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The Precautionary Principle: A Public Policy Tool to Support the Application of Heritable Human Genome Editing?

Olga C. Pandos [1]

[1] Lecturer, The University of Adelaide, Adelaide Law School, North Terrace, Adelaide, South Australia 5000 Australia

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ABSTRACT

The Precautionary Principle ('PP') is a legal, ethical and regulatory chameleon. It acts as a guide to decision-making, in conditions of scientific uncertainty. Therefore, a fundamental aim of it is to offer some certainty under conditions that are largely uncertain. The advent of Clustered Regularly Interspaced Short Palindromic Repeats ('CRISPR') technology epitomises an emerging technology which does not lend itself to regulatory convenience. Its far-reaching scientific, ethical, social, legal and regulatory implications, renders the task of applying a rigid, uniform framework or decision-making mechanism impossible. Unsurprisingly, the current regulatory approach for Heritable Human Genome Editing ('HHGE') is highly prohibitive, manifested as a blanket moratorium. However, as the technology continues to mature, it is prudent to consider pathways for its eventual legal and regulatory permissibility.

Subsequently, this principle offers a means to formulate future public policy and regulation. The primary aim of this article is to advance an argument for the practical utility of this principle in supporting a therapeutic use of HHGE. Namely, to prevent Huntington's Disease – a fatal monogenic genetic disease. As observed with somatic genome editing, it is feasible to presume the first therapeutic use of HHGE may target fatal monogenic genetic diseases (caused by a single mutation). Through the application of the framework provided by the World Commission on the Ethics of Scientific Knowledge and Technology, this article argues this principle does not necessarily translate to a strict regulatory prohibition. In the context of emerging technologies, its application must be tempered to accommodate for research development, thereby enabling technological advancement.

Introduction

The Precautionary Principle ('PP') is a legal, ethical and regulatory chameleon. This is evidenced from its various conceptual formulations and interpretations, the phraseology adopted in its definition and the circumstances in which it may be invoked. It is purported to be a tool influencing decision-making and policy where an activity creates uncertainty and risk/s of threat/s[1]. For this reason, it is highly relevant to the formulation of public policy and regulation of emerging technologies, such as Clustered Regularly Interspaced Short Palindromic Repeats ('CRISPR') technology.

This principle has philosophical, theoretical and regulatory underpinnings, which further perpetuates its elusive character. However, its various dimensions confer an inherent malleability, enabling its application to be tailored to specific issues and public policy contexts. Consequently, the PP is said to be at the "science-policy interface"[2].

This article argues the PP may be used as a public policy tool to support the permissibility of Heritable Human Genome Editing ('HHGE'), in *certain circumstances*. Namely, to prevent, treat or correct fatal monogenic genetic diseases. These are diseases caused by a single mutation to a gene. The term *Heritable Human Genome Editing* refers to the use of CRISPR technology to edit reproductive cells, such as the female egg and male sperm, to achieve a pregnancy. Importantly, these edits are heritable and will be passed on to subsequent generations. Its intergenerational impact has rendered HHGE highly contentious and subject to immense scrutiny[3]. A global moratorium on HHGE has been implemented, in response to the alleged birth of the CRISPR Babies in 2018[4]. However, as the technology matures, it is integral to consider pathways to enable its application. In Australia, this would likely require legislative reforms, which are currently highly prohibitive, criminalising HHGE[5].

In order to advance this central argument, the 2005 framework developed by the World Commission on the Ethics of Scientific Knowledge and Technology ('COMEST') will be applied to a proposed use of HHGE – to prevent Huntington's Disease. Within this framework, a working definition of the PP is accompanied by four components to guide its practical interpretation and application. These components will be relied upon to support an argument for the use of HHGE to prevent Huntington's Disease. Thereby, indicating it does not necessarily translate to an immediate condemnation or prohibition of HHGE.

What is the Precautionary Principle?

Since its inception in the early 1970s, the PP has been increasingly adopted by many international jurisdictions[2,6–10]. It has become a prevalent fixture in law and policy areas that are accompanied by knowledge deficits and risks to public health.

There is no single, universal definition of this principle[1] and some 19 different versions of it have been reported[11]. A consensus regarding its construction, interpretation and application has not been reached[12–14], despite its comprehensive interrogation by many commentators from various disciplines. This reality forms the basis for opposition to its ambiguous nature. For example, variability in its formulations and interpretations are problematic if its intended use is a policy-making tool[15].

Cass Sunstein, a Professor of Jurisprudence, aptly summarised a commonly accepted purpose of the PP:

> Avoid steps that will create a risk of harm. Until safety is established, be cautious; do not require unambiguous evidence. In a catchphrase: *Better safe than sorry*. In ordinary life, pleas of this kind seem quite sensible, indeed a part of ordinary human rationality. People buy smoke alarms and insurance. They wear seatbelts and motorcycle helmets, even if they are unlikely to be involved in an accident. Shouldn't the same approach be followed by rational regulators as well?[16]

In simple terms – invocation of this principle merely supports the notion that it is better to be safe than sorry.

The 1992 Rio Declaration on Environment and Development was the first international instrument to explicitly enumerate a definition of the PP[6]. Principle 15 of the Declaration proffered its "classic definition"[17]:

> In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. *Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation*[18].

This definition establishes a relationship between the proposal of a new technology which carries uncertainty and risk and the need for a regulatory response. Therefore, it is often applied within the context of public policy, to justify regulatory decision-making. The Rio Declaration also usefully provides the key ingredients of the PP – risk, harm, scientific uncertainty and the need for preventive action/s. The COMEST described this definition as containing a "triple negative notion"[19]. Whereby, "the absence of rigorous proof of danger does not justify inaction"[19]. This captures one of the contentious features of this principle – the need to prevent harm, through risk management and mitigation, using preventive measures. Notably, there is no guidance within its definition that indicates a number of significant factors. These include: the nature/type of risk and harm, the acceptable margin of safety, the severity of knowledge deficits, an evidentiary threshold quantifying risks and harms, defining when it ought to be invoked and the available types of preventive measures. This reinforces the common criticisms associated with its ambiguity[16].

Despite the lack of granularity in relation to its definition, this introduces a unique feature of the PP. Its malleability enables it to be a purpose-built public policy tool. If the rationale underpinning this principle is a universally

accepted premise – the need to be cautious when regulating emerging technologies – its enforcement can be likened to that of an ethical principle. The plurality of a society supports the notion that ethical principles may be universal, though their translation in practice will differ according to a society's social, cultural, political, religious and ethical fabric. This was emphasised by Andrew Stirling, Professor of Science and Technology Policy, "a sensitivity to the prevalence of different sets of values, interests and priorities in different political, cultural and geographical contexts will lead inevitably to the manifestation of different regulatory outcomes under different jurisdictions"[9]. In this way, ethics continues to maintain its role at the forefront of the evaluative processes adopted for emerging technologies. It ensures regulators who apply the PP do not confine themselves to a myopic evaluation of a proposed application of HHGE that is purely quantitative.

The literature delving into the definitions and interpretations of the PP or the precautionary approach, is rich and vast. Consequently, this article confined the definition of the principle within the context of science and technology studies and specifically, emerging technologies. Although it has various theoretical and normative underpinnings, these fall outside the scope of the article. Its practical utility will be explored to determine whether it lends support for the permissibility of HHGE, under *certain circumstances*.

The World Commission on the Ethics of Scientific Knowledge and Technology Report

A primary objective of the 2005 COMEST Report was the creation of an "ethical platform", in which the PP was applied as an "overarching consideration", relevant to risk management[19]. It sought to inform decision-makers (regulators) and the public about the implications of emerging technologies[19]. The COMEST concluded the burden of proof is ascribed to the party who proposes the use of an activity or new technology[19].

The definition of the PP as articulated by the COMEST, will be applied to the use of HHGE to prevent Huntington's Disease – a fatal, monogenic genetic disease.

The COMEST provided the following "working definition" of the PP:

> When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm. Morally unacceptable harm refers to harm to humans or the environment that is
>
> - threatening to human life or health, or
> - serious and effectively irreversible, or
> - inequitable to present or future generations, or
> - imposed without adequate consideration of the human rights of those affected.[19]

Interestingly, the definition qualifies the type of harm as "morally unacceptable", which introduces a religious undertone. For the purpose of this article, the term *ethical* will be adopted. This qualification contained within the definition indicates the importance of ethics in the appraisal of a proposed application of a new technology. It reinforces the PP operates under conditions of uncertainty, which may refer to causality between an activity and harm or the likelihood of possible harm[19]. The definition is also accompanied by four components, guiding its interpretation and application. These are: plausible hypotheses, review, proportionality and a participatory process. Each will be discussed in turn.

PLAUSIBLE HYPOTHESES

The COMEST refers to "the judgement of plausibility", which is premised upon scientific data and analysis[19]. A fundamental challenge raised by a new technology, such as HHGE, is uncertainty and ignorance. The long-term health consequences and intergenerational impact of HHGE cannot be foreseen or quantified. Therefore, when determining plausibility as a decision-maker, this task is highly complex. Often, it results in the strictest form of regulation – a ban or moratorium. Currently, this is the regulatory response adopted for HHGE by many jurisdictions. This is a sensible and unsurprising response, enabling time for responsible research and development, to fill knowledge gaps and facilitate data collection. It is imperative to be cognisant of the environment in which the PP operates, when applied in the context of a new technology.

The COMEST offer further clarification regarding the definition of plausibility. When determining whether to invoke the PP, a decision-maker is required to formulate a hypothesis regarding a causal relationship between an activity and harm[19]. The mere possibility of a risk, despite it being unquantifiable, is sufficient to enliven this principle[19]. A plausible hypothesis may be perceived as "a more serious possibility" of occurring[19]. However, plausibility does not need to be correlated with probability, particularly in the context of emerging technologies[19]. This is a symptom of ignorance with respect to unknown risks[2]. Often, in the presence of ignorance, there are hypotheses regarding potential unknown impacts that cannot be foreseen or known.

In light of these considerations, the concept of probability may only be determined where there is "sufficient evidence"[19]. Where there are knowledge or data gaps, the judgement of plausibility (whether a hypothesis is true) should be suspended, as ignorance impedes upon the exercise of this judgement[19]. Despite this, the COMEST encouraged the exercise of practical judgement, to determine the appropriate recourse of action[19]. This indicates that a decision-maker ought to actively consider how to act or respond to any possible hypothesis, including those that are mere or unknown possibilities[19].

The COMEST's approach to plausibility adopts a science and data centric approach to risk probability. Where data is available, plausibility should be influenced by probabilities of risk and harm occurrence. However, the COMEST do not offer guidance pertaining to practical judgement that ought to be exercised where ignorance impedes upon the calculation of probabilities. The use of guiding principles may be of utility to assist in exercising practical judgement. It leads to an outcome of reliance

upon the decision-maker to use their expertise and experience to exercise this judgement.

REVIEW

The PP is applied under circumstances in which there is significant scientific uncertainty pertaining to the causality, severity, probability and nature of harm[19]. Consequently, a form of scientific analysis is necessary and compulsory[19], when implementing this principle. To ensure its proper application, scientific analysis must be ongoing and precautionary measures must be subject to review[19]. Further, the requirement of periodic reviews attempts to enforce accountability upon decision-makers to ensure measures or actions remain relevant and appropriate. Thereby, the inclusion of a review period or ongoing monitoring forms an integral part of responsive regulation.

PROPORTIONALITY

The COMEST concluded that any proposed actions or measures must be proportional to the "seriousness of the potential harm" and the accepted level of protection[19]. The type of intervention should be contingent upon these two criteria, which do not operate to limit the actions or measures available. Adopting a plain interpretation of the term proportionality – it may be implied that a decision ought to ensure the means to achieve an end are considered appropriate[20] or reasonable.

Notably, proportionality does not necessarily advocate for a ban or moratorium. The concept of *zero risk* does not exist when confronted with a new technology. As such, an acceptable level of risk may be tolerated, in order to realise the potential benefits offered by HHGE, including prevention of fatal monogenic genetic disease/s. For example, actions that prevent inevitable death and suffering may be perceived as more ethical than a failure to act for fear of uncertainty[19]. Any measures that seek to limit the possibility of harm or contain the harm, should be explored on a case-by-case basis[19]. Importantly, this exercise requires active consideration of the benefits and risks associated with the activity. The risk-benefit profile of a proposed application of HHGE becomes an integral part of shaping public policy and regulatory responses.

PARTICIPATORY PROCESS

A choice of action or measure to enforce the PP, must be a product of an inclusive participatory process[19]. This is reflective of a deliberative democratic process, which acts as a conduit between decision-makers and the public, to explore the "moral implications of both action and inaction.[19]" The COMEST emphasised the ability to participate in public policy debates is an ethical principle present in modern democracies[19]. This condition may be perceived as a limitation for jurisdictions that do not have a liberal democracy. However, it is important to highlight the need for deliberative democratic processes or consultations to shape a regulatory response to HHGE. In particular, individuals who would likely use HHGE must be consulted.

The COMEST provided an arbitrary framework defining the principle, with its associated components to guide its practical enforcement. Using this framework, this article will apply the PP to Huntington's Disease, to advance an argument for its legal permissibility. This indicates that its application under conditions of uncertainty and ignorance does not necessarily translate to a strict ban of HHGE. Rather, it promotes responsible regulatory measures that enable technological development.

Heritable Human Genome Editing for Huntington's Disease

This article argues the PP may be used as a public policy tool to support the permissibility of HHGE, in *certain circumstances*. Namely, to prevent, treat or correct fatal monogenic genetic disease/s. In these specific circumstances, the application of this principle lends support for the use of HHGE, as a lifesaving therapeutic to prevent future suffering and early mortality. Further, cautious and regulated use of HHGE in these circumstances is arguably ethical, given the known risk/s of Huntington's Disease ('HD') incidence and mortality arguably outweigh those associated with HHGE.

DISEASE AETIOLOGY

Huntington's Disease is a fatal neurodegenerative monogenic genetic disease, caused by a mutation to the *HTT* gene[21,22]. This gene encodes a protein called huntingtin, which is responsible for the functioning of nerve cells (neurons)[21]. The inability to properly synthesise the huntingtin protein leads to abnormal protein shape, causing the destruction of neurons[21]. This occurs in neurons contained within the brain's basal ganglia, which regulates body movement and the cortex, which controls working memory and executive functioning[21]. It has been reported that HD affects approximately 3 to 7 out of every 100,000 people, with a higher prevalence in individuals of European descent[21].

There are two primary types of HD – juvenile and adult onset (most common)[21]. This article will only consider the use of HHGE for adult onset HD. For individuals with adult onset HD, symptoms often occur after the age of 30 years[21]. Following the onset of symptoms, life expectancy varies between individuals[21,23]. However, the progressive neurodegenerative nature of the disease often leads to death between 10 to 30 years of onset[21]. Clinical symptoms are significant, including chorea (uncontrolled physical movements), ataxia (loss of coordination), loss of mobility, dysphagia, slurred speech, loss of executive functioning (memory, decision-making), cognitive impairment, depression, irritability and disorientation[21–23]. Quality of life of the individual is significantly reduced as the disease progresses. Currently, there is no cure for HD[21]. Treatments can be targeted to manage and address symptoms as they arise and worsen[21,23].

Huntington's Disease has an autosomal dominant inheritance[21,22], which means only one disease-causing allele is required for disease manifestation. Therefore, it confers a 50% chance on all offspring of developing HD. Although the prognosis of HD may not be as severe as other monogenic genetic diseases, such as Tay-Sachs Disease (death between 3 to 5 years of age), it remains a therapeutic candidate for HHGE due to its genetic cause and inheritance. Namely, in families with the mutation, it is highly likely that prospective parents will not be able to conceive a genetically-related child, without HD.

Currently, where HD is known to be present within a family's genetic lineage, pre-implantation genetic testing is available to determine whether an embryo is disease affected. In light of the 50% risk of inheriting HD, prospective parents may wish to pursue a pathway which corrects the mutation, such that HD can no longer be passed down to subsequent offspring. Under these circumstances, HHGE could be undertaken to modify and correct the DNA of the embryo, to prevent the disease. If successful, this treatment will restore the function of the gene, thereby removing disease predisposition. For the purpose of this article, it will be presumed that HHGE is perceived as a preclinical treatment option, that has available information regarding the nature of the treatment, risks, benefits and costs, if it were to be approved. Under these circumstances, how could the PP be applied to support the use of HHGE?

THE APPLICATION OF THE PRECAUTIONARY PRINCIPLE

In order to advance the central argument of this article, the definition of the PP provided by the COMEST will be applied to the proposed application of HHGE – to prevent HD. The practical utility of this principle as a public policy tool will be investigated. Importantly, it will be shown its invocation does not advocate for a blanket moratorium on all applications of HHGE. In this instance, it supports the permissibility of HHGE to prevent HD.

First, it is clear the proposed activity (using HHGE to prevent HD) invokes the PP. Decision-makers involved in shaping future public policy are confronted with an activity accompanied by scientific uncertainty, ignorance and knowledge and data deficits. However, this need not immediately necessitate a blanket prohibition. The enforcement of the principle requires careful consideration of responsible development of research, with regulatory oversight.

TYPE OF HARM/S

Second, it is integral to consider the nature and plausibility of harm/s. The application of HHGE is accompanied by risks to human health, many of which are uncertain or unknown. As previously observed, the mere possibility and unquantifiable nature of harm is sufficient to enliven the principle. There are scientifically plausible, yet uncertain risks associated with HHGE. Notably, pursuant to the COMEST's qualification of the type of harm – HHGE may lead to ethically unacceptable harm/s. These harms may threaten human life, may be irreversible and may lead to inequitable outcomes for present and future generations. The intergenerational impact of HHGE creates these risks. Given the edit is undertaken in germline cells (reproductive cells), the ability to reverse edits remains a concern. Further, the heritability of edits presents challenges in relation to quantifying or foreseeing long-term health impacts on subsequent offspring[3]. For these reasons, the future interests and welfare of offspring are relevant considerations when determining the future permissibility of HHGE[3].

Currently, the global moratorium on HHGE ensures that any application is not imposed in the absence of adequate consideration pertaining to human rights. This refers to the final criterion identified by the COMEST when defining an ethically unacceptable harm. A strict and prohibitive regulatory response was necessary following the alleged birth of the CRISPR Babies. It reflected a strong condemnation of unethical, unscrupulous applications of HHGE. It also recognised the importance of ensuring safety and efficacy prior to its use in humans and the need for prudent regulation.

Although this proposed application of HHGE meets a majority of the criteria defining an ethically unacceptable harm, it does not automatically preclude HHGE. Rather, it highlights the need for the PP to guide future regulation and policy. In this way, the principle requires a decision-maker to consider appropriate regulatory safeguards and measures that allows research to continue, whilst promoting reviews and consultative practices as the technology matures.

PLAUSIBLE HYPOTHESES

In practice, decision-makers must exercise a "judgement of plausibility"[19]. Plausibility requires a hypothesis to be made identifying a causal relationship between the proposed activity (HHGE to prevent HD) and harm (an ethically unacceptable type). In the circumstances of HHGE, the degree of ignorance with respect to its long-term health consequences and intergenerational impact, renders the task of undertaking precise scientific analyses difficult. Consequently, practical judgement ought to be employed to ascertain appropriate steps for regulation in light of this ignorance and uncertainty.

From a practical perspective, the risks of the technology's technical limitations enable a causal relationship to be identified. The technical limitations of CRISPR technology generally apply to HHGE. These are predominantly concerned with the safety and efficacy of the technology. There are three recurring limitations – off-target effects, on-target unintended effects and mosaicism[24,25]. Together, the impact of these technical limitations may not be fully realised immediately.

Off-target effects refer to genetic changes made to regions of the genome, that were unintended during the editing procedure[26]. Although these effects may be benign, there is a risk that it may be "dangerous", depending on the location and effect[26]. For example, an off-target effect may cause an increased risk to diseases, such as cancer[27,28] or rare and unknown diseases[24]. Often, the risk of off-target effects is a product of the technology's naivety, in that the specificity of the guide RNA, which transports the genome editing machinery to the intended location, may be compromised.

On-target effects refer to unintended changes to the target site and may have implications on other genes near the target site[27,29]. These changes may cause insertions or deletions of genetic material, or complex rearrangements[27]. Although the intended edit may be successfully undertaken at the precise location, it may be that the unintended consequence is still observed[26].

Finally, mosaicism describes circumstances in which some of the cells within a modified organism have been edited[30]. In practice, this means that there is a risk the embryo does not contain the intended edits (if any)[24,26]. This is problematic if the target gene encodes a critical cellular function[26], such as a protein involved in mitosis

(cell division process) or transcription (the process of synthesising RNA from DNA). Reported risks associated with mosaicism include the creation of rare diseases and interference with necessary cellular functions for cell survival[24].

These technical limitations create a plausible causal relationship between undertaking a genome editing procedure, such as HHGE, and harm/s. While HHGE may intend to, and successfully, correct the mutation causing HD, there remains a plausible risk of off-target or on-target effects and mosaicism occurring. These harms will likely be characterised as unacceptable harm/s. However, they do not necessarily constitute unethical harm/s. For instance, many new technologies, such as *In vitro* Fertilization and mitochondrial donation, were accompanied by risks to human health, including future generations. While some may argue those risks were unethical, subsequent development and advancement of these technologies has led to widespread benefits globally. Importantly, it is only through research that we are able to develop and refine the technology. This does not minimise the valid concerns pertaining to safety and efficacy. However, ongoing research will address technical limitations and direct the technology (if appropriate) toward pre-clinical studies and perhaps, clinical trials[31]. In the absence of research, this proscribes any possibility of utilising CRISPR technology as a therapeutic candidate.

Further, let us consider plausible hypotheses from an alternative perspective. Namely, where the PP has led to an omission to act, through the outright prohibition on HHGE. There are quantifiable, known risks associated with a diagnosis of HD. Its inheritance, prognosis and significant clinical features are known. Quality of life is a significant factor to consider in light of the progressive deterioration associated with symptomatology. For individuals with HD in their family, the quantity and subsequent quality of life must be taken into consideration when weighing the plausible hypotheses accompanied by HHGE. A failure to act in this instance to prevent HD may be characterised as an ethically unacceptable risk. In circumstances where a fatal monogenic genetic disease can be corrected and prevented, this negates the argument that all risks associated with HHGE are ethically unacceptable. Where the fate of a disease affected embryo is premature death, why not attempt to prevent future suffering and mortality? Although there is merit to argue HD has a delayed onset, this should not minimise its candidacy for HHGE. Quantity does not equate to quality of life. It remains a fatal disease, with significant impacts on quality of life. Further, the global average life expectancy at birth is 71 years[32]. Hypothetically, if an individual were to experience an onset of HD symptoms at the age of 30 years and goes on to live another 30 years, death at the age of 60 years remains premature in our society. Premature mortality is a significant consideration when determining a permissible application of HHGE. Additionally, the quality of life of that individual will progressively deteriorate until death.

It is inevitable that HHGE will continue to mature as a technology. It is imperative to ensure a pathway forward is pragmatic and cautious. As research continues to collate valuable data and knowledge, the PP will promote the application of HHGE to prevent HD. Further, it advocates for ongoing review and oversight to ensure HHGE is applied in an ethical manner, with regulatory constraints.

REVIEW

In practice, mandatory or periodic reviews are a fundamental component of responsive regulation. In the context of an emerging technology, its rapid advancement requires ongoing review to ensure regulation remains relevant and appropriate. This oversight ensures unnecessary harm/s are minimised or prevented. Decision-makers ought to consider regulatory approaches which enable HHGE to proceed under scrutiny, with the implementation of long-term monitoring mechanisms.

In this instance, periodic reviews could be facilitated via three avenues. First, the legislation which legally sanctions HHGE can mandate periodic statutory reviews. The period of review is at the discretion of lawmakers and requires an investigation into the entire statute to ensure it continues to meet its objectives. Second, reviews could occur at the government level via the appointed regulator. For example, the Australian Therapeutic Goods Administration or the US Food and Drug Administration. Ethics committees often operate within these regulatory bodies, offering oversight of a new technology. Third, should HHGE be undertaken in conjunction with an assisted reproductive technology, the clinic which offers the service could also provide oversight. This would extend to long-term monitoring of offspring subject to HHGE following birth. In order for responsible development to occur, data collection and knowledge expansion regarding the risks, benefits and outcomes of HHGE is necessary.

PROPORTIONALITY

This criterion requires that the intended action (response to the proposed activity) must be proportional to the "seriousness of the potential harm" and the accepted level of protection[19]. Proportionality is rendered more complex in the context HHGE, as the intergenerational impact remains unknown. However, it is important to identify the primary risks and benefits of the proposed activity, to determine the accepted level of protection (or risk tolerance). For the purpose of this article, a comprehensive analysis of the risks and benefits will not be undertaken. However, it is relevant to identify some of the primary risks and benefits of HHGE to prevent HD. This will attempt to inform risk tolerance.

Some of the primary risks associated with HHGE include: the cumulative risk/s of both HHGE and an assisted reproductive technology[33]; following blind injection of the CRISPR system into all cells, the success of HHGE cannot be ascertained until the embryo is cultured; correction of the mutation does not eliminate the risk of *de novo* mutations (new mutations occurring); risk of off- and on-target effects and mosaicism; short- and long-term health consequences are unknown; risk tolerance of prospective parents will differ according to each individual. The most concerning risks pertain to its intergenerational impact, the consequences of which are largely unknown in relation to the severity, type and duration of the harm/s.

In contrast, it is prudent to consider some of the primary benefits associated with HHGE: the correction of the disease-causing mutation; prevention of HD; if successful, removal of HD from the genetic lineage of a family (noting parents remain carriers); prevention of future suffering and premature death; reduced disease burden (including the economic benefits); providing opportunity to prospective parents to have a genetically-related child, without HD.

The process of evaluating the risks and benefits is difficult. However, the application of the PP encourages the use of participatory processes to ascertain public opinion. This will significantly assist in determining the weight ascribed to risks and benefits and importantly, risk tolerance. The COMEST observed that:

> People consider a number of dimensions or risk attributes when they judge risks and decide whether or not they consider a given risk acceptable or not. The degree to which people consider a risk acceptable or not depends not only on the magnitude of the damage and the probability that damage will occur, but on other risk dimensions as well. A given risk tends to be seen as less acceptable if the (perceived) controllability of consequences is lower; if the nature of the consequences is unfamiliar and dreadful; if one is exposed to the risk involuntarily; if the benefits of the activity are less clear and smaller; if the effects are more acute and more nearby in space and time; if risk and benefits are unfairly distributed; and if the likely harm is intentional … Attitudes towards risks vary from person to person and across cultures. Some people have a risk-seeking attitude whereas others have a risk-averse attitude[19].

For some individuals, it may be that the benefits outweigh the risks. Although HHGE is accompanied by uncertain risks, no new technology is risk-free. Further, HHGE is being pursued within a therapeutic context, with an intended benefit of a great magnitude. Any attempt to reduce the disease burden associated with HD and remove future risk from the genetic lineage is significant. On the other hand, individuals may believe the risks outweigh the benefits and those uncertain risks are ethically unacceptable. Options remain available to prospective parents who have the HD disease-causing mutation, including pre-implantation genetic testing and adoption. Alternatively, individuals may choose to remain child-free. These are highly personal choices and preferences, emphasising the importance of participatory processes to shape future public policy in this domain. Individual ethical, cultural, social and religious values will influence perceptions of risks, benefits, ethical/unethical harm/s and parenthood.

From an objective perspective of a decision-maker, these risks do not necessarily advocate for a ban on all applications of HHGE. The question of proportionality is highly individualistic. However, as the technology matures, becoming safe and efficacious, a blanket moratorium on HHGE is arguably no longer proportional to the seriousness of harm. The PP ought to allow scope for this development to occur. Therefore, research involving CRISPR technology on germline cells should be permitted, in order to gather data for analysis and expand much-needed knowledge. This principle certainly promotes caution and rigorous oversight. However, as knowledge and data deficits are addressed, the safety and efficacy profile will be better ascertained. Thereby leading to greater regulatory control over the technology.

PARTICIPATORY PROCESS

In order for the PP to be a public policy-making tool, it is unsurprising that the COMEST advocated for the inclusion of participatory processes to ascertain societal attitudes. As highlighted in the context of proportionality, the ethical implications of action or inaction, is largely influenced by the values of a given society. The importance of a deliberative democratic process cannot be undermined. It is imperative that decision-makers engage in productive and inclusive dialogues about HHGE and possible permissible uses. These consultative practices may take the form of community consultation sessions, citizen's juries and targeted consultation with key stakeholders (such as regulators, experts and individuals with a lived experience of a genetic disease). Importantly, information regarding HHGE should be communicated in an accessible manner to all individuals, with cultural and linguistic awareness.

These processes ought to be undertaken early, prior to formal regulatory approval of HHGE. This dialogue should be continuous, to better understand public perceptions of HHGE and any ethical, social, cultural or religious considerations. Responsive regulation reflects a society's value system, which governs ethically acceptable or unacceptable applications of a new technology.

This discussion has highlighted the PP does not purport to be "a complete decision rule"[10], a decision-making methodology[10], an absolutist principle which requires regulators to view risks of emerging technologies through a lens of catastrophe[36,37], or a *one size fits all solution* to technological determinism. This principle acts as a guide to decision-making, in conditions of scientific uncertainty. A fundamental aim of the principle is to offer some certainty under conditions that are largely uncertain. The advent of CRISPR technology epitomises an emerging technology which does not lend itself to regulatory convenience. Its far-reaching scientific, ethical, social, legal and regulatory implications renders the task of applying a rigid, uniform framework or decision-making mechanism impossible.

Conclusion

The PP is a broad concept, which is deliberate in its ambiguity. For this reason, it offers a diverse spectrum of approaches or responses to new technologies that carry uncertainty and risk. For example, this is evidenced by *strong* and *weak* versions of the principle[17]. In this instance, a strong version is currently observed in response to HHGE. It has resulted in strict regulation that seeks to avoid or eliminate risk[17]. This is manifested as an imposition of a moratorium on HHGE. Some common criticisms have argued this creates a situation of "paralysis by analysis", in which scientific uncertainty is

repeatedly used as a justification for strict regulatory measures[34]. Similarly, other criticisms argued a strong version is illustrative of excessive regulation, which stifles innovation by discouraging any investments in technological development[17]. Further, it lacks pragmatic value, as every new technology carries risks, which cannot be reduced to zero[17]. The reality is that "infallibility is never guaranteed by science.[35]"

The application of the PP should not be binary – as either strong or weak. Following the application of the COMEST's framework, this binary view is narrow-minded and compromises its practical utility. Alternative viewpoints and solutions must be explored if this principle is to be utilised as a public policy-making tool. Some applications of a new technology, like HHGE, are rightly subjected to a strong precautionary response. However, the accumulation of data and knowledge will render many applications, such as those involving somatic genome editing to cure sickle cell disease or prevention of HD proportional to plausible harm/s. Application of the principle must be tempered to accommodate for research development, which enables technological advancement. Therefore, it retains its appeal as a constructive principle guiding decision-making. Despite its ambiguity, it establishes a system of norms, principles and values that governs ethical decision-making.

Application of the PP, as articulated by the COMEST, supports the use of HHGE to prevent HD. This article has sought to identify the practical utility of this principle in formulating a public policy response to HHGE – notably, the ingredients for a regulatory approach. This argument *does not* suggest the principle supports the use of HHGE in *all circumstances*. Alternatively, it promotes the use of HHGE under *certain circumstances* to prevent, treat or correct fatal monogenic genetic disease/s. Huntington's Disease was selected as a proposed candidate for HHGE, as it is a fatal, neurodegenerative monogenic genetic disease. Its dominant inheritance and severe clinical profile cause premature death, suffering and diminished quality of life. For individuals living with this disease in their genetic lineage, HHGE offers an alternative pathway to genetic parenthood that could remove future risk of inheritance. This article advanced a thought experiment to navigate ways in which the PP could lend support to the campaign against a blanket prohibition on HHGE. Further, the inclusion of ethical principles within the COMEST's framework, such as proportionality and participatory process, reinforces the importance of ethics as the anchor by which regulatory decisions may be justified. Notably, proportionality is a useful principle, which encourages decision-makers to consider risk tolerance. It has been shown the PP does not necessarily translate to a strict regulatory prohibition in response to new technologies, including HHGE.

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