuities, seeing genome editing as a modern *biotechnology*, which raises questions about whose interests are served by its use and the broader impacts of such technology on society.[3] However genome editing was described, the need for attention to attendant ethical issues and appropriate governance immediately became apparent, particularly in the case of contentious uses, such as heritable changes to the human genome.[4]

Governance encompasses formal governmental controls embodied in legislation, regulation, and court decisions, often taking the form of permitting and registration processes. This is often referred to as hard law or hard regulation. But it also takes the form of soft governance, which includes a broad range of influences over the incentivization, research, development, and deployment of technologies. It begins with the factors that influence when and where research is done, such as funding priorities and conditions, e.g., ethical limitations on source materials like human embryos or other human tissue. It also includes norms from professional bodies, voluntary codes/standards or even consumer pressure, such as the tendency in recent years to steer away from animal testing in cosmetics whenever possible. And once in the market, the presence or absence of health insurance coverage may strongly affect the

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[1] Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science. 2012 Aug 17;337(6096):816-21. doi: 10.1126/science.1225829. Epub 2012 Jun 28. PMID: 22745249; PMCID: PMC6286148.

[2] Doudna JA, Charpentier E. Genome editing. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014 Nov 28;346(6213):1258096. doi: 10.1126/science.1258096. PMID: 25430774.

[3] For a discussion of such matters see section 1 of the Nuffield Council on Bioethics report 'Genome Editing: an ethical review'. https://cdn.nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf

[4] Baltimore D, Berg P, Botchan M, Carroll D, Charo RA, Church G, Corn JE, Daley GQ, Doudna JA, Fenner M, Greely HT, Jinek M, Martin GS, Penhoet E, Puck J, Sternberg SH, Weissman JS, Yamamoto KR. Biotechnology. A prudent path forward for genomic engineering and germline gene modification. Science. 2015 Apr 3;348(6230):36-8. doi: 10.1126/science.aab1028. Epub 2015 Mar 19. PMID: 25791083; PMCID: PMC4394183; Lanphier E, Urnov F, Haecker SE, Werner M, Smolenski J. Don't edit the human germ line. Nature. 2015 Mar 26;519(7544):410-1. doi: 10.1038/519410a. PMID: 25810189.

rate of diffusion into a patient population, and the threat of liability (and availability of liability insurance) may strongly affect how a technology is packaged, marketed, and monitored. In sum, governance comprises a broader set of mechanisms than statutory regulation and includes both hard and soft law instruments.

This paper describes the governance approaches taken by the US, UK, and European Union authorities, which in all cases reflect their respective approaches to biotechnology governance more generally. Genome editing has simply been folded into existing regimes, albeit at times with the need to address novel questions about how to identify and assess specific risks. That said, due to genome editing's capacity to either mimic or alter existing forms in nature, these regulatory regimes are increasingly being amended to allow for more nuanced predictions about the likely effects of an edit, whether on human and animal health or on the environment.

Despite this evolution in approaches, broadly speaking the US has taken an approach to biotechnology – including genome editing – that focuses on assessing risks and benefits of the end product, whether pharmaceutical or agricultural, and uses the same existing product-category regulations regardless of whether genome editing has been used in development or production. By contrast, the EU has adopted a more overarching precautionary approach in which all non-pharmaceutical products developed with modern biotechnology – including genome editing – are subject to a comprehensive review scheme triggered by use of modern biotechnology techniques for genetic manipulation – a so-called 'process-based' approach. As a former member of the EU, the UK continues to utilize the same regulatory approaches based on assimilation of EU law post-exit, but divergence is now possible and likely, notwithstanding inevitable constraints imposed by the requirement to continue trading with the EU.[5] This paper offers overarching observations about the distinctive choices concerning whether and how an emerging technology such as genome editing is regulated, which may provide insights into the effects on speed of development and commercial deployment, as well as risks and benefits that uses of a technology may generate over time. It uses gene drives as an example, given some of the parallels between this technology and artificial intelligence. Other applications, such as pharmaceuticals and foods, are noted but not explored in depth.

2. PROCESS-BASED VS PRODUCT-BASED REGULATION

Regardless of whether one is speaking of soft or hard governance tools, a fundamental choice is whether to focus on governing the technology *per se* or on specific applications and products of the technology. The former has the advantage of leading to a more easily grasped overall governance approach, such as a single comprehensive legislative scheme to govern all applications, often within a

[5] For example, see the proposals for pro-innovation regulatory reform in the UK in the recent report on the PAGIT Framework: https://www.bsigroup.com/siteassets/pdf/en/insights-and-media/insights/white-papers/bsi_pagit_v3.pdf

single regulatory entity. Such simplicity is often attractive to regulators. It also has the advantage of permitting a focus across applications on the unique aspects of a technology that have generated its specific capacities or attributes. One example might be nanotechnology, where the size of a nanoparticle and subsequent change in surface area to volume ratio may lead to a consistent change in chemical properties across multiple applications.

The disadvantage of this approach, however, is that such changed properties (or other attributes of a technology) may have very different effects on risk-benefit ratios or other typical regulatory considerations, depending upon the specific application. This was one reason why the US chose, in the 1980s, to take this latter approach to the emerging area of biotechnology, when it adopted the so-called 'coordinated framework' to survey existing regulatory agencies and specify when and how their jurisdiction applied to products produced with this new technology.[6]

In addition, the US in the 1980s was in the midst of the Reagan revolution, a period in which great emphasis was placed on de-regulation in favor of free market controls.[7] The creation of a wholly new bureaucratic procedure to govern biotechnology qua biotechnology was not consistent with the prevailing anti-government, anti-regulatory zeitgeist. By contrast, the EU was, and is, characterized by a greater general acceptance of the central role played by government in ensuring its citizens are protected against the harmful impacts of biotechnology (and commercial interests more broadly). The UK, perhaps, oscillates between these positions. In general, despite the value of 'regulatory science', it is worth remembering the historical, political, and cultural determinants of regulatory policies.

The coordinated US framework proved workable, provided the results of biotechnology processes remained recognizably familiar as drugs or pesticides or other regulated products, and thus the framework remained unchanged until updated nearly 30 years later. But over the years, examples of products that fit only awkwardly within existing statutory regimes began to accumulate. One example is found in genetically altered animals, where the regulated "article" per the FDA governing statutes was not the altered animal itself but rather the genetic construct used to introduce alterations, a construct that would be reviewed and approved as an "animal drug." While this did allow for the necessary premarket review of the safety of construct, both for the animal and for any other animal or any human that ate the altered animal, and allowed for environmental assessments of any ecological consequences, it failed to reflect the need for a better coordinated review of the safety and aesthetics (e.g. taste, texture, reaction to storage or various cooking techniques) of the altered animal alongside other considerations, such as the inherent dignity of animals or the importance of traditional species traits, and indeed whether the alteration necessitated changes in labeling and naming/categorization of any

[6] David T. Kingsbury, "Regulation of biotechnology in the United States: One and a half years of using the 'coordinated framework'" Trends in Ecology and Evolution, Volume 3, Issue 4PS39-S42 (April 1988)

[7] Abner Mikva, "Deregulating Though the Back Door: The Hard Way to Fight a Revolution" 57 Univ of Chicago Law Review 521-541 (1990).

resulting foods. This was one of the challenges that led to the lengthy delay in FDA approval of the first genetically engineered Atlantic salmon.[8]

Another example of a product of modern biotechnology failing to fit comfortably within existing statutory authorities would be engineered microbes for environmental release (EMERs). In a 2024 study by the Linde Center at the California Institute of Technology, EMERs were identified as having either tortuously complicated regulatory pathways or having no pathway to approval at all.[9] The Linde study cites gaps in authority and expertise among EPA, FDA, and USDA, and claims that the Coordinated Framework's focus is exclusively on facilitating entry of products into the market while limiting risks to health and the environment, but it fails to attend to the full range of ecosystem effects and need for ongoing surveillance. Further, the study notes that the US regulatory statutes do not capture "ethical tradeoffs and goals" and that these laws "do not allow or require consideration of the broader harms or benefits of deploying EMERs. Instead, they largely focus on either keeping things as they used to be, minimizing human intervention, or maximizing yield of a particular favored resource."[10]

In sum, in the US, one cannot easily summarize "how" biotechnology or any particular kind of biotechnology - such as genome editing - is "governed." Rather, one must ask "how does the US govern the development of therapeutic medical products that are produced using genome editing?" or "how does the US govern the introduction to market of foods produced or altered using genome editing?" The 2017 version retains the application-specific approach, focusing on clarifying ambiguities and overlaps in agency jurisdiction, particularly over new kinds of applications.[11]

That said, there is an increasing emphasis on risk-based governance within the constraints of existing statutes, often by distinguishing products made by genome editing that still resemble those that could be made with more traditional technologies from products made by editing (or other modern biotechnology processes) that could not realistically be found in nature or could not be made with conventional methods. Building on this distinction, the SECURE Rule governing genome editing in plants (discussed in Appendix B) exempts certain modified plants from regulation when they could have been produced through conventional breeding and are not expected to pose greater plant-pest risks than their conventionally bred counterparts. These exemptions draw on the long track record of plant breeding, which offers extensive evidence that such risks can be managed safely. This streamlined

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[8] https://www.fda.gov/animal-veterinary/intentional-genomic-alterations-igas-animals/aquadvantage-salmon

[9] Marken, J.P., Maxon, M.E., and Murray, R.M. "Policy Recommendations for the Regulation of Engineered Microbes for Environmental Release." Linde Center for Science, Society, and Policy, Caltech. June 2024. doi: 10.57959/bgny-v542 (Caltech, June 28, 2024).

[10] Marken, supra, excerpting from Alejandro E. Camacho & David Dana, A Missed Opportunity to Address Ecological Risk from Emerging Biotechnologies: President Biden's Executive Order on a "Sustainable' Bioeconomy and an Agenda for Future Reforms, 85 Ohio St. L. J. (forthcoming 2024-2025).

[11] https://www.epa.gov/sites/default/files/2017-01/documents/2017_coordinated_framework_update.pdf

process encourages innovation by reducing regulatory burdens for developers of genome-edited crops. In these cases (discussed below), lack of familiarity with the end product or the platform technology becomes a proxy for a *presumption* that the product must be unsafe until proven otherwise or such safety concerns are offset by sufficiently compelling benefits. This can influence whether to require assessment and government approval of a product before it can be marketed (a pre-market approach) versus relying primarily on post-market monitoring. More dramatically, the authors of the above-cited Linde study have called for a more centralized biotechnology authority, echoing some aspects of the EU approaches, when they write: "Congress should establish and fully fund an Environmental Biotechnology Regulatory Office (EBRO) with a "special regulatory authority" to develop new risk assessment frameworks and grant regulatory approval for EMERs that fall outside of clear jurisdictional boundaries of the existing regulatory agencies."[12]

In contrast to the US, the EU has at times taken the former, more comprehensive approach, choosing to treat all applications of recombinant DNA methods (genetic modification (GM)) as subject to an overarching regulatory scheme, such as foods developed from GM organisms (GMOs).[13] The EU had followed a largely product-focused regulatory scheme through the 1970s but altered its approach with the advent of recombinant DNA technologies, prompted, according to some scholars, by the following concern: "The new techniques of genetic engineering allow the identification of many useful genes and their transfer to other organisms that didn't possess them before. Biological barriers are by-passed, and new organisms are created with novel properties not previously existing in nature. Micro-organisms with novel properties could cause adverse effects in the environment if they survive and establish themselves, out-competing existing species or transferring their novel traits to other organisms."[14] The move toward a more 'process-based' regulation uses an initial trigger for regulatory capture based on the technology platform or enabling technology that generated the product. Whether and how a product is captured by a regulatory scheme, for example how early in its life cycle and in what way, can have a major influence on the probability of its reaching market and its subsequent trajectory.[15]

Complicating this approach, some new technologies create confusion about whether they fundamentally alter the categories used in earlier schemes. For example, genome editing may or may not be in the same category as earlier forms of genetic engineering. This may become pertinent when deciding whether to place something in the presumed safe *vs* presumed dangerous regulatory category. Genome editing can make changes that do not require insertion of 'foreign' DNA sequences, otherwise

[12] It should be noted that the results of the 2024 presidential election in the U.S. suggest that creation of a new regulatory authority is extremely unlikely under the administration being sworn into office in January 2025.

[13] https://www.efsa.europa.eu/en/topics/genetically-modified-organisms

[14] Patterson and Josling, citing European Commission. DG XI/A/2 Biotechnology. The European Community and the Contained Use of Genetically Modified Micro-organisms. Brussels: CEC, n.d.

[15] Technology readiness levels (TRLs) are one way to indicate the stage of the life cycle that a product might be at. https://www.defproc.co.uk/analysis/technology-readiness-level-trl-explained/

unknown in a particular species, so an altered organism may not be "transgenic"[16] even though its properties have been changed significantly. Should the fact that it was edited and is cisgenic (*i.e.,* only has genes found in other members of that same species) mean it is in a different category and/or presumed safe while transgenic organisms are presumed dangerous? Indeed, should a genome edited crop that contains no foreign DNA be regulated in the same way as a counterpart produced by traditional breeding methods, which itself can itself introduce multiple random changes into a genome through techniques such as chemical mutagenesis? The EU and UK authorities have wrestled with these questions in recent years. The problem points to the importance of choosing definitions, such as "GMO" or "genetically engineered" that serve a particular purpose, and in recognizing that for different purposes it may be necessary to use different definitions and categories.

The EU regime is associated with a slower, more cautious approach to novel technologies and products. The process-based, more precautionary attitude toward genome editing and biotechnology in the EU "puts a priority on anticipating and guarding against environmental damage [and] is based on preventive action to safeguard ecological space (even in advance of scientific proof or need), … places the duty of care (or onus of proof) on those who propose change … [and] does not take into consideration the relative costs and benefits of regulation to industry and the public."[17] In theory, it might also engender a greater degree of public confidence in the safety and benefits of approved products, but at least with respect to engineered (and genome edited) foods, this has not appeared to be the case, and in fact, the comprehensively cautious approach may have reinforced public skepticism about these products. One academic paper traces some of this to underlying cultural and historical forces that distinguish US and European consumers: "The European traditions of an aesthetic appreciation for food, a skepticism toward science wrought of destruction by military and Fascist technology, and a protection of domestic markets, stand in marked contrast to scientific and utilitarian attitudes toward food, a scientific optimism unscarred by war, and general support for free markets and trade in the United States."[18] On the other hand, public skepticism toward bio-engineered foods may lie in how their primary benefits are largely hidden from consumers, accruing instead to producers and shippers. By contrast, public support for drugs and therapies using modern biotechnology appears to be strong in all jurisdictions, perhaps due to the visibility of their benefits for patients with serious diseases.[19]

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[16] Cisgenesis is the genetic modification of a recipient with a naturally occurring gene from a crossable – *i.e.*, sexually compatible - organism. Transgenesis is the genetic modification of a recipient with one or more genes from any donor species (closely related or not) that is sexually incompatible with the recipient.

[17] LE Patterson and T Josling, Regulating Biotechnology: Comparing EU and US Approaches, http://aei.pitt.edu/28/1/TransatlanticBiotech.pdf, in A Jordan, ed., ENVIRONMENTAL POLICY IN THE EU (London; Rutledge) (2005). eBook ISBN 9781849771221

[18] C.F. Runge, G.L. Bagnara and L.A. Jackson, "Differing U.S. and European Perspectives on GMOs: Political, Economic and Cultural Issues" Estey Centre Journal of International Law and Trade Policy Volume 2 - Number 2 (2001).

[19] https://geneticliteracyproject.org/gmo-faq/why-is-there-controversy-over-gmo-foods-but-not-gmo-drugs/

It is also possible that genome editing raises concerns simply because it involves controlled alterations to DNA, a molecule that is increasingly portrayed in popular culture as the 'blueprint' for life, making human DNA in particular the closest 20th century equivalent to the soul. Accordingly, genetics, genomics, and genetic alteration in almost any context can stir deeply held feelings and commitments. In sum, while it is possible to operate either process- or product-based systems with varying degrees of precaution, as a rule, one regulatory approach is process-based and somewhat more precautionary, with a horizontal integration that focuses on all possible applications of a particular technology. Another is product-based, with more focus on traditional risk-benefit preventive strategies. But as noted *infra*, the phenomenon of novelty, coupled with the self-propagating characteristic of many engineered organisms in the environment, are leading even product-based systems to move toward a more risk-tiered system. It seems that the adoption of either regulatory approach is consistent with varying degrees of precaution in practice.

Table: Alternative Models of Regulation Used for Biotechnology (including genome editing) [20]

Philosophy of Regulation	Precautionary: Proactive regulatory approach anticipates environmental hazards that have not already been documented but which could conceivably occur.	Preventive: Reactive regulatory approach attempts to minimize environmental harm whenever the existence of harm has been scientifically demonstrated.
Basis of Regulation	Regulation based on process by which product is produced.	Regulation based on safety, quality, and efficacy of product regardless of method of production.
Type of Regulation	Horizontal Regulation: Cross-cutting regulations need to be adopted to insure a basic level of human and environmental safety.	Vertical Regulation: Existing sectoral regulations modified to insure human and environmental safety of new biotech products.

3. PREMARKET, POSTMARKET, AND TIERED REGULATORY APPROACHES

For many regulatory systems, another fundamental choice is whether to treat a technology or an application category as presumed to be dangerous until shown to be sufficiently safe, versus presumed to be safe until shown to be unduly dangerous. For those presumed to be dangerous, market entry is refused until some application to an independent entity results in an approval for sale. In the US, for example, new drugs may not be introduced into the market until approved by the Food and Drug

[20] Adapted from Patterson, Lee Ann. "Biotechnology Policy: Regulating Risks or Risking Regulation," in Policy-Making in the European Union, 4th Edition, edited by Wallace, Helen and William Wallace. Oxford: Oxford University Press, 2000., as presented in LE Patterson and T Josling, "Regulating Biotechnology: Comparing EU and US Approaches" http://aei.pitt.edu/28/1/TransatlanticBiotech.pdf, in A Jordan, ed., ENVIRONMENTAL POLICY IN THE EU (London; Rutledge) (2005). eBook ISBN 9781849771221

Administration (FDA), and indeed, may not even be tested until the FDA has specifically allowed their use under controlled trial conditions. Once evidence of adequate safety and efficacy for a particular indication has been demonstrated to the FDA's satisfaction, the drug may be marketed for that indication.[21]

The advantage of such a premarket approval system is the ability to avoid large-scale injury to members of the public, most of whom are unable to independently assess the risks and benefits of a drug and thus need the help of a regulatory authority to screen out dangerous and/or ineffective products. The disadvantage is the degree to which this slows movement of innovative products to members of the public with unmet need. It also has a market distorting effect, as the need to navigate the regulatory process means that repeat players i.e. incumbents, such as large pharmaceutical companies, have a significant competitive advantage over smaller, one-time players, who are potentially disruptive, which may impede innovation.

By contrast, most new foods in the US go on the market without any pre-market approval process, provided the manufacturer could demonstrate (if asked) that they meet the definition of "generally recognized as safe," which is commonly understood to mean the foods use familiar ingredients and production methods, even if in new ways. A key finding by the US FDA was that modern biotechnology production methods are not intrinsically dangerous, and thus there was no need to treat all engineered foods as in need of premarket approval. A system was developed for voluntary premarket consultation so the FDA would be aware of what was being developed and have an opportunity to register concerns if such a food could not be considered GRAS due to some particular aspect of the engineering used. Once a food is on the market, post-market monitoring is designed to detect problems with food quality, allergens, toxins, or other aspects that might cause injury.

The advantages of this system are the speed and ease of market entry for innovative products, which benefits both producers and consumers. The disadvantage is the risk of injury to multiple members of the public unless and until a causal connection can be traced between a flawed food product and an outbreak of illness. In addition, with respect to bioengineered foods in particular, the lack of stricter premarket controls has exacerbated the mistrust of these foods that already was present within segments of the public, and arguably has fed the misleading belief that non-engineered varieties are safer or more nutritious.

An alternative to either presumptions of danger (accompanied by premarket controls) or presumptions of safety (accompanied by solely post-market controls) are risk-based approaches that do a preliminary assessment of likely danger in a new product and then regulate accordingly. In the realm of agricultural uses, the US regulatory framework has evolved over time from one that treated all animal genome

[21] Professionals may prescribe it for indications beyond the one for which it was tested and labeled, but the company may not actively market it for those extended uses absent additional evidence and approvals from FDA. This creates an incentive for companies to perform those extended tests and so gain market advantages.

editing as presumptively dangerous to one that is now looking to create a risk-based approach in which certain categories of genetic alteration are presumed to be safe absent evidence to the contrary while others are presumed unsafe until proven otherwise. In 2023, the FDA announced risk-based regulatory exemptions for certain low-risk genome-edited animals, such as those with traits that could be achieved through traditional breeding. This effort is designed to reduce regulatory burdens and encourage innovation, particularly for small-scale and academic developers.

For intentional genomic alterations (IGAs) in animals, for example, the US is moving to a more explicitly risk-based approach, adjusting the level of premarket scrutiny to the predicted level of risk that certain manipulations and alterations will present. As noted by the FDA, IGAs in animals "may include random or targeted DNA sequence changes, including nucleotide insertions, substitutions, or deletions, or other technologies that introduce specific changes to the genome of the animal." In addition to the variety of techniques, these changes have a range of intended uses, such as reducing allergenicity or increasing heat tolerance, that pose different kinds of hazards and levels of risk to human and animal health. Looking at the techniques and applications, FDA created three categories of regulatory oversight, with category 1 allowing for free entry into the market and only postmarket monitoring for problems; category 2 requiring notice and some information to the FDA but allowing free market entry provided the agency does not detect a reason to require further information; and category 3, which entails a true data submission, review, and approval prior to market entry. Note the contrast between this risk-based approach (which is akin to the approach used for medical devices) as compared to the more generic presumption of danger and requirement for premarket review and approval for all new drugs in the US. A risk-based approach, involving tiering, is at the center of new UK regulations for the pre-market assessment of foods derived from precision bred organisms *i.e.,* genome-edited organisms that lack transgenes (see Appendix B for further details).

4. RISK ASSESSMENT AND MANAGEMENT

Risk assessment follows a common pattern in all well-regulated jurisdictions. It begins with evaluating hazards[22] to human and animal health and to the environment, involving efforts to quantify the spectrum and magnitude of adverse effects, and the probability of those effects coming to fruition. Next, mitigation measures are identified and incorporated into an overall "risk" assessment that can be used within a regulatory scheme, either one that has absolute levels of acceptable and unacceptable risk or one that relies on a balancing between potential benefits and unescapable risks. These mitigation measures are a form of risk management, using a variety of techniques ranging from surveillance, to public notice and labeling, to reversal and alteration of changes, to development of countermeasures.

[22] A hazard is something that has the potential to harm you. Risk is the likelihood of a hazard causing harm.

Risk management may also include attention to who may develop, market, or deploy an application, for example with requirements for special training and/or certification of professionals who then have exclusive right to use or market the application. Often this will be grounded in a more general licensure scheme, such as limiting prescribing or selling of some medical products to physicians and pharmacists in the US. It can also extend to detailed oversight of how the professionals interact with end users of a product or procedure. One example is the range of powers held by the UK Human Fertilisation & Embryology Authority (HFEA), which regulates in vitro fertilization (IVF) clinics by identifying educational and experiential criteria that must be met by the person responsible at such a clinic, by licensing the clinic to perform certain procedures, and by inspecting establishments to ensure they meet the requirements of the HFE Act and the HFEA's code of practice, with sanctions enforced by a dedicated license committee if necessary. This authority would extend to genome editing applications used in conjunction with human assisted reproduction, if any were ever approved for use.

Risk assessment and management methodologies are complicated by many factors. Chief among them is the absence of the comprehensive underlying data needed to predict specific effects; the inherently subjective nature of evaluating some of these effects; and the uneven distribution of effects within the population or the environment. For example, one hazard associated with genome editing is the possibility of edits being made in unintended and poorly understood areas of the genome. There are yet insufficient data to allow regulators to quantify the likely frequency of this off-target, low predictability event for every type of editing effort. Nor is it yet possible to predict with certainty the health or other effects of every possible unintended edit, let alone the weight that individuals might place upon this uncertainty when deciding whether a particular genome editing therapy is worth trying. And in the environmental context, unintended edits might have deleterious effects that are quite localized, which requires evaluating the significance of harms in the context of the underlying region or population, which may already be disadvantaged and less resilient than others. This complex distribution of risks and potential benefits, therefore, becomes a challenge for any approval process that is grounded in risk assessment and management.

5. TESTING OF PRODUCT SAFETY AND EFFICACY

Risk assessment and management are based on data that emerges from rigorous testing of both platforms and specific applications. While funding policy and some overall bans might address more sociological or ethical concerns, the regulatory focus tends to be on concrete harms and benefits.[23] In the context of human health, testing is aimed at assessing such things as disease prevention and cure, symptom relief, enhanced function, and longevity and stability of benefits accrued, while also looking for evidence of untended effects, unstable effects, lack of efficacy, unpleasant or dangerous side effects (rare and common) and any other adverse event associated with the experimental intervention. In the agricultural context, testing is used to assess the risk of creating unintended genetic alterations affecting

[23] One notable exception may be heritable germline editing, discussed in the appendix, for which concerns about societal impacts may have been the most significant driver of legal prohibitions on the technology, even if it were ever developed to the point of a reasonable risk/benefit ratio.

plant health and growth, the risk of triggering unwanted responses (for example, driving pests to evolve rapidly toward evading the new resistance trait), and the risk of unforeseen effects that pose a threat (for example, introducing a new allergen, toxin, or anti-nutrient). Much of the testing is also aimed at providing evidence of the likelihood of such benefits being realized, and at the stability of the benefit. For example, if a genetic alteration is predicted to confer resistance to a plant pest, then testing is used to see just how much resistance is achieved in the field and whether the resistance is stable over the lifetime of the plant or, in some cases, is heritable and stable across multiple generations of the crop.[24]

Evaluating the frequency and significance of adverse events and side effects is the job of the regulatory agency, but this is made complex due to several factors. First, there may be a gap in available regulatory science, for example, an absence of tools with which to measure the frequency of off-target edits associated with each of the various kinds of editing (conventional CRISPR/Cas9, base editing, prime editing etc.[25]) and the delivery modalities for genome editing (ex vivo *vs* in vivo delivery, choice of vectors such as AAV, lentivirus or lipid nanoparticles, etc.). Second, there may not be enough data on past efforts to evaluate the significance of an off-target effect, which might be benign or problematic. Third, with respect to side effects and adverse events, their significance is highly subjective. For protocols that involve bone marrow transplant for *ex vivo* editing, with its associated hospital stays and unpleasant and risky side effects, patients may have widely varying notions of how serious and unpleasant these are, and regulators may be hard pressed to develop a single objective measure to use when balancing them against potential benefits. But in the end, it is the regulators that will determine whether an acceptable benefit-risk ratio has been achieved (with assistance from advisory committees and commentary from patient representatives) and it is regulatory agencies who will determine whether to approve a genome edited tissue or cell product for marketing.

In the US, the testing regime for pharmaceuticals or cell-based therapies developed using genome editing is the same as that used for all drugs and biologics. The framework is based on a series of laws that were adopted beginning in 1906, with the most recent structural iteration, which required a balance between efficacy and safety, dating back to the 1960s and 1970s. The testing itself may be carried out by government agencies, by government-funded independent investigators, or by the private sector *i.e.*, companies applying to market the product, depending upon the statutory scheme and the jurisdiction. In the US, for example, pharmaceutical companies perform their own research and

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[24] Some of the details of regulation of the products of genome editing in distinct jurisdictions and sectors are surveyed in the Appendices, with a view to highlighting commonalities and differences in approach.

[25] Some accessible videos on different genome editing techniques are available at: https://www.bing.com/videos/riverview/relatedvideo?q=genome+editing+for+beginners&mid=38C9EFAEB11D3E5A05D738C9EFAEB11D3E5A05D7&FORM=VIRE, https://www.bing.com/videos/riverview/relatedvideo?q=prime+editing+explained&mid=4ADFC0E8053B635E2D9C4ADFC0E8053B635E2D9C&FORM=VIRE and https://www.bing.com/videos/riverview/relatedvideo?q=base+editing+explaiine&mid=CAF38B1FA2A033801EEACAF38B1FA2A033801EEA&FORM=VIRE

clinical trials, either in-house or by funding independent investigators, and then submit the data to the FDA, which evaluates the methodology as well as the results. This relieves the government of the unmanageable burden of performing all possible testing itself, leaving it to industry to determine which trials are worth pursuing. But the system does have the weakness of undermining some degree of public confidence, and it is not uncommon to hear expressions of distrust in the safety of pharmaceuticals specifically because the government only oversees testing by a self-interested entity rather than performing the task itself.[26] At least, however, pharmaceuticals are subject to a pre-market review, allowing for detailed scrutiny of the industry tests. Consumer confidence is most vulnerable to being undermined when the products are subject only to voluntary pre-market review or solely post-market review, as is the case for many engineered foods.[27]

The most significant drivers have been periodic scandals and public health catastrophes. The mid-20th century tragedy of babies born with shrunken limbs due to *in utero* exposure to the widely prescribed drug thalidomide led not only to a tightening of evidence standards for safety, but also to a requirement to show efficacy for the intended use, as there is no such thing as absolute safety but rather a need for a judgement call about when a use is compelling enough to offset an irreducible level of risk i.e. when is it *safe enough* to use. Frustration with the time and expense needed to bring new drugs to patients, along with concerns about international competitiveness, led to a series of reforms in the 1980s and into the 21st century that have expanded the categories of evidence that can be submitted to meet agency standards for market approval. In particular, more so-called 'real world evidence' may now be used to supplement sometimes smaller randomized clinical trials, even though real world data may be more difficult to interpret due to confounding factors.

Another innovation, both in the US and Europe, was a mechanism for market approval based on 'surrogate markers,' that is, changes in the body that strongly suggest a clinical benefit will be realized in the future.[28] Approvals on this basis are then subject to post-market surveillance and reporting designed to confirm or refute this prediction, with the EU having a stronger mechanism that the US for rapidly removing a product from market if clinical benefit is not confirmed.[29] There have been multiple amendments since then, but the basic principles have remained the same. The 1990s and early 2000s

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[26] Marc A. Rodwin, Independent Drug Testing to Ensure Drug Safety and Efficacy, 18 J. Health Care L. & Pol'y 45 (). Available at: http://digitalcommons.law.umaryland.edu/jhclp/vol18/iss1/3

[27] https://encyclopedia.pub/entry/28395

[28] Heather McKenzie, "FDA's Accelerated Approval Pathway Drives Momentum for Intractable, Fatal Diseases" December 2, 2024. https://www.biospace.com/drug-development/fdas-accelerated-approval-pathway-drives-momentum-for-intractable-fatal-diseases?utm_term=2ABB28FA-A7B4-4538-B652-B86F698FC955&utm_medium=email&utm_content=64E2A82A-5B45-4774-BEF4-83DD051ED167&utm_source=SmartBrief

[29] Charo, RA. "Yellow lights for emerging technologies" *Science* 2015 Jul 24;349(6246):384-5.

featured FDA's move to clarify its regulation over human cell and gene therapies as part of its regulation of drugs and biologics. Genome editing has slipped into this framework.[30]

In a comparable system, EU law requires each marketing authorization holder and national competent authority to operate a pharmacovigilance system. The overall EU pharmacovigilance system operates through cooperation between the EU Member States, European Medicines Agency and the European Commission and collects information about how drugs function in patient populations. At times, as in the US, a post-authorization safety study (PASS) is required to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for assessing the protocols of imposed PASSs and for assessing their results.

Testing, and evaluation of the resulting data, also requires development of standard definitions and standardized measurements. These may be developed by professional societies or by government agencies. For genome editing, and biotechnology in general, one influential standard setting body is the American Society for Testing and Materials, now known as ASTM International.[31] It produces volumes that set forth standardized definitions, which themselves are developed in accordance with international principles for standards development set forth by the World Trade Organization.[32] Government agencies may also be tasked with developing standardized definitions, tools, and evaluation methodologies. In the US, much of this is done by the National Institute of Standards and Technology."[33] And the European standards are under the responsibility of the European Standardisation Organisations (CEN, CENELEC, ETSI) and can be used to support EU legislation and policies.[34] In the UK, the British Standards Institution (BSI) is the body responsible for producing national and international standards. With respect to pharmaceutical development, the most significant source

[30] An important part of the testing regime focuses on how drugs and biologics work after they have been approved. Post-market data may come from formal clinical trials or other structured experiments using the approved drugs, as a so-called Phase 4 study, or it may come in the form of reporting from patients and physicians who have had side effects, adverse events, or lack of efficacy. This latter set consists of noisy data that can be challenging to interpret but which can generate hypotheses which can be further investigated, either by analyzing possible mechanisms of action or by initiating a Phase 4 study. In either case, it is regulators who will work with the sponsor to design and interpret the data, and regulators who will then decide if there is a need to revise the label (which includes instructions for use, indications and contraindications and dosages), to send a warning letter to physicians or, in dire circumstances, to withdraw approval entirely. https://www.fda.gov/drugs/surveillance/postmarketing-surveillance-programs

[31] https://www.astm.org/about/overview.html

[32] Those principles for developing standards and definitions include transparency, openness, impartiality, consensus, effectiveness, relevance, coherence, and provision for inclusion of those concerns relevant to developing countries. https://www.wto.org/english/tratop_e/tbt_e/principles_standards_tbt_e.htm

[33] https://www.nist.gov

[34] https://single-market-economy.ec.europa.eu/single-market/european-standards_en#:~:text=European%20Standards%20are%20under%20the,support%20EU%20legislation%20and%20policies.

of international coordination for premarket testing is the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which brings regulators and industry together to develop common guidelines on topics ranging from definitions to statistical methodologies.[35]

6. A GOVERNANCE EXAMPLE – GENE DRIVES

Gene drives may have particular salience for those working on governance of artificial intelligence, because both areas suffer from a fear that the technology can become self-driven and elude human control.

Gene drives are a way to introduce a beneficial genetic trait that will act in a 'selfish' fashion, enabled by CRISPR-Cas9, to rapidly diffuse through an entire wild population. There have been proposals to use gene drives in different animals for a variety of purposes, but one notable use that has gained much attention is to combat mosquito-borne diseases. No such gene drive system has been formally approved for release anywhere in the world. However, a related but self-limiting system, which lacks a CRISPR/Cas9 'drive' component, is that produced by UK company Oxitec, known as 'friendly *Aedes',* which is already approved for field trial in Brazil, and alters the genome of male mosquitos so that their female offspring die off before being able to transmit dengue fever through their bites.[36] Gene drives are being designed that can be used to introduce an anti-dengue trait along with another genetic modification that gives the trait a reproductive advantage, so with every new generation of mosquitos, the anti-dengue trait is preferentially passed along rather than the normal 'wild type' trait.[37] Over time, this can alter an entire population, and do it far more quickly than ordinary evolutionary forces. Finally, gene drives may also introduce a female sterility trait into a wild population, dramatically reducing its overall size and therefore its pathogenic potential.[38]

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[35] The ICH grew out of efforts in the 1980s by the European Community to integrate its domestic pharmaceutical approval and marketing systems, and ICH was later joined by other major pharmaceutical regulators such as the US, Japan, and others. The ICH issues detailed guidelines addressing quality assurance, such as the conduct of stability studies, or defining relevant thresholds for impurities testing; safety guidelines on how to identify risks like carcinogenicity; efficacy guidelines for conducting clinical trials; and multi-domain guidelines for things like how to report and transmit data.

[36] Spinner SAM, Barnes ZH, Puinean AM, Gray P, Dafa'alla T, Phillips CE, Nascimento de Souza C, Frazon TF, Ercit K, Collado A, Naish N, Sulston E, Ll. Phillips GC, Greene KK, Poletto M, Sperry BD, Warner SA, Rose NR, Frandsen GK, Verza NC, Gorman KJ and Matzen KJ (2022), New self-sexing Aedes aegypti strain eliminates barriers to scalable and sustainable vector control for governments and communities in dengue prone environments. Front. Bioeng. Biotechnol. 10:975786. doi: 10.3389/fbioe.2022.975786; See also https://www.telegraph.co.uk/global-health/science-and-disease/oxitec-grow-your-own-genetically-modified-mosquito-colony/

[37] Kubendran Naidoo & Shüné V. Oliver, "Gene drives: an alternative approach to malaria control?" *Gene Therapy* (2024)

[38] Hammond et al Gene-drive suppression of mosquito populations in large cages as a bridge between lab and field. *Nature Comm*. 12, article number: 4589. (2021)

As with any potentially powerful technology, gene drives could have unintended consequences, such as spreading beyond the intended local population, or affecting other species that depend on the presence of the wild-type version of the edited population. And because gene drives become self-propagating through the activity of CRISPR/Cas9, there is the risk of one spreading without limit.

For this reason, gene drives are being developed with built-in mechanisms that ensure continued human control. These include techniques to control how quickly the new trait is allowed to spread within the intended population; to stop the gene drive completely; to reverse the gene drive; or to ameliorate the effects of the drive. The controls can be grouped into buckets roughly as: (1) temporal, spatial and reversible control of gene editors; (2) countermeasures and prophylaxis to inhibit off-target effects; and (3) remediation, by removing engineered components and returning the population to baseline.[39] Testing is then done to ensure that these controls are in place and effective before any drive may be commenced outside a controlled laboratory setting.

Governance of gene drives is made complicated by several factors shared with artificial intelligence. First, as noted above, gene drives are self-propagating and so require precautionary measures to be built into the technology or its monitoring systems so that unwanted effects are detectable and correctable by human controllers. Second, gene drive technology is intrinsically indifferent to political boundaries, so transnational cooperation is essential. While gene drives may encounter different situations once a boundary is crossed (such as different kinds of pesticides in use) and artificial intelligence algorithms may run into different kinds of obstacles once a boundary is crossed (such as different levels of transparency in databases), both technologies are capable of functioning across-borders, so where functionality is desired, a cross-border coordination of rules may be necessary. Third, both technologies are potentially transgenerational in their effects, whether biological in the case of gene drives or social (in terms of how information is gathered, analyzed, and distributed for AI), so risks and benefits must be evaluated against multi-generational consequences, which become more uncertain and difficult to estimate the further one goes out in time. Finally, the potential for using gene drives in general arises from a number of ongoing research areas that are not yet solutions. Some will argue that secondary technological solutions to potential problems generated by primary uses of technology threaten a form of infinite regress - with layer upon layer of tech, each of which raises concerns of its own.

At present in the US, gene drives are governed in the same manner as other biotechnological innovations, which is by reference to the application for which they are developed. Those that involve genome editing of insects to prevent disease transmission, such as mosquitos, fall at the intersection of jurisdiction by three agencies, the FDA, the US Dept of Agriculture, and the Environmental Protection Agency. It has been necessary for the agencies to develop memoranda of understanding to clarify which products and applications will be regulated and by which agency. What they have in common, however,

[39] https://www.darpa.mil/program/safe-genes

are regulatory pathways that require pre-market trials to demonstrate safety and effectiveness to the satisfaction of the regulators. An additional element in the US context is the guarantee of an opportunity for community input. This stems from the National Environmental Policy Act, which requires major federal actions (such as approving a gene drive) to be accompanied by an assessment of possible environmental impacts. The assessment is published and made available for comment. If there is sufficient concern that the assessment fails to reflect environmental consequences accurately, the federal action may be challenged in federal court.

While the US has a product-based regulatory process, rather than one regulation covering all things that are made with modern biotechnology, in the end the regulatory pathway can look quite similar for products that are already subject to premarket controls, like drugs and genetic modifications that result in pesticide that are incorporated into the organism itself. For mosquitos, the altered genetic construct that is incorporated into the mosquito, thereby changing the mosquito's characteristics, can be viewed as the equivalent of a drug (though there has been work on moving jurisdiction to EPA by treating the alteration as a form of pesticide).

There are currently no finalized regulations specifically for gene drives in the EU. In the UK, approval by the ACRE committee of the Department for Food and Rural Affairs would be required to permit lawful release of a gene drive, and no such permission has been sought or given at the time of writing. Because gene drives require bacterial Cas9 to propagate, they are considered transgenic rather than merely genome edited (precision bred) - an example of genome editing and transgenesis going together.[40] The fact that GM is involved means that, in Europe at least, there will be opposition to gene drives from NGOs and some publics simply by virtue of the fact they are GMOs, irrespective of additional environmental concerns.[41]

At a global level, the World Health Organization has taken the governance lead with guidelines for gene drive testing and release.[42] Because gene drives do not respect political boundaries, transnational and international governance is particularly relevant. Modified mosquitos are classified as living modified organisms under the Convention on Biological Diversity, and so will be regulated for biosafety according to mechanisms described under the Cartagena Protocol for Biodiversity in the 173 countries that are signatories to the Protocol and as a result, within countries, multiple ministries and departments will

[40] This isn't always spotted - genome editing isn't only about tweaking gene variants - it allows large transgenes to be put into particular parts of a genome e.g., safe harbors.

[41] Some of this opposition is based on a critique of scientific hubris - of scientists allegedly having excessive confidence in their own knowledge and capabilities, which is also relevant to AI. See Andy Greenfield, 25th Anniversary of Cloning by Somatic Cell Nuclear: Cloning, mitochondrial replacement and genome editing: 25 years of ethical debate since Dolly. Reproduction 162(1): F69–F78 https://rep.bioscientifica.com/view/journals/rep/162/1/REP-20-0635.xml?body=article-info

[42] World Health Organization, "Guidance framework for testing of genetically modified mosquitoes, second edition (19 May 2021) https://www.who.int/publications/i/item/9789240025233

collaborate to assess animal and human safety, environmental effects, and human benefit,[43] and performance standards and testing methodologies will need to be developed and harmonized for cross-border governance.

In these countries, it is common to find a unified governance structure for products of modern biotechnology, one that emphasizes premarket controls under the auspices of a biosafety regime that is administered by one or more of the health, agriculture, and environmental protection ministries. As is typical of other regulatory regimes, sponsors must provide safety data to get permits to begin field trials, and then provide evidence of safety, effectiveness for intended use and consideration of downstream environmental effects before being granted permission for commercial use. National systems vary in the degree to which they defer to one another's findings or allow evidence from trials in another country to be used for their own domestic approval processes. And gaps in regulation of gene drives persist due to a lack of coordination among countries and the lack of unanimous agreement to the CPB and CBD.

Further, as noted by the WHO, "Within international conventions that address the transboundary movement of GMOs or exotic agents, and that therefore may apply to [genetically modified mosquitos], there is general consensus that, prior to release into the environment or implementation, there should at least be a notification, as specified in the CPB, but preferably also a bilateral or multilateral consultative process with other countries to which the [genetically modified mosquitos] may move…. Countries that are parties to such conventions must develop their own regulations to implement the requirements. For countries that are parties but without laws or regulations, the CPB describes an Advance Informed Agreement process that would apply prior to the first intentional transboundary movement of GMMs intended for environmental release in the receiving country (Article 7, paragraph 1). An example of how this provision has been implemented in Europe is found under Regulation (EC) No 1946/2003 of 15 July 2003 (26). This regulation aims to set up a common system for notifying and exchanging information on the transboundary movements of GMOs to third countries. The goal is to ensure that movements of GMOs that may have adverse effects on the sustainable use of biological diversity and on human health take due account of
the environment and health."[44]

In sum, for Europe, gene drives fall under the strict regulations for genome edited organisms that were promulgated in 2018 when the European Court of Justice (ECJ) ruled that genome editing shall be regulated under the 2001 GMO Directive that heavily restricts transgenic organisms created using genes from another species,[45] even though most genome editing techniques do not result in the introduction

[43] James SL, Dass B, Quemada H. Regulatory and policy considerations for the implementation of gene drive-modified mosquitoes to prevent malaria transmission. Transgenic Res. 2023 Apr;32(1-2):17-32. doi: 10.1007/s11248-023-00335-z. Epub 2023 Mar 15. PMID: 36920721; PMCID: PMC10102045.

[44] World Health Organization, "Guidance framework for testing of genetically modified mosquitoes, second edition (19 May 2021) https://www.who.int/publications/i/item/9789240025233

[45] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32001L0018

of "foreign" genes.[46] This ruling reaffirmed the EU's regulation of the process used to create genetically engineered seeds rather than the characteristics of the final products, as is the case in the US. If allowed, gene drives will be regulated by the European Food Safety Authority, the EU Commission and EU countries. One of the requirements for the approval of genetically modified animals is a comprehensive environmental risk assessment.

7. CONCLUDING COMMENTS

As noted above, key regulatory choices include the mix of soft law and hard law; regulating the platform technology or each different sectoral application; pre-market controls or post-market controls; or some combination of all these techniques. The upshot is a regulatory ecosystem characterized by complexity, both nationally and (especially) internationally.

The regulation of genome editing occurs against the backdrop of existing sectoral regulatory frameworks and their norms. So, the question is not how genome editing is regulated in some general sense, but rather how considerations of the risks of using genome editing contribute to product assessments in different sectors. Nevertheless, it is possible to extract some common elements of such risk assessments simply by virtue of genome editing being a technology that generates controlled genetic variations, great and small, in almost any species, for different purposes. Ideally, the result is to generate a genome that incorporates a novel, desirable change (or changes) and no others. Desirability will be judged by the intended (plausible) benefits of the genetic change and any associated (anticipated) risks. The ideal genome editing protocol will support this outcome *i.e.*, will have an extremely high degree of specificity for the intended target and no others and will have similarly high on-target fidelity. How much tolerance exists for deviation from this ideal will vary from sector to sector - from embryo to adult human, from crop plant to farmed animal, likely reflecting pre-existing standards and norms of different types.

Genome editing is likely to be most powerful when used in conjunction with other technologies. Engineering biology (synthetic biology) will use genome editing and AI to generate products that have powerful capabilities used to secure potentially beneficial consequences, and which could be employed to combat climate change, support food security, or meet other global challenges. But the power of such technological confluence will also raise concerns - of dual-use, misuse, and unanticipated adverse outcomes. Regulators will need more research on so-called "regulatory science" to better assess the range, significance, and likelihood of off-target effects; to understand where use in one context can provide generalizable knowledge about risks and benefits in a different context; and to make predictions about long-term stability of edits and their effects, among other things. Much of this progress will also require progress in genomics and our understanding of how genomes comprise integrated genetic

[46] This is now under debate, with a proposal to distinguish cisgenic engineered organisms and subject them to a different regulatory regime. https://food.ec.europa.eu/plants/genetically-modified-organisms/new-techniques-biotechnology_en

(informational) systems, such that the consequences of perturbation (mutation) are better understood, *i.e.,* precision in terms of the genomic changes made does not necessarily equate to precision in terms of our understanding of the phenotypic consequences. In addition, there is an inherently subjective element to evaluating risks and potential benefits. While experts may offer an objective measure of the frequency of a side-effect or adverse event, or an objective measure of improvement in a bodily function, patients may vary widely in how much they dislike a side-effect, how much they value an incremental improvement, or how much risk of a serious adverse event is acceptable. Further, there may be politically and ethically significant aspects to the distribution of risks and potential benefits within the population. Thus, regulatory policy will need to be sensitive not only to the recommendations of experts but also to the opinions of the general public - expressed in public dialogues that will place conditions and at times even limits on applications, as the price for public trust and support for innovation in this space.

APPENDICES

APPENDIX A: A CLOSER LOOK AT GENOME EDITING IN HUMANS

Somatic (Non-Heritable) Genome Editing in Humans - US Perspective

Human somatic cell genome editing involves modifying the DNA in non-reproductive cells to treat or prevent diseases. Unlike germline editing, changes made to somatic cells affect only the individual and cannot be inherited by future generations. In the United States, this field receives research funding, often (but not exclusively) from the National Institutes of Health, and is subject to a regulation, primarily under the auspices of the Food and Drug Administration.

While the NIH does not directly regulate therapies, it plays a significant role in shaping policies and funding basic and preclinical research as well as some clinical research. The NIH's Recombinant DNA Advisory Committee (RAC), now part of the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC), provides guidance on genome-editing research, focusing on ethical, safety, and societal implications.

The FDA is the primary federal agency overseeing the development and deployment of clinical use of genome-editing technologies in human cells. Under the Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Service Act (PHSA), the FDA regulates somatic cell therapies as biologics and drugs. Regulation of biologics focuses primarily on infection control and purity/potency evaluations, while regulation of drugs focuses primarily on safety and efficacy for the tested indication.

The agency requires investigational new drug (IND) applications for any clinical trials involving somatic cell genome editing. These applications must demonstrate preclinical safety, manufacturing quality, and preliminary efficacy evidence based on in vitro studies and, in many but not all cases, animal studies. Manufacturers must also comply with Good Laboratory Practices (GLP) for preclinical testing, Good Manufacturing Practices (GMP) for production, and stringent clinical trial protocols.

Most experimental treatments must pass through four main phases of clinical trials before they can be submitted for approval. Each successive phase involves more participants and helps answer critical questions that allow researchers to determine if the experimental treatment is ready to be submitted for approval by the FDA, which is required before it can be marketed to the public.

Clinical trials can only begin with permission from the FDA and under the oversight of an IRB (institutional review board), which evaluates the rigor of the protocols, the appropriateness of the proposed subject population and the content and process of obtaining informed consent from study subjects. Genome-editing trials often require additional scrutiny due to their novel risks and societal implications. Novel risks may include such things as the need for study subjects to undergo onerous chemotherapy to condition bone marrow before stem cells are extracted for ex vivo editing and then returned to the body, a procedure that has its own risks as well discomfort and time spent in hospital, and which may have significant but unavoidable adverse effects such as (in at least one case) causing infertility.

Typically, the four main phases of clinical trials are:

Phase 1 – Assessing metabolism of experimental drug, along with initial safety and dosing testing – this may be done with small numbers (<100) of healthy volunteers or, in some cases, with patients who have the disease of interest
Phase 2 - Evaluating effectiveness and side effects – initial exploration of efficacy and side effects, often with various doses, in relatively small study population
Phase 3 - Confirming efficacy, sometimes compared to standard treatments – large scale, often multi-center trials aimed at confirming efficacy, looking for less common side effects and continuing to explore optimal dosing
Phase 4 - Ongoing study of long-term effects after approval

Following the trials, a New Drug Application (NDA) and a Biologics License Applications (BLA) must be approved before the genome editing therapeutic product may be marketed. The FDA review is assisted by expert advisory committees that work with agency personnel and the sponsors to review the data and evaluate whether the research protocols were rigorous enough to demonstrate that the potential benefits to the patient population outweigh the side effects and risk of adverse events. Genome editing also carries risks of off-target effects and unintended genetic changes. Regulators emphasize minimizing these risks before clinical trials are undertaken, and IRBs emphasize informing study subjects about these uncertainties.

Somatic (Non-Heritable) Genome Editing in Humans – UK/EU Perspective

The use of genome editing to treat a disease - by somatic cell editing ex vivo, followed by reintroduction of engineered cells (as with CASGEVY treatment of sickle cell disease[47]), or delivery of genome editing components in vivo - falls under the classification of an advanced therapy medicinal product (ATMP). The competent authority/regulator for market authorization of an ATMP is the Medicines and

[47] https://www.gov.uk/government/news/mhra-authorises-world-first-gene-therapy-that-aims-to-cure-sickle-cell-disease-and-transfusion-dependent-thalassemia

Healthcare products Regulatory Agency (MHRA), itself sponsored by the Department of Health and Social Care. The MHRA offers scientific advice and has an Innovation Office. All ATMPs must undergo clinical trials, like any other medicine, and the MHRA provides approval for these following an application process. The MHRA assesses the safety, efficacy, and quality of all ATMPs. If an ATMP is combined with a medical device, medical device regulations must also be satisfied. In addition, there is increasing emphasis on including public attitudes and patient perspectives into the analysis of risks, benefits, and justifications for use for innovative cell therapies.[48]

Genome editing safety considerations are the conventional concerns with unwanted off-target and on-target events. In the case of edited cells in vitro, there may be concerns over the potential of off-target events to inactivate tumor suppressor genes or activate oncogenes. There may also be concerns about large chromosome-level events[49] (such as large deletions) caused by error prone DNA repair processes, which may go unrecognized because of the difficulty of detecting them and which may be genotoxic. But the ability to carefully analyze the genome of edited cells - from an expanded population - prior to re-introduction allows optimization of editing components. The use of editors that do not introduce double-strand breaks (base editing, prime editing) may also allay safety concerns. The challenge of controlling the activity of genome editors delivered in vivo is, however, much greater.

The MHRA's functions in the EU are performed by the European Medicines Agency (EMA).

Germline (Heritable) Editing Regulation in the US

Human germline genome editing involves altering the DNA of eggs, sperm, or embryos in a clinical context, with a view to their use in assisted reproduction, introducing changes that can be passed to future generations. Federal funding for research that destroys or puts at risk human embryos has been prohibited since 1996. This ban effectively limits federal support for most research involving germline editing, including pre-clinical studies on embryos or reproductive cells. Except for a few individual states, however, such purely in vitro research is legal and can be funded by non-federal sources, such as philanthropies or individual state funds like CIRM, the California Institute for Regenerative Medicine.

If one wished to pursue clinical research, that is, to transfer edited embryos into a woman for gestation, then FDA has jurisdiction, and the clinical trial could not begin without FDA permission.
But while the FDA has the jurisdictional authority to regulate heritable editing, a 2015 appropriations rider prohibits the FDA from reviewing applications for research that involves germline genetic modifications in embryos intended for pregnancy, effectively halting clinical development in the U.S.

Germline (heritable) editing regulation in the UK

[48] Regulatory Round-up, November 2024. https://ct.catapult.org.uk/news/regulatory-round-up-november-2024?mc_cid=17100c4868&mc_eid=8dddeae35c

[49] https://www.nature.com/articles/d41587-021-00017-3

Making heritable edits in an embryo is permissible in the UK, but only in a research context. The regulator is the Human Fertilisation & Embryology Authority (HFEA), which regulates all human embryo research and IVF treatment. Whether a license is granted to an applicant for research on an embryo depends on the competency of the applicant, suitability of premises, whether the scientific aims and objectives are consistent with those outlined in the Act, and whether the requirement to use human embryos to achieve those aims has been demonstrated. The editing of the embryonic genome in this context is certainly not prohibited by the Act, although there remain certain sensitivities around human embryo research and genetic technologies that could attract media and public attention.

The use of genome edited embryos clinically is explicitly prohibited by the Act (no alteration to the nuclear genome is permitted) - such an embryo would not be a 'permitted embryo'. There is a possibility that the Act may be reopened for amendment in the coming years. If so, some will argue that clinical use of edited embryos should be permitted, allowing heritable human genome editing (HHGE). The potential benefits are likely to be restricted to the prevention of transmission of serious single-gene (monogenic) conditions[50], in a way comparable to preimplantation genetic testing (PGT-M). The immediate risks include the potential negative impact on the embryo, caused by i) delivery of editing components and the likely requirement for embryo biopsy/PGT after that; ii) the potential for undesired (and undesirable) on-target and off-target events and iii) mosaicism.[51] A wider harm-benefit analysis would include potential impacts on the prospective mother of the procedure, including IVF-related risks. A separate set of investigations will be required to consider ethical and governance issues, such as those outlined in the 2017 US National Academies consensus study report[52] and WHO proposed framework,[53] both prepared with participation by UK experts. In addition, a public debate will be required to consider potential social impacts, positive and negative. It is likely the HFEA would play some role in promoting/convening such a debate - the decision on whether to permit HHGE would ultimately be Parliament's. It would be the HFEA's responsibility to assess the safety/efficacy of any proposed methodology for embryo genome editing being considered for clinical use - as it did with another germline intervention, mitochondrial donation (MRT)[54] - and its responsibility to devise a regulatory framework, including licensing.

EU/international perspective

[50] Though note the recent discussions on multigenic/polygenic genome editing (not yet feasible) to alter inheritance of complex human genetic traits: Visscher et al (2025) Heritable polygenic editing: the next frontier in genomic medicine? *Nature* https://doi.org/10.1038/s41586-024-08300-4

[51] Embryonic mosaicism occurs when two or more cell populations with different genotypes are present within the same embryo.

[52] https://nap.nationalacademies.org/catalog/24623/human-genome-editing-science-ethics-and-governance

[53] https://www.who.int/publications/i/item/9789240030060

[54] https://www.hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf

Across the EU, there is considerable variation regarding human embryo research. It is permitted and highly regulated in some, banned in others, but heritable germline editing is illegal throughout by a mix of domestic law[55] and signature on the Oviedo Convention[56]. Public attitudes vary considerably - some countries in Northern Europe may align with the UK in taking a pragmatic approach to permitting HHGE if it can be shown to have a reasonable balance between potential harms and benefits. Others will oppose in principle for cultural, ethical, religious, and historical reasons. The situation is fluid and there is not much of a consensus, other than a shared belief that heritable germline editing is currently unsafe because there is not suitably safe and effective methodology for embryo genome editing,[57] *i.e.*, one that introduces only the desired on-target edit and no off-target edits.

APPENDIX B: A CLOSER LOOK AT GENOME EDITING IN PLANTS

Genome editing in plants - US

The regulation of genome editing in plants in the United States is overseen by multiple federal agencies under the Coordinated Framework for the Regulation of Biotechnology. This framework ensures that new plant varieties produced through biotechnology, including genome editing technologies like CRISPR, are safe for the environment, agriculture, and human consumption. The three main agencies involved are the U.S. Department of Agriculture (USDA), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA).

The USDA's Animal and Plant Health Inspection Service (APHIS) is responsible for regulating plants that may pose a risk to other plants or agricultural systems. Historically, genetically modified organisms (GMOs) were regulated if they involved plant pests or were developed using certain techniques. However, the USDA has updated its rules to reflect advancements in genome editing. Under the SECURE Rule (Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient) implemented in 2020, certain categories of modified plants are exempt from regulation because they could otherwise have been developed through conventional breeding and are unlikely to pose an increased plant pest risk compared to conventionally bred plants. These exemptions apply only to plants because the long history of plant breeding provides extensive experience in safely managing associated plant pest risks. Modifications that APHIS has previously reviewed in the same plant and found not subject to regulation are also exempt from regulation. This streamlined process encourages innovation by reducing regulatory burdens for developers of genome-edited crops.[58]

The EPA regulates genome-edited plants that are designed to produce pesticidal substances, such as those containing plant-incorporated protectants (PIPs). The EPA ensures that these substances are safe for human health and the environment. Genome editing techniques used to develop plants with

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[55] https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/eu-germline-embryonic/

[56] https://www.coe.int/en/web/bioethics/oviedo-convention

[57] https://nap.nationalacademies.org/catalog/25665/heritable-human-genome-editing

[58] https://www.aphis.usda.gov/biotechnology-guidance/questions-answers-biotechnology-regulatory-services

pesticidal traits are subject to risk assessments like those for traditional GMOs, focusing on environmental impacts like effects on non-target organisms and potential resistance development in pests.
The FDA oversees the safety of food and animal feed derived from genome-edited plants under the Federal Food, Drug, and Cosmetic Act. Developers of new plant varieties are encouraged to consult the FDA through its voluntary premarket consultation process. This process evaluates whether the edited plants are as safe as their conventionally bred counterparts. Genome editing technologies like CRISPR often expedite the regulatory pathway because they allow precise modifications without introducing foreign DNA.

Genome editing in plants - UK

The UK legislation governing genetically modified organisms for deliberate release into the environment is derived (and assimilated, following EU exit) from EU legislation. This has effectively inhibited almost all cultivation of GM crops in the EU/UK due to its onerous requirements. Recently, the UK has begun to diverge from the EU by an Act of Parliament[59] that effectively exempts some form of genetically altered organisms from GM regulations. These organisms (known as precision bred) are defined as being the product of modern biotechnology (most likely genome editing - but the Act is silent on the nature of the technology used and focuses on the genome(s) produced) where the altered genome *could have resulted from* traditional processes. This is in response to lobbying by scientists and other stakeholders that convinced the UK government that plants (and animals, but see below) with deletions or point mutations but containing *no* transgenes ('foreign DNA') from sexually incompatible species should be considered no more unsafe than the same plants/animals generated by traditional processes of breeding, which include the use (in plants) of chemical and X-ray mutagenesis to generate genetic diversity in a random, genome-wide fashion prior to selection of desired traits. Novel products of such traditional breeding are not subject to detailed pre-market assessment in respect of safety; instead, all producers are subject to General Food Law[60] provisions.

Despite this approach to traditionally produced food, the framework for assessing the safety of food derived from precision bred organisms (regulated in the UK by the Food Standards Agency (FSA), with assessments to be performed by its Advisory Committee on Novel Foods and processes (ACNFP)) does require varying degrees of pre-market assessment, depending on the *Tier*[61] into which a "precision bred organism" (PBO) falls. Tier 1 PBOs (expected to form the large majority) will require a 'light touch' and be almost equivalent to traditionally bred products. Tier 2 PBOs will be those that have raised some concerns following an initial triage of potential safety concerns. The safety assessment pays attention to the following factors: whether the PBO is itself produced by editing the genome of what would

[59] The Genetic Technology (Precision Breeding) Act of 2023, https://www.legislation.gov.uk/ukpga/2023/6/contents

[60] https://www.food.gov.uk/business-guidance/general-food-law

[61] https://www.food.gov.uk/board-papers/genetic-technology-precision-breeding

otherwise be considered a novel food, i.e., any food that was not used for human consumption to a significant degree within the United Kingdom (UK) or the European Union (EU) before 15 May 1997[62]; the anticipated impact of the edit(s) on compositional features (including nutritional quality, allergenicity and toxicity) and *other* concerns, the latter being a way of potentially capturing concerns that were not anticipated when drafting the regulations and associated guidance. If concerns related to these areas are identified, Tier 2 PBOs may be subjected to additional assessments/tests in a bespoke fashion. The extent of such testing will not mimic the extent of testing currently associated with genetically modified plants, where the impact of the newly expressed (transgenic) protein, and its genomic insertion site, is a major focus.

In respect of the impact of genome editing methodology *as such*, producers of PBOs will be expected to provide a data package describing the intended genetic change, its impact on the plant and attempts made to assess the existence of off-target events and characterize the on-target event. Newer editing methodologies (such as base editing and prime editing) may assist in reducing unwanted events both on and off-target. There is even the prospect of epigenome editing and RNA editing, neither of which *should* affect DNA sequences. But note that proportionality dictates that off-target events caused by editors should not be elevated in their significance for safety over the potentially far higher number of such events caused by traditional breeding methods, such as use of genome-wide 'shotgun' mutagenesis.

It should also be noted that the regulatory segmentation of organisms used for food and feed purposes - into traditionally bred, precision bred or genetically modified - is an example of a process-based regulatory framework, where the first trigger for capture of a product is the overarching process/platform technology used to generate it. There are increasing calls[63] in the UK for a product-based regulatory approach which would focus testing (and determine how extensive it should be) based on the specific features of a product rather than the platform technology that produced it.

Finally, the decision as to whether an organism is genetically modified or precision bred in law is made by the Advisory Committee on Releases to the Environment (ACRE), which is sponsored by the Department for Environment, Food and Rural Affairs (DEFRA).

Genome editing in plants – EU

At the time of writing, any genome-edited plants (or animals) generated for commercial use are subject to genetic modification regulations in the EU. There have been proposals by the European Commission[64] to adopt a similar exemption process to the UK - plants produced by new genomic technologies (NGTs,

[62] https://www.food.gov.uk/business-guidance/regulated-products/novel-foods-guidance

[63] https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-genetic-technologies

[64] https://ec.europa.eu/commission/presscorner/detail/en/ip_23_3565

such as genome editing) that are 'comparable to naturally occurring varieties' would be exempt from GM legislation - but whether they will be approved by all EU nation states is unclear. The safety of food produced using genome edited organisms would be assessed by the European Food Safety Authority (EFSA).

APPENDIX C: A CLOSER LOOK AT GENOME EDITING IN NON-HUMAN ANIMALS

Genome editing of nonhuman animals - US

The regulation of genome editing in animals in the United States is primarily governed by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The FDA treats intentional genomic alterations (IGAs) in animals, including those produced through genome editing technologies like CRISPR, as animal drugs. This regulatory framework ensures that such modifications are safe for the animal, any derived products intended for human consumption, and the environment. The FDA evaluates IGAs in animals as drugs because they are intended to alter the structure or function of the animal. Developers must demonstrate the safety and efficacy of the genomic alteration for its intended use. The evaluation includes assessing the animal's health, the stability of the genomic alteration across generations, and the safety of any food products derived from the animal.

Genome editing in animals may target:

- Human health applications, such as producing animals that generate therapeutic products (e.g., biopharming).
- Agricultural purposes, including traits like faster growth, disease resistance, or improved food quality.
- Environmental benefits, such as reduced methane emissions in livestock or disease suppression in wild populations (e.g., genetically altered mosquitoes).

Risk Assessment: The FDA assesses the potential risks to humans, animals, and the environment. For food-producing animals, the FDA evaluates whether the genome-edited animal is as safe to eat as its conventionally bred counterpart. Environmental reviews are conducted under the National Environmental Policy Act (NEPA) to ensure no significant ecological harm.

While the FDA leads regulation, the U.S. Department of Agriculture (USDA) plays a complementary role, particularly for livestock. For example:

- If genome editing in animals affects agricultural practices, the USDA ensures compliance with existing animal welfare and disease control standards.
- The Environmental Protection Agency (EPA) may become involved if genome editing introduces traits that affect environmental interactions, such as pest-resistant or sterile animals.

In 2023, the FDA announced risk-based regulatory exemptions for certain low-risk genome-edited animals, such as those with traits that could be achieved through traditional breeding. This effort is designed to reduce regulatory burdens and encourage innovation, particularly for small-scale and academic developers.

Genome editing in nonhuman animals – UK

All the legal provisions for precision bred plants apply to animals. However, detailed guidance on meeting the legislative requirements for plant PBOs are far in advance of those required for animals,

which will be complicated by an ethical overlay that does not affect plants. The impact of genome editing on the health of animals is not necessarily a central concern, if such editing is highly specific and does not introduce large numbers of off-target events that might impact on animal health/welfare. Indeed, most proposed uses are aimed at introducing disease resistance into farmed animals, such as pigs and chickens, and could therefore have a positive impact on animal lives. However, it should be noted that such animals cannot be produced without subjecting other animals to procedures such as ovarian stimulation, egg collection IVF, embryo transfer surgery, surrogacy etc., which can cause harm. One objection noted in public engagement exercises[65] is not to genome editing as such, but to intensive farming practices and existing traditional breeding practices that have already resulted in animal harms and which, it is claimed, might be exacerbated and further entrenched by genome editing.[66] Such arguments are contested, and proponents note the potential benefits in addressing food security, animal diseases and climate change. It is unclear how delayed the lawful regulation of precision breeding in commercial animal farming in the UK will be when compared to plants.

Genome editing in nonhuman animals - EU

It is also the case that progress with amending legislation to permit the use of NGT for plant breeding and food production is far in advance of equivalent changes supporting the use of NGT for farmed animals. It is unclear how the political debate will play out in coming years.

[65] https://www.nuffieldbioethics.org/publication/public-dialogue-on-genome-editing-and-farmed-animals/

[66] https://www.nuffieldbioethics.org/publication/genome-editing-and-farmed-animal-breeding-social-and-ethical-issues/