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Promises and Challenges of Genome Editing:

The Work of Bioethics Reports

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Cas9	CRISPR associated protein type 9
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DNA	Deoxyribonucleic acid
EAB	Ethics Advisory Board (USA)
ES	Embryonic Stem
ELSI	Ethical Legal and Social Implications
FDA	Food and Drug Administration (USA)
GM	Genetically Modified
GMO	Genetically Modified Organism
HFEA	Human Fertilisation & Embryology Authority (UK)
HGP	Human Genome Project
IACUC	Institutional Animal Care and Use Committee
IBC	Institutional Bioethics Committee
IRB	Institutional Review Board
IVF	In-vitro Fertilization
MIT	Massachussets Institute of Technology
NASEM	National Academies of Science, Engineering and Medicine (USA)
NGO	Non-governmental Organization
NIH	National Institutes of Health (USA)
PGD/PIGD	Pre-Implantation Genetic Diagnostics
RAC	Recombinant DNA Advisory Board
RRI	Responsible Research and Innovation
SSC	Spermatogonial stem cell
STS	Science, Technology and Society

1 Introduction

The motto of the Oregon Health and Sciences University is, "we're here to do what can't be done." It is here, in the self-described "Magic Room" of Shoukhrat Mitalipov's lab in Oregon where CRISPR-Cas9[1] claimed to be first introduced into viable human embryos (Stein, 2017). Known as germline engineering, changes to human DNA that can be inherited have been considered taboo and are outlawed outright in signatories of the 1997 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine or Oveido convention (Council of Europe, 1997), as well as Brazil, China, India, Israel and the UK (Araki & Ishii, 2014). Although not illegal in the US, federal funding regulations against any research on embryos would normally preclude such research. Reporting on the Magic Room event to internet followers, the MIT technology review (Connor, 2017) connected the start of embryo editing research with a report by the U.S. National Academy of Sciences, Engineering and Medicine (NASEM, 2017) that gave a 'green light' to germline editing. What was in this report and how and why did it come to be? Expert reports like this both represent and become a part of the social context in which new technologies emerge. Before formal regulations are adopted, this example shows that bioethics reports can serve as a kind of tacit governance for emerging technologies and deserve closer attention.

1.1 Human Genome Editing

Genome editing is an emerging technology changing the field of genetics and molecular biology. Encompassing both a practice and specific biological tools for making targeted additions, deletions and alterations to the genome, genome editing refers to intentional changes to the structural or functional characteristics of biological entities. Since Doudna with Jinek, et al. published a method for such editing in 2012, the use of CRISPR-Cas9 and other genome editing tools has expanded dramatically, drawing attention to projected applications and restrictions on research. The researcher often credited for this so-called breakthrough in molecular biology and bioengineering, Doudna (Doudna & Sternberg, 2016) writes that only after the exhilaration of discovery did she start to think about the dangers of genome editing—that we are unprepared, and that unexpected uses of CRISPR highlight the need for more responsibility in research. Spurred on by researchers' own questions (Baltimore et al., 2015), bioethics bodies around the world issued statements and commissioned studies.

[1] CRISPR-Cas9 is a popular genome editing tool. CRISPR is an acronym for, Clustered Regularly Interspaced Short Palindromic Repeats, CAS-9 stands for CRISPR associated protein number nine.

CRISPR is an enabling technology. Genome editing allows the practical application of knowledge about gene function from decades of work decoding the genome. Genome editing in humans promises the ability to repair known sequences that cause genetic diseases, possibly insert genes that confer immunity, restore damaged tissue or inhibit cancerous cells. Eugenic applications are also possible, as are malicious ones. Even before the recent clinical setbacks, on October 19-20, 2017 in Vienna[2], biologists and social scientists came together and asked, **if CRISPR is enabling a better world, what world? Who stands to benefit and who will be hurt? Who decides?**

Whether out of a sense of responsibility or a fear of regulation, CRISPR pioneers gathered early on to propose guidelines to manage their own research (Baltimore et al., 2015). The resulting December 1-3, 2015 International Summit on Gene Editing recalled the gathering on Recombinant DNA at Asilomar in 1975, a conference establishing self-regulation by the molecular biology community(Hurlbut, 2015b). Following the meeting, the National Academies of Science, Engineering and Medicine developed a consensus report that gravitated toward the specific ethical dilemma of human genome editing (NASEM, 2017). In 2015, the Nuffield Council for Bioethics in the UK also started a study on ethical considerations in genome editing(Nuffield Council on Bioethics, 2016). As a launching point for new policy ideas and a rallying point for discourse, these reports reflect a profound struggle to make sense of the revolutionary potential of new tools like CRISPR, through which genome editing is not only more precise, but easy and cheap enough to bring the practice into clinics, high school labs, and other settings without the long biosafety history of large research institutions that remains the most salient legacy of the original Asilomar meeting.

The December 2015 summit in Washington, DC, differed in key ways from Asilomar 40 years before. It included different kinds of experts, such as bioethicists, and included presentations on constituencies and arguments missing from the previous debate (Thompson, 2015), environmental challenges (Gold, 2015) and biosecurity (Relman, 2015). The summit called for "An inclusive, ongoing global conversation … to assess the many scientific, ethical, and social issues associated with human gene editing" (National Academies of Sciences, Engineering, & Medicine, 2015, p. 6). Issues of ethics and governance are raised in the consensus report; however, instead of a pressing need for ongoing conversation, the summary recommendations

[2] Symposium, Editing Genomes with CRISPR: between scientific breakthroughs and societal challenges

emphasize that "the structure of the U.S. regulatory system is adequate for overseeing human genome-editing research and product approval"(NASEM, 2017, p. 59).

By contrast, the Nuffield Report begins from a premise that genome editing is a transformative technology and conveys an implicit responsibility toward society, based on public comments received and a broad view that the public has an underlying interest in the moral and ethical texture of the society in which they live. These two approaches contrast in their ways of thinking about responsibility and public engagement in emerging technologies and how we live with the power new technologies bring.

1.2 A Note About Place

Although this thesis focuses on the US, UK and Europe, many human genome editing developments are taking place in China, including active clinical trials. The Second International Summit on Human Genome Editing International Summit will take place in Hong Kong November 27-29, 2018[3]. The promises and challenges of genome editing are different and perhaps stronger for the Middle East, where autosomal recessive genetic disorders are more prevalent (Tadmouri et al., 2009) and in the global south where infertility has a deeper impact on women's lives (Fleetwood & Campo-Engelstein, 2010). Russia is a likely place for human genome editing given the strong tradition in biomedicine and genetics and openness to assisted reproduction. In a Russian review of genome editing techniques that includes a heading on 'Reprogenetics', the author concludes: "All of these combined will inevitably give birth to new-quality personalized genomic medicine in the next 3-5 years. Directed genome alteration techniques will be a new tool for doctors" (Rebrikov, 2016, p. 9)

Nothing similar to the previous prediction is present in either of the bioethics reports under review, which are careful to avoid technological determinism, over-simplified depictions, 'hype' about promises and a timeframe that might not come to pass. The reports do take global considerations into account: the different levels and types of jurisdictions involved in governance, as well as justice issues. However, in both reports an underlying aspiration toward a universal ethics for genome editing privileges American and British perspectives. Selecting these reports to study for the thesis amplifies this problem.

[3] http://nationalacademies.org/gene-editing/2nd_summit/index.htm

1.3 My Research

The study of science, technology, and society (STS) is an academic discipline engaged in researching how the concepts of science, technology and society fit together and mutually shape each other and us. STS offers ways to unpack these complex relations, looking at different elements in parallel without falling back on explanations that rely on deterministic narratives of technological progress (Winner, 1980) or social construction (Bijker & Pinch, 1987). Science is a formal activity that creates and accumulates knowledge by directly confronting the natural world and reduces it to written data through specialized equipment and procedures in the laboratory (Sismondo, 2010). Technology, as Jasanoff (2016) points out, comes from the Greek for *techne*, meaning skill and *logos*, meaning study of, and encompasses not only tools and electronic products, but processes and systems that that make up or seek to change life. In practice, Latour (1987) explains that science requires technology, laboratories have the power to change the world, and science generates nature-culture hybrids that complicate the boundaries between nature and culture. Latour uses the term, *technoscience*, to capture this entanglement. Society is a way to refer to how individuals interact and live in relation to one another. Society is not a single coherent and stable entity, but under constant transformation (Felt et al., 2013). STS studies how science and technology shape already complex societies and the way we live. Although often critical, STS can also be very constructive in drawing attention to questions of values, responsibility, and democratic principles that can strengthen the outcomes of scientific and technological work.

This thesis is a comparative study of two responses to human genome editing produced by expert committees and published by major institutional bodies, the 2017 US National Academies of Science, Engineering and Medicine (NASEM) report "Human Genome Editing: Science, Ethics and Governance" and the 2016 Nuffield Council on Bioethics report, "Genome Editing: an ethical review." Bioethics reports navigate through the complicated terrain of risk, hope and controversy, collecting opinions and deciding which arguments are worth considering, attaching them to technical considerations, and producing a set of reasonable positions for policy makers and the public to take up in discussion. In STS terms, governance refers to a form of exercising power and negotiating binding regulations which looks beyond laws to the network of concerned actors involved in decision making, as well as responsibility and enforcement. Co-production is an STS concept that draws attention to how technical developments and governance are deeply entangled. Using a comparative method will help unpack the assumptions about governance and framing of technical challenges in the reports that shape the observations about what genome editing is and what ethical challenges lie ahead. Comparison is a valuable tool in this regard, because differences show how things could have

been otherwise. The research question guiding this thesis is: ***How are societal and technical challenges in Genome Editing co-produced in official bioethics reports?***

Layout of the Thesis

The state of the art that follows outlines debates in STS that I wish to contribute to: the coproduction of biotechnology and bioethics and the assessment and governance of emerging technologies. Next, I introduce several STS concepts helpful in working through how these reports become influential. As spaces at the intersection of science and society, the reports are an important place of exchange. The analysis focuses on the performativity of the reports in setting up future public discussions about specific applications of genome editing. There are striking differences between the reports in how uncertainty is presented.

The analysis begins with governance and how public input and forums for discussing ethical and social challenges are addressed before moving to specific societal challenges. Anchoring to familiar debates is one discursive technique used in the reports to influence current and future discussions about genome editing. I look at how the reports write about unknowns and project changes, as well as the work of distinctions and categorization. Genome editing is transformative in practice, but the ability to manipulate genomes is not new. While both reports acknowledge this, the Nuffield's characterization of CRISPR-Cas9 as transformative and the National Academies assessment that the ethical challenges of genome editing are "not new" are comments on science and technology governance. Applications of genome editing bring values of individual self-determination, human dignity, and social justice into conflict. Keeping in mind the controversies over research on embryos and genetically modified organisms in agriculture, these major bodies are aware that bringing scientific and societal concerns together is not always without controversy. At times, it appears that the reports advocate for research practices and development outcomes that are more responsive and open to diverse voices and concerns – at others anticipation of public concerns has the function of avoiding discussion and potential controversy. The thesis examines different ways STS-trained people and STS concepts are present in the reports, as well as the role envisioned for publics and public discussion. It also explores how scientific authority is invoked and reinforced not only through the text but the production of the report documents. My research suggests that the issue of whether genome editing is presented as transformative or not new, is not an assessment of the technology, but a positioning of institutions in relation to the complex and overlapping governance of science. My conclusion is that scientific authorities manage the expectations for a public discussion. They do this by setting the agenda, naming societal challenges up for discussion and placing constraints on what is not, encouraging participants, means of participation and setting expectations about

what reasonable positions might be and establishing categories and a vocabulary to be used. The reports also set expectations on how the results of such discussions can be used and the potential impact on applications of genome editing in humans, human reproduction and food.

2 State of the Art

Bringing social and ethical issues into technology assessment is an evolving process with a complex history. STS has a long-standing interest in biotechnology and bioethics. STS literature about expertise and uncertainty, publics and public engagement inform the analysis of the reports. Scholars over the years have thought deeply about how to cope with emerging technologies and the debates about ethical, legal and social or responsible research and innovation and how they relate to institutional actors. These areas of STS research are important for going deeper into the bioethics reports from the National Academies of Science, Engineering and Medicine and Nuffield Council on Bioethics to see how and why they have an impact on scientific directions and societal impacts.

2.1 Biotechnology and Bioethics

The societal challenges presented by the reports recall ongoing debates in bioethics and biotechnology, including assisted reproduction, research involving human embryos, genetic modification of food and animals, eugenics, and human enhancement and past attempts, such as the Asilomar conference on recombinant DNA, to achieve closure. Critical and influential work in STS (Jasanoff, 2005; Nelkin, 1979)in these areas continues to inform the discussion and provide a lens through which to study how the reports anchor or distance themselves from these debates.

Biotechnology refers to products or technological applications that use living systems or living organisms. Hurlbut defines bioethics as, “the organized response to considerations that are ordinarily seen as belonging to the society side of the science–society nexus,” (2017, p. 11), while Jasanoff explains how the term establishes a new discourse, “Combining life (bios) and moral custom (ethos) in a single portmanteau word, bioethics offered the promise of bringing order and principle to domains previously governed by irrational, emotive, and unanalyzed reactions” (Jasanoff, 2005, p. 172).

2.1.1 Uncertainty in Biotechnology

Biotechnology is particularly interesting from the co-production perspective discussed later in the thesis as a nature/culture hybrid. One of the first recognitions of the uncertainty bound up

in the promise of biotechnology was the emergence of recombinant DNA in the 1970s. The new technology promised to be able to cure genetic diseases and improve nutrition and health, as well as transform the way diseases were studied and expand scientific knowledge. There was also a fear that the new technique could inadvertently lead to new plagues, monsters and strange human/animal hybrid creatures. Hurlbut (2015a, 2015b) traces how dealing with this tension set a precedent that informs governance of emerging technologies today.

In 1975, molecular biologists working with recombinant DNA organized a meeting at the Asilomar conference center. They agreed on standards to protect themselves and avoid negative outcomes, establishing a moratorium on the research until procedures were in place: a new regime of internal review, containment and isolation under the heading 'biosafety.' The participants focused discussions on technical problems and called for technical solutions, in a way that left non-experts out of the discussion (Wright, 2001). The Asilomar strategy of self-regulation, adopted in practice by the NIH Recombinant Advisory Committee and institutional biosafety committees, diffused public anxiety and preempted legislation (Hurlbut, 2015a). This arrangement reinforced expert risk assessment as the governance model for emerging technologies. Notably, public participation was not allowed at the Asilomar conference, even as it is remembered for its transparency and openness. STS pioneer, Dorothy Nelkin wrote at the time, "recombinant DNA is a sensational technology with ethical and social implications that require public control," (Nelkin, 1979, p. 92) questioning the ability of the NIH to both promote and regulate biomedical research. Asilomar is also used as an example that "scientists are in the best position to make judgments about whether and when a technology is sufficiently developed to warrant public attention to its "impacts" and "consequences" (Hurlbut, 2015a, p. 12). As discussed later, the controversy over genetically modified organisms in food was an impact and consequence of recombinant DNA that was unforeseen and outside of the biosafety regime's purview (Jasanoff, Hurlbut, & Saha, 2015). Today, many of the unrealized promises of recombinant DNA are revived in the hopes of Gene Therapy and now Genome Editing. Despite the STS critiques, Asilomar is celebrated as the beginning of responsible innovation and set by some groups of scientists as an example not only for emerging biotechnologies, but also in artificial intelligence (Hurlbut, 2015a). Although participants at the meeting were concerned with the use of recombinant DNA in bioweapons production, these discussions were intentionally left out of the scope (Wright, 2001). Social, ethical and legal concerns were pushed to other forums because of their potential disruptive nature.

2.1.2 Bioethics

The 1970s also saw the institutionalization of bioethics. Bioethics grew out of growing awareness of abuses in human subjects' research; trials on prisoners, withholding cures for decades, and testing on patients in mental institutions highlighted the need to design clinical trials that do not violate human dignity, that is trials that inform participants of risks and receive consent for voluntary participation. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974 and began work on the Belmont Report (1979) in 1976, eventually issuing guiding principles for human subjects' research that serve as the foundation for the bioethics regime. Formalized bioethics started initially with a review board; now bioethics committees, forms, and trainings are required for research programs large and small when human subjects are involved. This institutionalization transformed how and where discussions about ethics take place, a topic continued in the following section. The first bioethics boards set a precedent for future discussions, and the debates continue in the discussion of genome editing, shaping the course of biotechnology.

Hurlbut (2017) provides a historical account of the mutual entanglement of assisted reproduction and bioethics. The Ethics Advisory Board (EAB), formed in 1974 to review government funded research projects involving human subjects, is pulled immediately into the question of In-Vitro Fertilization (IVF) following the birth of Louise Brown in the UK. The board sets out to establish a consensus about how a human embryo can be used and whether it should be afforded the same protection as a living person. They draw on expert testimony and public hearings in a process that spans five years. Hurlbut's (2017) account tracks moments where scientific research is used to naturalize technological intervention; research showing that a significant number of human embryos fertilized in the womb fail to develop is used to naturalize the frequent failure of in-vitro fertilization. Both in-vitro and in-vivo fertilization are characterized as processes that may or may not lead to birth. The analogy shifts the discussion to therapy rather than engineering – to restoration instead of transformation (Hurlbut, 2017). Categorizing IVF as a therapy, also allows concerns about IVF to be categorized as private, medical concerns.

Still the question of whether research involving embryos that would never lead to a birth was ethical, remained unclear. Hurlbut (2017) relates how strong opposition to human embryo research by one committee member faded in the presence of an alternative scientifically plausible inception date, after the possibility of a cell division creating twins. This change of heart was part of a theological discussion about individuality, identical twins, and the soul but

was translated into scientific language. Concerns about the moral status of the embryo and unused embryos created by the IVF process were passed to the future. Indeed, later the Warnock committee in the UK would codify this as the 14-day rule, based on research establishing a 'primitive streak,' and institute the term 'pre-embryo' (Jasanoff, 2005) to create a moral distinction, but not closure on the question of when human rights begin.

As a precedent for future bioethics deliberations, the EAB is notable for setting up the process to: seek consensus, use science as a constitutional foreground for discussions, and confront moral questions in as limited a way as possible (Hurlbut, 2017). Jasanoff's (2005) comparative work on the co-production of life science and governance labels this US tendency the 'view from nowhere.' Constructing objective scientific evidence in the US (Jasanoff, 2011) involves excluding or removing bias, often through peer review and using quantifiable measures to come to a consensus. Jasanoff (2011) contrasts how bioethics committees in the UK and Germany function differently. In the UK, prominent public servants guide the process to create assessments that are reasonable. In Germany interest groups work towards a solution, while maintaining dissenting opinions. These epistemic cultures, or nationally situated ways of knowing, lead to different operating principles: muddling through (UK) and the precautionary principle (Germany).

The meaning of the primitive streak was not obvious; it was socially constructed in order to resolve uncertainty about the allowability of research on embryos. STS Researchers hold that scientific controversies cannot be decided by experimental evidence alone - closure depends on other factors external to the experiment (Latour & Woolgar, 1986 [1979]). Hurlbut asserts that the 14-day designation in the EAB report was a "pragmatic, unprincipled and essentially undiscussed" (2017, p. 73) outcome of the report process, which was later given moral significance by the Warnock commission.

The result, set against the historical context of Asilomar and the EAB, is the institutional compartmentalization of biosafety, scientific merit via peer review, and human subjects' protection, each with separate review processes. Institutional review committees, the structure in which this self-regulation is carried out is criticized for being both too narrow in scope and interested in the reputation and funding of the institution (Jasanoff, 2016).

More recently bioethics is associated with 'Ethical, Legal, and Social' programs attached to major research programs, such as the Ethical, Legal, Social implications (ELSI) program attached Human Genome Project (HGP) where funding for social science research is set aside in

the project budget. This program has come under critique from STS scholars. The program managed to be both too close to the results, and not close enough to the research (Hilgartner, Prainsack, & Hurlbut, 2016). In addition to the internal conflict between promotion and regulation already noted by Nelkin (1979), the ELSI program lacked oversight or reform authority, and was not part of project design, coming instead after as public relations. Another issue is that of funding, because the funding was set up as a percentage of the total project funding, it was often seen as taking resources away from research. Hilgartner et. al's (2016) critique is not limited to the HGP, extending to the many other programs that followed in the US and Europe, arguing that such programs may be more inclusive and avoid controversies, but aren't able to regulate or exert significant changes, ultimately rejecting using 'ethics' as a mode of governance. Their work also serves to distance STS from bioethics and ELSI programs, charging that these programs are built on distinctions between facts and values, defining norms, and seeing technological advancement as a goal in and of itself that has been challenged by key concepts in STS such as co-production, cultural studies of science, and the precautionary principle.

2.1.3 The Stem Cell Debate

The arguments and distinctions for whether and when an embryo obtains the legal status of a person have drawn on both science and ethics, however neither consensus processes used in bioethics nor scientific evidence have held up under public scrutiny. The great diversity of views on the subject preclude permanent closure in official bioethics discussions. Bioethics bodies do take up the embryo question again, particularly as excess embryos from IVF start to be seen as a resource to researchers and clinicians (Jasanoff & Metzler, 2018). The UK established the Human Fertilisation & Embryology Authority (HFEA) in 1990 to oversee both clinical and research uses of human embryos, while the US banned federal funding for embryo research but otherwise left institutional research boards to self-regulate. Ethics concerns are formalized and included in technical assessments of safety and efficacy in different ways and at different stages. HFEA in the UK approach underwent extensive public consultation before approving extensions of IVF such as, pre-implantation genetic diagnosis, human admixed embryos using animal egg cells, and three parent embryos; without the "public uproar and political deadlock that characterized comparable debates in Germany and the United States" (Jasanoff & Metzler, 2018, p. 16).

Decisions about what constitutes allowable research go beyond official bioethics bodies; in one case, questions about human embryonic stem cell (hESC) research were presented in an election to provide funding specifically for stem cell research. The issue turned away from the

issue of the connection between stem cells and individuals, toward providing cures as a social good. Thompson (2013) documents how a 'pro-cures' frame came to dominate technical, political and ethical understandings of hESC research in California. This frame was rooted technically in an unrealistic innovation trajectory from basic to clinical research that would provide life-saving cures, politically in state research institutions as a driver for economic growth, and ethically as a counterbalance to pro-life concerns by focusing on saving lives. Discursive moves allow for bioethical consensus in other controversial areas; for example 'human cloning' becomes 'nuclear transplantation to produce pluripotent stem cells' (Hurlbut, 2017). While this discursive move side-stepped the controversial question of when life begins, it also sidelined questions about distributive justice – would average Californians be able to afford the cures when many didn't even have basic health insurance? Thompson notes that "procedures and institutional roles put in place in the past determine what issues are subject to debate in what forum, and by whom, sometimes sidelining other issues (religious, social justice) from coming under consideration" (2013, p. 56).

2.1.4 Genetic Testing and Identities

Parallel to advances in embryonics and assisted reproduction have been advances in genetics and molecular biology. While agricultural practices dating back centuries could speed up evolution in new plants and animals, it was at the level of breeding, not reproduction. Following the transition to civilian operations of military science after World War II, many physicists became interested in biology at its smallest levels, in this new field of molecular biology. Biology became something to take a part, to understand, to think deeply about. The idea of a "genetic code" emerged at the same time as cybernetics and information theory spread in the post-WWII period, orienting molecular biology toward "DNA-based explanations of heredity" (Kay, 2000, p. 5). Our understanding of heredity and health, of life itself, is embedded in cultural practices that stabilize and naturalize genes as technology.

The Human Genome Project started by the National Institutes of Health in the US was a major undertaking to better understand the "code" by mapping the entire genetic sequence of one person. Hilgartner's history of the project shows how at each step the organization and design of the project were contested and could have been done differently. Contrasting the 5 year plans in the beginning of the project to the competitive race for patents near the end, Hilgartner (2017) goes into the laboratory to look at how 'knowledge control regimes,' principally intellectual property rights, emerge alongside advances in biotechnology. Studying biotechnology patents makes clear not only how economic interests shape scientific research,

but also how nature/culture boundaries are constructed (Jasanoff, 2005). Advances in genetic sequencing by the Human Genome Project and private companies led the way to genetic testing.

Genetic testing has revived interest in the performativity, that is the social implications, of the genetic code metaphor and narratives of genetic determinism. Rabeharisoa and Callon (2004) studied the entanglement of medical research and collective action in muscular dystrophy (MD). While MD patients produced and shared knowledge on their illness, encouraging interest from physicians and researchers, new scientific information brought several neuromuscular diseases together under the heading of muscular dystrophy (MD). The establishment of Muscular Dystrophy further spurred the collective action of patients and researchers in a new research model that focused on generating a genetic map of muscular dystrophy and effective therapies using privately raised money.

Although generally seen as an improvement to both research design and health, not everyone is happy about genetic testing. One interviewee, referred to as Gino, refuses to have his children genetically tested to see if they will develop the disease or be carriers (Callon & Rabeharisoa, 2004), both calling attention to and refuting the power of genetic information to shape identities. Their study is also an example of the principle of symmetry that guides STS research, which focuses on actions rather than intrinsic qualities and investigates successes and failures with the same empirical methods (Bloor, 1991 [1976]). To the extent that technology is portrayed as politically neutral, it naturalizes social changes as either progress or unintended side effects. STS accounts, such as the story of Gino, document the effects of technology in a parallel way, tracing overlapping and complex outcomes, ambivalence, and cultural shifts linked to genetic testing.

New work from Noa Vaisman (2017) about genetic testing in a very specific case brings into contrast a new debate about human rights – that is the very definition of what it is to be human. Setting transhumanists and privacy advocates against advocates for social justice, she challenges informed consent and formal practices of human subjects' protections. The genetic test of 'shed-DNA' such as that from a comb or toothbrush, against their wishes, established the lineage of the 'living disappeared,' children taken from political prisoners during the last civil-military dictatorship in Argentina. The judge ruled that testing shed-DNA does not violate privacy or choice, while upholding the right to refuse a blood test. The tests forcefully reconstituted the individuals identity. Vaisman argues that identity is not constituted by DNA, but rather that a human subject is "both intertwined with his environment and emerges through and in his or her relations with others in the world," (2017, p. 15) . She argues that the human

rights regime should be more attuned to our lived world and technological innovations. Genetic testing has come so far without significant health benefits, a disappointment that drives the search for genetic solutions, the unrealized promises of stem cell and gene therapy are shifted onto genome editing (Reardon, 2017).

2.1.5 GMO Controversy

Whereas with recombinant DNA and Stem Cells, bioethics bodies tried to pre-empt public reactions, agricultural applications were largely outside of the scope of biosafety and bioethics review committees. The question of how to regulate agricultural biotechnology was answered very differently in different places. In the US, biotechnology patents and a regulatory focus on the safety of genetically modified products. The Asilomar model failed to anticipate public concerns with agricultural biotechnology (Jasanoff et al., 2015), provoking protests and lawsuits. The US regulation, or lack thereof of genetically modified crops contrasted with the patent regime in Europe and extreme precaution towards GMOs in Germany that singled out the process (Jasanoff, 2005). In the UK, the challenge of GMOs did not fit into existing governance models, combined with public skepticism of government handling of mad-cow disease, created an opportunity for a new kind of 'deliberative ethics' (Jasanoff, 2005) that was able to consider social and cultural concerns outside of the scope of biosafety and bioethics reviews. The UK government invited participation from environmental groups (Jasanoff, 2005, p. 57) into the advisory committee on the risks of commercial biotechnology, opening expert-driven policy on GMOs up to more public scrutiny. The resulting policies reflected more of the European system of labeling and regulating genetic modification processes. In revisiting these debates on genome editing, the UK may shift their approach away from process toward products[4].

2.1.6 Governance Co-Produced

Processes, including bioethics, genetic testing, deliberative ethics, reproductive technologies, patent regimes, are technosocial hybrids, the outcome of decades of negotiating policy and technological developments. They are entangled in genome editing. The legal status, regulatory framework, and ethical boundaries of genome editing are just as emergent as the technology itself: they are being formed together, coproduced (Sheila Jasanoff, 2004). As more and more laboratories adopt CRISPR tools for genome editing, STS scholars are also turning their attention toward CRISPR.

[4] GMO regulations in the UK are still process based, however it appears that when the change could have occurred through traditional breeding, genetically edited crops will not be subject to the regulations. See the webpage, https://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Commons/2018-03-07/131586.

In anticipation of the National Academies of Sciences organized gathering, Jasanoff, Hurlbut und Saha (2015) warned that the 1975 Asilomar summit to anticipate potential challenges in recombinant DNA has been mis-remembered as a success. While some of the worst fears of genetically altered monsters and plagues never came to pass, the GMO controversy is also the legacy of this meeting that failed to ask or imagine impacts from deliberate release from the laboratory. Instead of pushing research to the limits, the CRISPR research and development agenda might focus on how to protect public health, safety, and social values; "the emergence of a far-reaching technology like CRISPR is a time when society takes stock of alternative imaginable futures and decides which ones are worth pursuing and which ones should be regulated, or even prevented" (Jasanoff et al., 2015, p. 2). Hurlbut (2017) points out the CRISPR research creates a large demand for human embryos, the supply of which continues to grow with private IVF practice. CRISPR also puts additional pressure on the 14-day rule for embryo research. Hilgartner writes that governance questions about the "wise use of new and powerful gene editing technologies such as CRISPR… have only increased the need for theoretical frameworks equipped to analyze the processes- within the laboratory and beyond it—that are reordering the worlds in which we live" (Hilgartner, 2017, p. 224).

2.2 Governance of Emerging Technologies

In 1975, Dorothy Nelkin wrote, "The complexity of public decisions seems to require highly specialized and esoteric knowledge, and those who control this knowledge have considerable power. Yet democratic ideology suggests that people must be able to influence policy decisions that affect their lives" (1975, p. 37). Today, genome editing fits this description once applied to recombinant DNA. Deliberation on the promises and challenges of genome editing depends on some understanding of technical and specialized knowledge, however many people do not trust institutions and scientific experts to make decisions in their interest. This is the paradox of scientific authority (Bijker, Bal, & Hendriks, 2009). Building on co-production, Bijker et al. (2009) describe the 'Paradox of Scientific Authority': in simple cases, science and technology assessments are based on scientific and technological accounts of quantifiable risks. When emerging technologies require tradeoffs between economic and social goals, they become complex, when the risks are unknown, they become uncertain, requiring technologies of humility, and when they become ambiguous, broader participation can help navigate an acceptable course. This section covers STS works on dealing with promises and challenges of emerging technologies, the work of expert committees and the importance of public engagement.

2.2.1 Promise and Anticipation

The 'future' plays an interesting role in STS, where much work explores how "the future, as a dimension of the present, is constructed through practices as well as through discourse and thus contributes to the production and reproduction of social reality" (Konrad, van Lente, Groves & Selin, 2016, p. 473). The extension of this is that "technology and society are coproduced and could evolve in radically different directions" (p. 479). Instead of *the future*, Felt et al. (2013) use the term *futures* to capture multiple and overlapping possibilities. This openness to uncertainty challenges both social and technological determinism (Akrich, 1992), as well as the myth of the linear progress (Sarewitz, 2016). Historical accounts of technology are often written as a chain of events – discovery, application, marketing, saturation, often with a visionary vanguard: Ford, Oppenheimer, or Ventnor (Hilgartner, 2017). Once a technology is in society, it is difficult to imagine how it could have been otherwise, although scrutiny usually reveal contingencies, false starts, and failures. Rather than looking specifically at failed promises and overstated hype narrowly, a long look shows how a group of technologies, such as genetic manipulation, are "embedded in the broader cultural promises associated with technology and its contribution to solving social problems," (Konrad, et al., 2016, p. 484), something of interest in this thesis. Looking back also informs ideas about the future, helping to anticipate possible outcomes. Recognizing the performativity of expectations for the future, one stream of STS research has moved toward shaping the present. By pushing certain readings of the future – either dystopian or desired, futures serve as resources (or instrument) for intervention for engagement-minded STS people (Konrad, et al., 2016). Anticipating also serves institutions that promote research, anchoring promises of biotechnology to alleviate societal challenges, particularly in health, to research support in the present.

Returning to stem cell research, in California the promise of cures (Thompson, 2013) drove public investment in research. Recombinant DNA also promised relief from the burden of genetic disease. Agricultural biotechnology promised more nutritious food. Promises connected to desired futures drive research. Research funding, whether from public or private sources, connects the work back to society through these promises of a desirable future. Social significance is attached to short or long term project goals in research design and funding justifications with varying levels of accountability (Sarewitz, 2016). These goals are often oriented toward larger social challenges such as curing cancer outside the scope of the project. The goals may even exacerbate other social challenges, such as healthcare disparities. Coordination is lacking between projects; project outcomes are not measured against public health outcomes, but publications. In academia, publications become their own sort of capital in the academic system (Fochler, 2016). In the private sector, biotech firms often fail (Birch, 2016);

Fochler (2016) found that investigators at biotech start-ups in Austria were motivated by the protected time and space for their research, as much or more than the financial success of the firm. Sarewitz (2016) argues that research in and of itself is the actual aim of many investigator driven projects.

Major institutions, such as the National Academies of Science and the Nuffield Council on Bioethics can act to prioritize and organize distributed research projects towards larger goals - but they also privilege the scientific community's imagination of the future over desired futures of the public at large (Hurlbut, 2015b). Public concern at nascent stages of research are often dismissed as impediments to progress and asked to defer to the "agenda setting authority of science governance" (Hurlbut, 2015b, p. 147). Operating under the modus of self-regulation, scientific institutions work to bring these imaginations into being, making them seem inevitable and reinforcing their authority over governance discussions about emerging technologies (Hurlbut, 2015b). These discussions have been enshrined in a process of regulatory science, whereby either specific studies or literature reviews are carried out to inform policy (Grundmann, 2017; Jasanoff, 2011).

The promises in genome editing that both create the most hope and the greatest concern are tied to interventions in reproduction. Funding and legal restrictions create uncertainty about how far research can and should go. Calls for a public discussion (Baltimore et al., 2015) are also requests for clarification about what is allowed. The reports can be seen as one of the first steps to changing restrictions, in opening up the topic and laying out the terms of the discussion to follow. In response, precisely to these calls for public discussion Jasanoff et al. (2015) warn that letting experts set the agenda could result in a narrow focus on biological risks, rather than risks to social relationships and cultural values, and make it difficult for non-experts to contribute.

2.2.2 Regulatory Science

In the standard view of science, "uncertainty exists only in areas where not enough research has been done yet" (Bijker et al., 2009, p. 26), but the history of science shows us that science has often increased our appreciation and realization of uncertainty along with some increases in confidence (Ravetz, 2004). Beck (1992 (1986)), Perrow (2007)and Ravetz (1999) take apart the concept of risk and highlight uncertainties and vulnerabilities in technologies and technological systems. With knowledge comes non-knowledge, from the German, *nichtwissen,* distinguished from ignorance and nescience in including also deliberately excluded or avoided *negative knowledge* (Gross, 2007). Technical assessments are often focused on measurable and quantifiable evidence; STS scholars examine how scientific evidence is produced as researchers

interact with nature using specialized equipment and reduce the object to data. In STS, equipment is often referred to as "inscription devices" (Latour & Woolgar, 1986 [1979]) because they take a sample, for example of dirt or blood, and turn it into written information. Qualitative descriptions as well as cultural meaning of the samples are left out, becoming unknowns. In pursuit of the new, technologies not only create solutions, but also new problems such as climate change, toxin-linked cancers, asbestos-linked lung disease, microplastic accumulation, and antibiotic resistance. Callon, Lascoumes and Barthe (2009) call these unexpected and undesired effects, 'overflows,' and links them to ineffective risk/benefit analyses that attempt to eliminate or reduce uncertainty. Leaving things out of a risk assessment because they are incalculable or inconvenient creates negative knowledge.

Another way of understanding the construction of scientific evidence is through the idea of paradigms. A paradigm is a formalized set of basic assumptions and practices guiding the scientific community, or a subset thereof, in a given time (Kuhn, (1964) 1996). Within a paradigm, scientific work takes the form of puzzle solving, filling in missing pieces; ideas or procedures outside of the paradigm are generally ignored or classified as exceptions. Accounting for unexpected results can lead to alternate and competing explanations – in the 1930s and 40s, inheritable characteristics were attributed to proteins even as observations didn't make sense (Kay, 2000). As these anomalies pile up, they can lead to crisis and then scientific revolution, resulting in the emergence of a new paradigm – such as the DNA based genetic code - that accounts better for the empirical observations.

Scientific evidence is then neither sufficient for making decisions about how to live with technology, nor is it self-evident; its authority is socially constructed (Grundmann, 2017). Hilgartner (2000) envisions the committee process as a dramaturgical performance – the committee members and staff are the actors, and the advisory body is the director. The performance on the front stage differs dramatically from the organized chaos backstage, kept separately through the strict control of information. The presentation of the consensus report represents closure and draws on not only the reputations of the institution and committee members, but the stage management of the performance for its authority.

In scientific publishing, research results must first pass the scrutiny of other experts in peer review, an exchange that improves the reliability of the knowledge and reifies scientific authority (see Jasanoff, 2011). The scrutiny, acceptance and exchange of ideas is then the basis for constructing facts. Jasanoff critiques how this same practice was extended to "knowledge used to serve policy needs" (2011, p. 307), where particularly in the US, constructing objective

scientific evidence involves excluding or filtering out bias, often through peer review and using quantifiable measures to come to a consensus. The practice of speaking with a collective voice, such as in a consensus study, "generates authority in a self-authorising way," (Nowotny, 2003, p. 152), but is not enough to guarantee acceptance on issues that go beyond science. Anomalies occur not only in scientific observations, but in how scientific and technological issues are dealt with under current political and regulatory system. Evans and Palmer (2018). Thinking of the regulatory challenges of emerging technologies as anomalies, allows the possibility of thinking outside of the current system. Different ways of dealing with emerging technologies range from modifying the regulatory system, to moratoriums and prohibitions, to system change. Using the example of gene drives, Evans and Palmer (2018) describe how multiple interpretations of the same technical information within different political and regulatory contexts contribute to different scientific explanations of gene drives and their impacts. With reference to Jasanoff (2004), Evans and Palmer conclude that "an actor's definition of a gene drive is co-produced with the type of regulatory system that the actor believes in" (2018, p. 224).

2.2.3 Ethics

Even when scientific evidence gains consensus and explanations and definitions converge, to make sense of technical, societal and governance challenges presented by new biotechnologies requires acknowledging uncertainty about the effects outside the laboratory, in the complex setting of a human, a population, the environment. Bijker et al. capture the challenge in this phrase: "The translation of scientific results into guidelines that can be socially implemented is … less straightforward and more problematic than the standard view suggests" (2009, p. 27). Values are difficult to capture in the usual quantifiable format for scientific evidence. One way that institutions have attempted to bring values back into technological assessment and advice is through ethics. Ethics attempts to discern questions of right and wrong, or more pragmatically, allowable and unallowable directions of scientific inquiry or technological intervention. Ethics can take different roles in governing science. In the US ethical bodies are kept close to the research, in Germany public ethical deliberation takes part inside of the government, and in the UK, the Nuffield Council on Bioethics represents a model of public ethical deliberation outside both (Jasanoff, 2005). All three approaches are based on anticipation of concerns.

Where ethics has been used as a "symbolic form of public involvement" (Tallacchini, 2009, p. 289), expert opinions have spoken more for what public opinion ought to be, excluding some values as unreasonable, irrational, or unscientific. In the previous section, specific critiques with the bioethics regime were its inability to anticipate distributive justice concerns and concerns

with agricultural biotechnology, one general criticism is that making ethics the domain of experts is inherently undemocratic because they extend government control to normative issues without legislative or public involvement (Tallacchini, 2009).

Jasanoff (2016) writes about different institutional forums for keeping track of ethics – visible bodies such as Presidential councils or the Nuffield Council on Bioethics as well as the Institutional Review Boards (IRBs) tracking human subjects' protections at universities and research institutions. Other committees review research on animals (IACUC -Institutional Animal Care and Use Committee) and work with stem cells (ESCRO – Embryonic Stem Cell Research Oversight) Jasanoff writes that "the IRBs, IACUCs and ESCROs serve as almost invisible handmaidens to the research enterprise... They are entrusted with preventing flagrant ethical violations, but at the same time are expected not to block the progress of science as scientists see it"(2016, p. 232). Operating constraints allow discussion of certain issues – those tied to laws or funding restrictions but wouldn't involve questioning the overall direction or purpose or broader ethical and social questions.

Ethics has become almost a scientific practice, using the model of expert deliberation and peer review derived from the scientific community. Committees are responsible in first dividing ethical questions from other social and economic issues and then validating reasonable and rational arguments or principles that could then be used in other aspects of governance as objective knowledge rather than engaging in value-laden issues. In this way "the outsourcing of values contributes to the institutional framing of moral and social choices as a matter of neutral expertise and technical knowledge" (Tallacchini, 2009, p. 259). Despite their influence, the legitimacy of ethical committees and their recommendations are not universally accepted by publics in Europe or the US. Jasanoff reflects that despite repeated efforts, technology development programs in the U.S. have not found a satisfactory model for public ethical deliberation, arguing that ethical analysis takes an instrumental role to "reassure concerned publics that moral risks are under control" rather than serving "broadly democratic ends" (2016, p. 234).

For STS scholars, two kinds of ethics emerge, ethics, as the open-ended, value-laden search for what is right, and politicized "ethics" with the formal procedures and bounded areas of consideration used as a tool to de-politicize sensitive issues (Wynne & Felt, 2007). For Tallacchini, ethics has been "constructed as an isolated set of values, has been exploited for its symbolic capacity to evoke citizenship" (2009, p. 281). Ethics has become its own sort of soft law or tacit governance outside legislative processes (Tallacchini, 2009; Wynne & Felt, 2007).

Returning to the paradox of scientific authority, Bijker et al. (2009)argue that institutions need to be reflexive about the limitations of scientific evidence if they are to serve the public. Expert committees cannot resolve ethical and social aspects of technology, but their work frames the terms of the debate and sets up who should be involved.

2.2.4 Publics

The relationship between people and governance in a society, that is, what gets referred to as the public, requires examination. Who should be involved in "the democratic management of risks and benefits of science and technology" (Bijker et al., 2009, p. 35)? STS accounts of interactions between the public and scientific experts in the 1980s and 1990s were critical of the 'deficit model' that increasing public understanding of science would lead to acceptance of new technologies (Wynne, 1992) and later engaged in trying to make expert advice more socially robust by including other forms of expertise (Nowotny, 2003), discussed in more detail below. Today, as scientific bodies attempt to be more accountable, references to public opinion, public discussion, and public participation present an assumption of a singular public with straightforward attitudes and opinions. Wynne charges that both public attitude surveys toward and science bodies have "deeply inadequate imaginations of what a collective public might be," (Wynne, 2016, p. 117) calling instead for an understanding of multiple, overlapping changing *publics* in the plural.

In carving out *publics*, STS scholars often rely on the work of Dewey (2012 (1927)), who wrote that some controversies could only be settled through public involvement, defining the public as those affected by the problem at hand. Marres (2005) succinctly argues, "no issue, no public". Bijker, Bal and Hendriks prefer Latour's formulation that an issue becomes a problem and "generates a concerned and unsettled public" (Latour, 2007, p. 816). The concept of issue-defined publics has also been problematized as limiting the "self-constitution" of a public (Felt & Fochler, 2010) as well as in upstream assessments where there are not yet consequences but only uncertainties. In upstream logic, the inverse is true: "no public, no issue," (Asdal, 2008, p. 20) highlighting the role of controversy in making an issue. The rise of professional bioethics (Hurlbut, 2017) and ethics based soft law (Tallacchini, 2009) discussed previously is also tied heavily to concepts of the public or publics.

To this idea that people should be somehow involved, Wynne, Epstein, Callon (1999) have questioned how we define 'people' and 'public' and showed that lay people also have highly specialized knowledge. Still, as much as the concept of the public or publics are difficult to define, we must have some designator to discuss ethical and social issues. Stilgoe points to the

"'you's' 'we's' and 'they's'" (2015, p. 202) used in regular speech and how they are often unclear. Designations of lay people, citizens, patient, consumer and combinations are also used to achieve more clarity. Beyond terminology, thinking about publics also requires distinguishing between ambivalence and acceptance (Wynne, 1992), and questioning how participants are invited to participate (or not) and the material settings of the participation forum (Felt & Fochler, 2010). I will pick up the discussion of which ways voice is given or attributed to the public in the last section on Public Engagement.

Similarly, the presumed reader or audience of consensus reports concerning emerging technologies is not the public, but certain publics. Bijker et al. (2009) describe the accompanying letters, presentations, and distribution of the reports of the Gezundheidsraad (The Health Council of the Netherlands) within professional networks, some of which might be seen by many and others only by individuals. Hilgartner (2000) documents how backstage information became *public* through a leak to the press and the National Academies cancelled publication of the report, inviting more people into the process than normally would be aware of even the finished report.

2.2.5 Public Engagement

The interplay of individuals and institutions is an important consideration in how much ethics can impact research design and project outcomes. A more democratic approach, such as those envisioned by STS scholars (Callon et al., 2009), opens these narrow depictions of responsibility and ethics, but raises many practical challenges in implementation. STS work on public engagement methods, such as the work at the University of Vienna by Felt and Fochler (2010), start with a strong rejection of what is known as the 'deficit model.' Public outreach efforts based on raising scientific literacy to foster acceptance for scientific and technological change have met serious challenges, not only because education does not always lead to agreement, but because the one-way communication format doesn't allow for input. Although strongly associated with the 1980s, the public deficit model has never left. STS researchers involved in the Nanotechnology SEI initiative, which sought to integrate social and ethical issues into scientific practice, report that in implementation, principal investigators repurposed simply re-invented public education models centered on "public-as-the-problem" (Viseu & Maguire, 2012, p. 201).

One response to the deficit problem have been large public surveys, most notably the Eurobarometer, and elaborate public participation performances (public engagement), such as the Danish consensus conferences. While public surveys can only assess what people know,

engagement activities that seek to inform and deliberate have raised even more criticism –in the selection of who can participate, biased presentations of the new technology, as well as whether the input has any real impact on policy or research.

Public engagement encompasses both activities designed particularly to inform policy, as well as other activities that seek public involvement and promote dialogue. An STS focus on methodological issues reveals weaknesses as well as strengths in these activities (Felt & Fochler, 2010; Felt, Schwarz, Strassnig, 2011). In their research on the appropriation of Danish style consensus conference in the UK, Horst and Irwin comment that "enthusiasm for deliberation and public dialogue is closely coupled to an expectation that consensus – or something similar – about the future development of science and technology will follow" (2010, p. 106). Where public engagement activities are designed to satisfy ELSI concerns and legitimize funding in potentially controversial areas, presenting a hypothetical future situation can be used to build consensus toward a common goal. This not only narrows the issues to those presented, but also downplays current practices and research (Felt, Schwarz, Strassnig, 2011). Another danger in 'consensusing' (Horst and Irwin, 2010) is that instead of opening up possibilities early on in a project or emerging technology, an instrumentally oriented discussion framework can create a "false consensus" which might be ideologically driven or otherwise inauthentic, in that "the more complex and multi-layered character of public and institutional meanings, identities and understandings" are lost (Horst & Irwin, 2010, p. 109). Horst and Irwin argue that instead of labeling some consensus practices false and searching for a true consensus, we should "observe and explore the performativity of *all* these calls for dialogue (2010, p. 119, emphasis in original)

In regard to genome editing, Rose, Korzekwa, Brossard, Scheufele, and Heisler (2017) write about their experience with a 115 participant panel discussion on Designer Genes at a science fair. Instead of stressing the outcome, the authors discuss the practice of public engagement in general. A challenge with 'morally charged' scientific issues is that simplifying issues has the potential to polarize reactions, while communicating complexity is difficult in time-limited public situations (Rose et al., 2017). Small, longer focus groups can be deployed faster, with careful attention to the framing, such as the discussions moderated by the University of Vienna leading up to the October 2017 symposium, Editing Genomes with CRISPR: between scientific breakthroughs and societal challenges[5]. While Rose, et, al (2017) raise questions for future studies on how engagement activities impact experts, the University of Vienna activity used

https://rri.univie.ac.at/aktivitaeten/workshopconferences/crispr-symposium/

carefully developed card-based information and scenarios to avoid deference to experts in the discussions. In practice, public voices are used as a resource for ethics experts in constructing public input, downplaying the constructive role of the expert. For example, in the case of the panel discussion on human genome editing (Rose et al., 2017), pre and post surveys showed that people learned something about genome editing and its potential risks and benefits, and maybe found it more morally acceptable, however did not change in overall concern about the ethics or role in human progress of genome editing in general. While they do carefully explain their methodology and potential problems with the sample, it's easy to take this data and say "After the panel, participants felt they had more knowledge about human gene editing, saw more risks and more benefits from the technology, and viewed gene editing as more morally acceptable" (Rose et al., 2017, p. 267).

2.2.6 Getting Involved in Responsible Research and Innovation

STS researchers are interested in how science is organized overall and observe science in practice rather than the more aspirational views of science presented in the press (Latour, 1987). Sometimes this leads to critiques of the organization and direction of research and engineering work (Jasanoff, 2003, Funtowics & Ravetz, 1993). Similarly, qualitative research on the experiences of people within scientific practice are often critical (Fochler, Felt & Müller, 2016). Another powerful line of critique from the STS community comes from attempts to address social, ethical and legal issues without ever addressing project designs or goals. Critiques of ELSI program attached to the Human Genome Project (HGP) (Hilgartner et al., 2016), and Nanotechnology SEI initiative (Viseu & Maguire, 2012) bring home the importance of having the authority to make substantive changes and respond to input and concerns from different publics.

Part of the issue lies in the fact that funding and programmatic direction for Ethical Legal Social Aspects (ELSA) research (European term) and public engagement have come from the funding institutions promoting science, such as the European framework programs (Felt, 2018) if not the very projects they are studying, like the HGP, (Hilgartner, 2017). Felt describes an effort to make ELSA programs meaningful, despite pressure towards "smoothing societal concerns" (108), "ritualized forms of reflexivity" (Felt, 2018, p. 109) and separating ethical, legal and social aspects (ELSA) from project design and management work. Through these programs a robust community of STS researchers emerged who took opportunities to experiment with new forms of participatory devices, took advantage of opportunities for participant observation and otherwise engaged with ELSA programs. The movement towards responsible, research and

innovation (RRI) came out of these experiences, and, faces many of the same challenges (Felt, 2018).

STS researchers stress that governing CRISPR requires 'candour', 'recognition of values and assumptions,' broad participation, consideration of alternatives and 'preparedness to respond' (Hartley, Gillund, van Hove, & Wickson, 2016). Macnaghten, Owen, and Jackson (2016) have called for changes in institutional governance of CRISPR that focus on framing risks through the Responsible Research and Innovation (RRI) platform instead of ELSI. What is RRI and how is it different? First, RRI seems to be broader in terms of what it considers. Stilgoe and Guston (2016) write that risk and ethics are one way of looking at responsibility, a way that scientists are comfortable with, but that does not address concerns about the direction of technology or the distribution of benefits and harms. Some elements of RRI outline by Stilgoe and Guston (2016) are: interaction between social scientists and scientists, inclusion of public input, consideration of scientific practice including lab culture and careers, accounting for uncertainty and building flexibility into plans. RRI looks to individual researchers and research groups as a way to challenge institutions (as represented by institutional oversight committees), and the very "ideologies and myths they cherish" (Felt, 2017, p. 17). Felt (2017) warns against methods of manufacturing accountability rather than cultivating responsibility. However, if researchers think of ethics as an administrative burden or impeding career progress, they are not empowered to care.

Time and timing are also important considerations in RRI that set it apart from other attempts. High levels of uncertainty early in emerging technology development make governance difficult, while later in development things become less flexible (Stilgoe & Guston, 2016) – RRI calls for public engagement at multiple stages and acknowledges the experimental nature of public engagement activities. Stilgoe and Guston (2016) also note the need for considering innovative uses of technologies that come long after research and development – a consideration important for CRISPR technology which has opened up the possibility of genome editing to school settings and DIY-laboratories .

One of the major differences between ELSI and RRI, is that STS researchers who had been critical of programs for ethics and public understanding of science (Wynne & Felt, 2007) are now involved in the development and implementation of RRI (Felt, 2018). Previous efforts to include professional bioethicists, philosophers and theologians have failed to affect research practice because they have failed to take research practices in account. Attempts to make research ethics more democratic by including lay people have also failed to change practice.

Including social scientists in ethical deliberations is important to understand the processes and practices at work (Brown, 2006). A person (with STS training) active in setting research or development agendas can be a "Co-producer of knowledge" (Macnaghten et al., 2016, p. 352), contributing to project design and keeping questions about the purpose, goals, beneficiaries, and harms of the project at the forefront. "Enlightened scientists and policymakers have recognised that STS could be part of a renewal of science's relationship with its publics" (Stilgoe, 2015, p. 49).

Guston and Stilgoe try to account for this move from engaged to embedded, relating that interactions between STS trained people and scientists and engineers in emerging technologies have resulted in reflection on the methodology. Thinking of the collaborations themselves as experiments has allowed STS people to stay involved while remaining critical. The job then for STS trained people is to "reconstruct as well as deconstruct," "to articulat[e] alternatives, reveal complexities and develop new styles of engagement" (Stilgoe & Guston, 2016, pp. 857, 869).

Even when programs, funding, and teams are in place, priorities can change. Both the ELSI program attached to the Human Genome Project and the subproject devoted to ethical dimensions of the Synthetic Biology Engineering Research Center saw reorganization and limitations on their impact. Paul Rabinow distanced himself from the latter project (Jasanoff, 2016) and Alan Irwin notes that "not every science–social science collaboration works out happily" (2014, p. 72). This thesis explores the framework for this discussion as envisioned in two reports: "Human Genome Editing: Science, Ethics and Governance" from the US National Academies of Science, Engineering and Medicine (NASEM 2016) and "Genome Editing: an ethical review" from the Nuffield Council on Bioethics (2016). Concepts from the STS discussion on governance appear in the reports, and STS scholars are part of production and review (Thompson as a Nuffield committee member and Hurlbut as a NASEM reviewer), but institutions are slow to change. As our understanding of the complexity of the governance of emerging technologies grows, the challenge remains how to get involved in ensuring the best outcomes.

3 Research Question

Research Question: How are societal and technical challenges in Genome Editing co-produced in official bioethics reports?

There is a great deal of uncertainty surrounding genome editing, linked to questions of can we? and should we? These questions are separate but intricately linked: what we study becomes

what we know, and what we know informs how we live together, technical and social aspects are co-produced. The committees, whether labeled as bioethics or scientific advisory committees, bring knowledge and social order together and define what genome editing is, in order to start to answer questions from research institutions about where to direct research and how to avoid getting in trouble. These questions of, *can we?* and *should we?* can go far beyond the operational concerns with research management and biotechnology commercialization. How does the work of these committees and the ensuing reports bring together knowledge orders and social orders to identify challenges worthy of further discussion?

1. How do the institutions establish credibility in the reports and what role do the reports play in reinforcing and extending their authority?

As institutions engaged in providing expert advice on emerging technologies, both the National Academies of Sciences, Engineering and Medicine and the Nuffield Council on Bioethics contribute to the discussion on genome editing, calling and organizing committees of experts and laying out a charge for the report. This question explores the stated reasons and scope for the report, as well as what the institutions say about their role and process. This question sets out to explore the scientific and other kinds of expert authority drawn on in producing the reports. To answer this question, the thesis will look at the scope, methodology and procedures as presented in the report, the credentials of experts and composition of the committees, and institution self-presentation on the website or front material, with an eye to the construction of objectivity and rhetorical strategies in presenting authority and credibility.

2. How are societal challenges identified and framed in the reports?

To answer this question, I will compare the two reports and how societal challenges, as well as promises, are made. The analysis starts from a premise that science should serve society and be responsive to societal challenges, including health, economic growth, fairness, and human dignity, and will look at how the reports describe these challenges and attach to previous debates, including research involving human embryos/stem cells, gene therapy, and GMOs. CRISPR-Cas9 and the biotechnologies that may follow are tools, whether and how they are used are discussed in the reports, often in relation to societal challenges. The comparative study presented here draws attention to societal challenges that are only presented in one of the report and raises the question at to the meaning of their absence or exclusion. The analysis will look at where societal challenges are set in opposition to each other and debated in the reports, such as in cases of the burden of disability and celebrating diversity and dignity, rare diseases

and healthcare disparities. The analysis will also look for instances where societal challenges are used as a justification to change existing governance, such as prohibitions on inheritable changes to humans or bureaucracies dedicated to tracing the process of genetic manipulation of food.

3. Who is the 'we': how are publics addressed in discussions about governance in the reports?

This question will look at discussions about publics and the forums where discussions about the proper direction, use, and lifting of prohibitions affecting genome editing might take place. To answer this question, the analysis will also focus on ways in which voice is given or attributed to different groups of people. When using words like some, most or many as prefixes to designate groups of people, are some voices privileged and others diminished? The analysis will also look at the basis (such as a direct submission, interview, literature reference, or news article) of values or policy positions attributed to certain publics in the report.

The use of genome editing tools is constrained by existing nation-state based regulations and other forms of governance. As a site where societal and technical issues come together, the reports contribute to the revisions and renewal of governance policies. The reports discuss overlapping jurisdictions and different modes of governance, from funding restrictions and legal prohibitions to international agreements, some binding and some non-binding; in the analysis I will compare how, if at all, each report addresses publics in describing how governance might change.

4. How are the debates represented in the reports?

The "work" of bioethics reports, alluded to in the title, is to bring together technical and social considerations together to support a discussion. Experts don't merely present reality, they represent aspects of it, and what is more, are actively engaged with the subject and intervene (Hacking, 1983). The report process involves information gathering, selection, and consolidation in a written report. The committee members bring their experience, values and questions to the process and use rhetorical strategies to create a persuasive, yet objective report. The presentations of the two reports are very different, how is this achieved? To answer this question, the analysis focuses on four key discursive elements: non-knowledge, projections, timescales, and classifications. *Non-knowledge* refers to notions of the unknown, including technical challenges that the reports assume will be overcome like off-target effects; principally unknowable things – like the point at which life begins; and negative knowledge - negative results that can be controlled before use – such as through pre-implantation genetic diagnosis.

Projections refers to anticipated possible outcomes, positive, negative, and complicated. *Timescales* – refers to how the reports deal with time – both in terms of continuity with the past (including whether genome editing is transformative), and short or long term visions of the future. Finally, *classifications* – refers to the practice of making distinctions, such as between inheritable and non-inheritable alterations to the genome. Comparing the argumentative practices of the two reports underscores the work done by the committee in selecting certain issues and frames from the vast information resources available.

5. What role do STS concepts and STS scholars play in the reports, and how can we think about their impact?

The Nuffield report, Chapter 2, *Science in Context*, and NASEM report Chapter 7, *Public Engagement* both include references to prominent STS scholars, with both citing Jasanoff et al. (2015) article, "CRISPR Democracy" (engaged STS). In a further step, STS trained people, like Charis Thompson are on Nuffield committee (embedded STS) and the report (Nuffield Council on Bioethics, 2016) includes references to the cultural and contingent practices of scientific research and technological development and complexity of publics throughout. What do we, as STS scholars make of the inclusion of STS key concepts; are the references performative or just lip service? To what extent does the reflection on the committee's central role in the paradox of scientific authority shape the recommendations of the report?

4 Theoretical Framework & Sensitizing Concepts

The analysis that follows focuses on moments where scientific and cultural understandings are entangled, such as descriptions of possible future cures that presume certain regulatory steps or descriptions of biochemical processes in metaphorical terms like editing or rewriting. This reading of the reports is based on the "idiom of co-production" (Jasanoff, 2004), which holds that there is no a priori distinction between scientific and cultural, but that everything is both natural and constructed at the same time. It also highlights how scientific facts and objects could have been understood differently, something made clearer in comparative work. Categorizations or distinctions between objects are an important space to see co-production at work. The reports bring together technical and societal considerations in a deliberate way and reveal this co-production at work. Together with the STS concepts of 'non-knowledge' (Gross, 2007) and 'technologies of humility' (Jasanoff, 2003), this thesis focuses on how the reports select and combine aspects of societal challenges and technical challenges in CRISPR. This theoretical lens shines light on how these choices work to promote discussions, research

directions, and regulatory changes that fit with the committees understanding of the relationship between science and society and their imagination of the future.

4.1 Co-production

Divisions between natural sciences and social sciences have made it difficult to study the intersection of science and technology with politics and culture – the vocabularies of anthropology, political science, economics and sociology are often incommensurate with datasets, preprints and blueprints. Co-production (Jasanoff, 2004), provides a vocabulary for the qualitative study of science. Science and nature, as with politics and culture are man-made categories. Jasanoff calls co-production an "idiom" (2004) to avoid conflating it deterministic theories or strict prescriptions of study found in a methodology. Like a theory or method, co-production provides a systematic way of analyzing information to provide explanations and draw conclusions. In studying the boundary between what is natural and what is cultural, the work that goes into categorizing and keeping separate one from the other becomes apparent. Take for example a fertilized human egg. It is as *natural* as it has been *created by humans*. In the study of human genome editing, it has been categorized– scientifically as a zygote and research object, politically as a pre-embryo or embryo, philosophically as a life or potential life. A mouse whose genome has been edited to model muscular dystrophy is scientifically a humanized mouse and research object, politically a patentable invention and animal subject, philosophically a mouse and a hope for a cure.

Co-production (Jasanoff, 2004) is the idea that not only do these definitions co-exist, but that they are mutually entangled and influence each other. Applied more broadly to emerging technologies, "our inventions change the world, and the reinvented world changes us" (Jasanoff, 2016, p. 1). Technologies are produced within their cultural contexts, with public funders and private investors as well as patients and customers in mind. At the same time, these new technologies change social dynamics and culture. CRISPR is both a defense mechanism found in e-coli and other bacteria, and a tool that offers nature-altering control over the genome. The reports help one to imagine how changes to the genome might be used to address social challenges such as rare genetic diseases, infertility, cancer, HIV, organ failure, and so on while also prescribing how this might be legally accomplished. Understanding science as a cultural activity, responsive to funding and non-binding regulations (Jasanoff, 2004) is fundamental to comprehend how these reports might matter. Contingent and provisional distinctions made in the report become a part of discourse. Genome editing tools like CRISPR are co-produced with values and beliefs about what it means to be human. This mutual shaping is concurrent and iterative.

Practically, co-production identifies opportunities for research. These 'pathways' or 'instruments of co-production' are "making identities, making institutions, making discourses, and making representations" (Jasanoff, 2004, p. 38). Co-production guides us to look at identities being remade just by the possibility of genome editing, asking, what are we allowed to do as humans? what are we allowed to do with humans? Following institutions, we see the efforts to establish and maintain credibility by NASEM and the Nuffield Council in positioning themselves as the source of knowledge. At the same time, "discursive choices also form an important element in most institutional efforts to shore up new structures of scientific authority" (p.41). The categorization and distinguishing of somatic and germline changes contribute to the making of a discourse that associates individual rights with genomic changes. Although trying to use this new language can be awkward, Jasanoff's (2004) "idiom of co-production" is a powerful concept for unpacking the complex layers involved in bioethics discourse and the work of and in the reports.

4.2 Non-Knowledge

Knowing is also a social process – knowledge is acquired in the framework of social relationships; ideas and observations are judged with an eye towards the of credibility and trustworthiness of their source and accepted and organized based on previous knowledge and experience. Selection and validation processes critical to knowledge societies necessarily leave information out. The concept of non-knowledge (Gross, 2007) or the German, *Nichtwissen*, literally 'not knowing', captures different aspects of the uncertain and unknown: principally unknowable things, things that are not-yet known, and unknowns which are disregarded as unimportant to the analysis (negative knowledge). Looking at non-knowledge on a continuum, Böschen et al. (2006) describe three aspects of non-knowledge: awareness of non-knowledge, intentionality, and temporal stability. Non-knowledge that is fully recognized, or 'not-yet known' speaks to non-knowledge as something that will eventually go away. 'Unknown unknowns' refer to non-knowledge that we are unaware of. 'Negative knowledge' is non-knowledge that has been consciously refused. These kinds of non-knowledge are sometimes later characterized as side effects or unknown consequences, bringing in a temporal aspect. Another aspect of non-knowledge is that of principally unknowable things; things we recognize as unknown that won't change with the passage of time or dedicated inquiry. Callon et al. (2009) describe the effort undertaken by modern society to manage non-knowledge and overflows of technological systems that don't perform precisely as intended. In governance, technology assessments and risk/benefit analyses are examples of strategies to manage non-knowledge that have often back-fired because the scope was not broad enough, things were intentionally left out or took time to produce knowledge. The precautionary principle comes out

of scholarship on risk (Beck, 1992 (1986)) and uncertainty (Ravetz, 2004) that advocates a different approach toward managing non-knowledge and is influential in European governance. The reports act to manage non-knowledge by reporting on the current state of research; including expected findings and potential pitfalls. The NASEM asserts scientific authority that certifies certain ideas and observations, and qualifies others, allowing readers to know about CRISPR research. The ways in which non-knowledge is characterized and framed also includes judgements about whether uncertainty is likely to be resolved or can be ignored, or whether it requires consideration as a principally unknowable thing. The characterization of non-knowledge is one of the key argumentative practices used by the reports.

4.3 Technologies of Humility

We live in a world full of uncertainties. Claims to understand the risks and benefits of new technologies are a form of hubris. In 2003, Sheila Jasanoff proposed a new approach to evaluating emerging technologies that focused on societal impacts and governance challenges. Calling on "technologies of humility," the approach starts with four questions: what is at issue? Who will be hurt? Who benefits? And how can we know? These questions represent the four areas of inquiry and assessment: framing, vulnerability, distribution, and learning, which are put into practice through qualitative social science assessment methodologies, and described as 'social technology'. This draws on an earlier understanding of technology as a skilled craft, from the "composite of Greek techne (skill) and logos (study of), "technology" in its earliest usage, back in the seventeenth century" (Jasanoff, 2016, p. 8). As a response to assessments of technology that focus on effectiveness and efficiency vs. side effects, it asks policy considerations not to exempt basic research or rely on peer review in policy making situations, practices that limit the public accountability of science. More importantly it asks evaluations to focus on vulnerability and uncertainty and not privilege quantifiable risks. At the outset, Jasanoff questioned whether introducing questions about framing, vulnerability, distribution and learning would be enough to drive serious institutional change, calling her proposal "pebbles thrown into a pond, with untested force and unforeseen ripples" (2003, p. 243). Since then, changes in technological assessment have taken place, many of which do look deliberately at how issues are framed, where opposition might come from (and in some cases of justice, harm and distribution), and how they might learn from past experiences or observe current trends. The depth, sincerity and impact of these changes is a matter for discussion. The reports are not simply performances of hubris, where the committee claims to know what is good and right, leaving only technical details up for discussion, but are they a part of the machinery of humility? This concept will help to unpack the rhetoric of risk/benefit used in the committee language and focus on how technology assessments are performed.

Jasanoff's approach is not the only one proposed by STS scholars; Nowotny (2003), Collins (2014), Callon (1999), and Wynne (1992) all offer new conceptions of expertise and public participation. What stands out in this approach for this particular study of reports is how expert advice is seen in an institutional context. The challenge is to make the STS critique of expertise relevant by relating expertise to the process of knowledge production and decision making (Grundmann, 2017).

5 Materials and Methods

My interest in CRISPR as an emerging technology is tied to questions about how to understand the incredible complexity of life and diversity of beliefs, alongside the constraining and enabling forces of technology. Emerging technologies are an open space for examining what is and what could be; while research material on emerging topics is limited, early engagement still makes influence possible.

5.1 Studying Documents

This study is based on the premise that documents, such as the reports in this study, have agency (Hull, 2012) and can shape science-society relations. Documents, such as the reports in this analysis, are not mere records, but productions that reflect, or document, the context of their creation – the people, institutions, audience and material factors at a specific time and place. More than that, their production is deliberate and generally has a purpose, Shankar, Hakken and Østerlund write that "Documents are often, maybe always, at the center of efforts to achieve coordination and control" (2016, p. 70) and delineate ways in which documents interact with their contexts, like the example of the NASEM report serving a s a "green light" to researchers (Stein, 2017). Returning to the subtitle of this thesis, the work of bioethics reports, is both the labor in creating the document, as well as the work it does in categorizing and ordering aspects and applications of genome editing. Shankar et al, go on to write that "documents specify desired connections among people, objects, times, places and events and thus constitute a structure of relevancies for discourses about organizational practices" (2016, p. 70). Ways in which the documents engage the topic of genome editing and the conclusions or questions they present matter because they inform policy discussions, structure opportunities and topics for public engagement and guide research directions: they tacitly govern what can or should be done.

5.2 Defining Genome Editing

The word, technology, comes from the Greek as a capacity to handle/do something. Definitions, like the two presented below can shift, depending on whether the focus is on the action or the object.

> *"Genome editing is a tool for making precise additions, deletions, and alterations to the genome – an organism's complete set of genetic material" (NASEM, 2017, p. 1).*

> *"… genome editing is the practice of making targeted interventions at the molecular level of DNA or RNA function, deliberately to alter the structural or functional characteristics of biological entities" (Nuffield Council on Bioethics, 2016, p. 4)*

Much like the bioethics reports that these definitions are taken from, the definitions of genome editing diverge but end up in a similar place: whether a tool or a practice, the focus is on alterations. Unlike CRISPR-Cas9, which is an organism that can be categorized by its biochemical makeup, genome editing is a concept used to capture several kinds of changes. In 2016 genome editing largely replaced the term gene editing due to new knowledge about epigenetics and non-protein coding genetic elements. Alterations in gene expression are added to disruption, substitution, targeted insertion of a transgene, and large deletions at chosen locations (NASEM, 2017, p. 88).

5.3 Materials

This thesis is a comparative study of the responses to human genome editing produced by expert committees and published by major institutional bodies. At the beginning of this process I read several statements and reports on genome editing including the Leopoldina and European Commission. I looked for a formal report from China and read about their bioethics governance. The reports I selected for the analysis, the 2017 US National Academies of Science, Engineering and Medicine (NASEM) report "Human Genome Editing: Science, Ethics and Governance" and the 2016 Nuffield Council on Bioethics report, "Genome Editing: an ethical review" stood out for their depth in covering technical, social and governance issues.

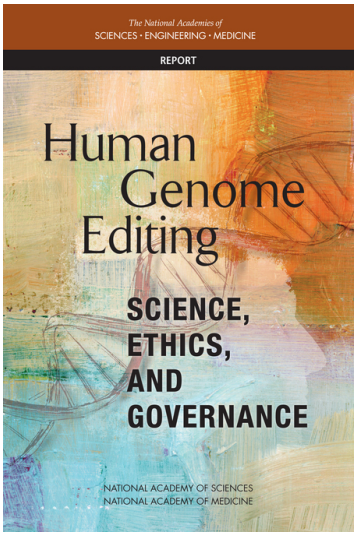

Figure 1: NASEM Report Cover (NASEM, 2017)

5.3.1 "Human Genome Editing: Science, Ethics and Governance"

The National Academies of Science, Engineering and Medicine (NASEM), a longstanding US government affiliated body, sometimes called the US brain-bank[6]. Established by the US federal government in 1863, members are elected from the scientific, engineering and medicine and health communities the institutional foundations are strongly rooted in tradition even as internal and external forces promote a more open approach to science-society relations than their stated mission of "solving complex problems," "informing public policy decisions" and "increasing public understanding of science" (NASEM, 2017, p. iii).

NASEM reports "document the evidence-based consensus" (NASEM, 2017, p. iv) of an authoring committee of experts. The charge given to the committee was to examine
the scientific underpinnings as well as the clinical, ethical, legal, and social implications of the use of human genome editing technologies in biomedical research and medicine, with a specific focus on the germline and potential applications and risks as well as regulatory options. The committee was specifically tasked to "provide a framework based on fundamental, underlying principles that may be adapted and adopted by any nation that is considering the development of guidelines. The report will also include a focus on advice for the United States" (NASEM, 2017, p. 17).

The resulting NASEM report is 329 .pdf pages and contains eight sections entitled: 1)Introduction, 2) Oversight for Human Genome Editing and Overarching Principles for Governance, 3) Basic Research Using Genome Editing, 4) Somatic Genome Editing, 5) Heritable

[6] Hilgartner (2000, p. 58) and Jasanoff (2005, p. 46) both draw on this designation by Phillip M. Bofey in the critical 1975 book, The Brain Bank of America: An Inquiry into the Politics of Science.

Genome Editing, 6) Enhancement, 7) Public Engagement, 8) Summary of Principles and Recommendations; and an appendix including A) The basic science of genome editing, B) International Research and Oversight Regulation, C) Data Sources and Methods, D) Committee Member Biographies, E) Glossary. The report was written by two co-chairs: Alto Charo and Richard Hynes and a 20-member committee, with the assistance of five staff members, 12 reviewers and two consultant editors.

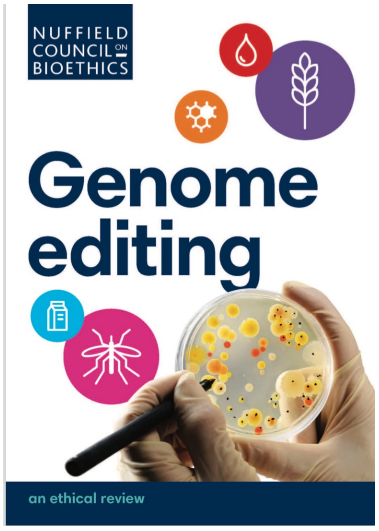

Figure 2: Nuffield Council on Bioethics Report Cover, (Nuffield Council on Bioethics, 2016)

5.3.2 "Genome Editing: An Ethical Review"

The Nuffield Council on Bioethics is a much newer body, characterized as a 'think-tank.' Founded in December 1990 against a political backdrop of privatization in the UK and the precautionary principle in Europe, it's authority is derived from its independence and the credibility of the council members, reinforced by the quality and reception of the work (Jasanoff, 2005). Since its founding, the relationship of the council to the UK government has grown closer, a significant portion of their funding now comes from government sources. Like NASEM, it has no regulatory powers and recommendations are non-binding, however the focus on ethics and deliberate inclusion of nonscientific experts in the council membership make the Nuffield Council on Bioethics a very different kind of institution. As an institution, it is more willing to experiment with processes and participation in bringing discussions of ethics and societal challenges in science and technology to a "more visible and accountable position in the public domain" (Jasanoff, 2005, p. 188).

The committee was asked to define ethical questions, review governance policies, deliberate on how to address the ethical questions and make recommendations for further work or policy and legislation relating to developments in genome editing research. (Nuffield Council on Bioethics, 2016, p. vi). The resulting Nuffield report is 136 .pdf pages and contains an introduction,

followed by eight sections entitled: 1) Genome Editing, 2) Science in Context, 3) Moral Perspectives, 4) Human Health, 5) Food, 6) The Natural Environment, 7) Other Applications, 8) Conclusions; and an appendix including 1) Method of Working, 2) Call for evidence, and 3) The Working Group. An 8-member working group chaired by Andy Greenfield and the 18-19 member Nuffield Council are responsible for the report although there is no mention of how it was written. The role of the staff – an 11 member secretariat is understated.

The reports are similar and different. Both reports are written to inform the public debate on genome editing. Both institutions claim independence and enjoy significant government funding, both serve to provide expert advice to policy makers. The NASEM and the Nuffield Council are not regulatory authorities and the recommendations of the reports are non-binding. The authority of the information provided rests on the institution and committees claims to credibility and objectivity. The studies are also overlapping; the US National Academies (NASEM) partnered with the Chinese National Academy and UK Royal Society to host the international summit in Washington, DC, where the NASEM committee first met and at least one member of the Nuffield report committee spoke (Thompson, 2015).

5.4 Methods

The analysis is based directly on the text of the documents and relies on grounded theory (Charmaz, 2006), an analytical methodology that seeks to empirically produce explanations from the data through qualitative social science methods. The research question, '*How are societal and technical challenges in Genome Editing co-produced in official bioethics reports?*' is not a question of what is in the report – something that might be accomplished by quantitative methods such as a word count or more sophisticated algorithm for text analysis. Qualitative methods analyze the process for collective sense making, such as shared and contested meanings and their expression. The reports are the object that perform an action, pointing to/making visible the co-production of social and technical challenges. The challenges are shaped by the committee members' knowledge through discourse about the future. Through the committee writing process, the authors transfer their own agency to the document, and the document is expected to stand on its own as a persuasive text.

Qualitative analysis uses systematic practices alongside the judgement of the researcher to discern meanings. To study the reports, I use grounded theory and the "little tools" document analysis method proposed by Kirsten Asdal (Asdal, 2008). I discuss the strengths and weaknesses of these methods below. Discourse analysis is another interesting method from the perspective that it highlights arguments or specific ways of talking that are not in the text,

however the consensus seeking nature of the reports make them poor material for this type of analysis. Much of the interesting discourse takes place 'backstage' (Hilgartner, 2000).

5.4.1 Grounded Theory

Grounded Theory analysis helps researchers define what is happening in the data, organize it, and grapple with what it means. Bottom up analysis builds empirically based generalizable statements that transcend anecdotal evidence; quotes selected are representative. "Specific use of language reflects views and values" (Charmaz, 2006, pp. 46-47), coding interrogates language and word choice. Coding the use of terms, analogies and metaphors methodologically traces how committees co-produce social choices or values (Jasanoff, 2004) with the emerging technology in contributing to the discourse on genome editing. I initially approached the text from an open standpoint – line by line – marking or coding words or phrases that dealt with my research question and sub-questions, links to other debates, definitions and recommendations, promises and challenges. I didn't start with a specific set of codes in mind, and tried to focus on actions. Some of the codes come from the text itself, what Charmaz (2006) calls "in-vivo" coding. I switched between the texts by chapters and changed or developed new codes through my engagement with the material. After a first pass, I organized the codes into categories and established sub-codes for a second more focused analysis.

I included codes for: defining ethical challenges, promoting public involvement, using existing regulations, naming governance issues, naming societal challenges and projecting, followed by subcodes for assigning accountability (naming governance issues), ethics of the past (naming societal challenges), recalling adverse events (making promises) meticulously indexing places in the texts that performed or discussed the codes. The focus on action is an intentional methodological choice.

The work is a bit messy. Some codes, such as, challenging intellectual property, which looked initially promising ended up not having such a strong role in the story, although this omission is telling. Other codes transformed through input from a graduate working group, such as the focus on non-knowledge and projections instead of temporary problems and cures. Decisions about the categories for the codes and the structure of the thesis were made together.

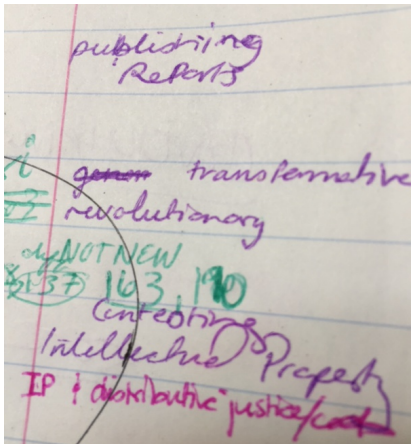

Figure 3: Grounded Theory Initial Coding

Grounded theory is an established method for STS that works well with document analysis and produces data for qualitative

analysis. One challenge in using grounded theory for this material is that the documents already come with categories, subcategories, and a structure. In the NASEM report – the focus on consensus constrains grounded theory analysis since backstage arguments and points for discussion are left out of the text. The Nuffield text is reflexive about the process and introduces many meanings for terms, co-opting much of the analytical process. Where grounded theory makes sense is in tracing implicit boundaries and assumptions that guide the writing, particularly as they differ from summary to text, chapter to chapter and document to document. The deliberate construction of the document allows us to also observe explicit boundary work.

5.4.2 "Little Tools" document analysis

Kristen Asdal (2015), a Norwegian economic historian and STS scholar has developed a technique specifically aimed at institutional documents that comes out of the history of Actor-Network-Theory. This technique sees the document as an actor, who has been given agency by the writers and continues to do work after the publication. Asdal's (2015) examination of government documents provides a methodology for understanding persuasive documents that focuses on the document as a tool, or something that helps accomplish a task. This analysis uses a parallel approach that considers alternatives to and omissions from the text. These important elements cannot be captured by coding. Asdal proposes the guiding question: *What is the issue?* to frame the analysis, using several sub questions to create a picture of the document as an agent or actor capable of action apart from its creators.

What is the issue?

- In what way is it an issue?
- What is at stake?
- Who are the main characters (how does it shift)?
- Who gets the benefit of the doubt?
- Who is excluded, diminished or preempted?
- Who are the experts?
- What are the new entities that are named and accounted for?
- Who writes for whom?

Asdal's (2008) original paper on "little tools" regards a government document that made the review of a coal power plant an environmental issue, rather than a matter of construction and energy production. She has also used this technique to show how the work of documents shifted

a discussion about wild vs. farmed cod to frozen vs. fresh. The strength in the questions, is in bringing what is not written into the text up to the same level as what is written.

This method is helpful in avoiding deterministic explanations based on context or individuals involved, but in looking specifically into the text and what it does in context. Although some of the answers become more obvious through comparison, these questions look at each document individually. Both a strength and a drawback of this type of analysis is that much of the interpretation is left up to the person doing the analysis, which requires a high level of reflexivity. Together the methods look carefully at what is in the texts as well as what is *not.* A comparative lens strengthens the analysis – with the caveat that the US/UK contexts are far from universal.

6 Analysis

This thesis starts from the premise that instead of asking what to make of specific technologies, we should ask what kind of a world do we want to create? What tools and practices do we have and need to make it? Who will benefit? Who will be harmed? Who decides? This aspirational view of world-making relies on bringing societal issues into technological developments at an early stage. Societal issues are however, contested, conflicting and overlapping. Returning to the research question: *How are societal and technical challenges in genome editing co-produced in official bioethics reports?* This thesis focuses on the reports as a site where societal issues are defined and related to legal, technical and ethical aspects, looking at discursive techniques employed and the performative aspects of this work.

6.1 Story about Governance and Public input

Two reports: Human Genome Editing: Science, Ethics and Governance and Genome Editing: an ethical review; provide expert guidance on a set of tools and practices known as genome editing. They tie the technology to societal impact -- making promises about what might be, but also presenting ethical challenges for others to resolve. These challenges are mainly presented as matters of public concern. Both reports start from a premise that a public discussion on genome editing, 1) should happen and 2) will benefit from the knowledge presented in the reports. However, they are initiated from different institutions in different epistemic cultures, recruit different kinds of experts and diverge in their approach. One starts with an overview of the current state of affairs in science, ethics and governance. The other with a discussion of "science in context" (Nuffield Council on Bioethics, 2016), asking readers to put aside misconceptions about science as an honor bound international community with separate and pure basic science.

6.1.1 Human Genome Editing: Science, Ethics and Governance

From the beginning, the NASEM report sets individual concerns apart from societal concerns, establishing a divide that is maintained throughout the report. For the most part, the future public discussion only applies to societal-level concerns – the design of the report is divided by application, basic, somatic, germline, and enhancement with increasing levels of public input. For research labeled as basic, 'public' input consists of 1-2 generally sympathetic community members who serve on institutional bioethics committees (IBCs), institutional review boards for human subjects (IRBs), and institutional animal care and use committees (IACUCs) for animal welfare. In addition to the limited participation, the scope of what can be considered is also limited, in human subjects' reviews, "concerns about culture or societal morals, while important, are generally not within an IRB's remit"(NASEM, 2017, p. 151). Clinical research, under the heading "somatic," may be subject to in-depth review and 5 minutes of public discussion as part of the NIH RAC process, but the committee only meets a few times a year and many protocols are not selected for review; the last meeting took place December 16, 2016, with no meetings scheduled[7]. The US Food and Drug Administration (FDA), which oversees both clinical trials and genetically modified food stuff, may choose to hold a public meeting. Asdals' (2015) assertion of 'no public, no issue' may reflect the public relations aspect of whether these meetings take place. Despite reflection on the limitations of public input into these applications, the report affirms the current system and makes a claim that it "accepts as given the current legal and regulatory policies that apply in each country (NASEM, 2017, p. 45).

In contrast, applications that are currently illegal or prevented through a combination of bans on funding and protocol review by the RAC and FDA are presented as areas for "extensive, inclusive, and meaningful public input" (NASEM, 2017, p. 177). For genome editing in general, including applications currently in use, **transparency**, rather than public input, is named as a key principle in the report. In other words, meaningful public input appears to be invoked only in situations where the existing governance prevents certain applications. If "thorny issues around acceptable uses of the technology in humans will depend on more than scientific considerations, and *may* increasingly involve weighing factors beyond the individual-level risks and benefits" (my emphasis NASEM, 2017, p. 25), the corollary is that individual-level risk is appropriate in uncontroversial areas. The report uses informed consent as the basis for many of its arguments about the acceptability of basic research and somatic genome editing. The challenges of governance through informed consent – identifiability of private information or

[7] Meeting dates, agendas and notes available at URL: https://osp.od.nih.gov/event/rac-meeting/ as of October 21, 2018

biospecimens (NASEM, 2017, p. 40), uncertainty in first in human trials (p. 47), possibility of withdrawing from long-term follow up (p. 123), inability of fetuses and unborn future children to consent (p. 123) are presented as the governance challenges of genome editing. This grounding in the informed consent regime is the primary boundary set up in the report, essentially using procedural limitations to define ethical questions.

Within the human subjects' research regime, of which informed consent is a critical part, the provision to minimize harm, enshrined in risk/benefit calculations, is the primary restriction against enhancement. The argument presented by the report is that even a small risk would not be justified for enhancement if there were no "real benefits" (NASEM, 2017, p. 151). However, the benefit is left to the regulator and IRB to decide, and presumably would not take cultural or societal issues into account. Where laws against eugenics exist, they pertain to involuntary procedures, such as those carried out by the state (p. 121) and not to fairness or justice, which returns again to informed consent as a primary governance mechanism.

As the issues raised by genome editing appear to go beyond individuals' ability to consent, the national academies report seeks consent from the public. This emerges as a concept of "international and professional norms" included in the principle of responsible science (NASEM, 2017, p. 11), with "broad public input" (p. 7) or "broad ongoing participation and input by the public" (p. 8). It recalls the goal of achieving "Broad societal consensus about the appropriateness of the proposed application" emerging from the International Summit on Human Gene Editing (NASEM, 2015, p. 7). In turning to a concept of public consent to supplement informed consent, the report is serving to provide information and procedural recommendations for an informed consent process.

Who is the public? The NASEM starts with the American public, as distinct from other state-based governments and publics. "Different societies will interpret these concepts in the context of their diverse historical, cultural, and social characteristics, taking into account input from their publics and their relevant regulatory authorities (NASEM, 2017, p. 8). In some case this is broken down into publics. In naming societal issues, the report draws on many groups of people, such as religious groups: Christian traditions/St. Francis's canticle of creation, belief systems of native American nations, Jewish tradition, Muslims and Buddhists and nonreligious people (p. 127); parts of the medical profession and patient groups (129); disability rights community/activists (p. 126); and transhumanists (p. 123). For the most part however, arguments are not attributed to societal groups or individual speakers, but to undefined groups of people labeled as *some*, *others*, or *many*. Although public survey data (p. 140) is used to

establish that there is public discomfort with enhancement, surveys are not promoted as a solution. The report's conception of the public goes beyond easy to reach audiences and interested groups and makes clear that all public engagement methodologies involve tradeoffs and challenges. More on how this engagement is envisioned is addressed later in the analysis.

6.1.2 Genome Editing: An Ethical Review

> *"The public have an **interest** in science in terms of its expectation of net social benefits, and **invest** in science both financially and through the trust placed in scientists to contribute to the delivery of these benefits. But more profoundly than this, the public have an underlying public interest in the overall moral and ethical texture of the society in which they live" (Nuffield Council on Bioethics, 2016, p. 21, emphasis in original)*

Where the NASEM report ends with public interest, public interest is the starting point for the Nuffield Report. The committee started with a call for public input that serves as the foundation for the report: "The strength and unreconciled diversity of public opinion in this area cannot be denied and constitute, in themselves, good reasons for engaging with it" (Nuffield Council on Bioethics, 2016, p. 116). The report raises questions not just about whether genome editing should or should not be allowed, but about distributive justice and values. A basic premise and repeated assertion of the Nuffield report is that new developments in genome editing, in particular CRISPR, are transformative (Nuffield Council on Bioethics, 2016, pp. 19, 26, 34). This transformative potential challenges the assumptions underlying existing governance, including 1) the ability of the scientific community to self-regulate, 2) strict divisions between basic and clinical research, and 3) formal, institutionalized laboratories as the site of experimentation. This transformative character of CRISPR also challenges governance regimes based on non-binding and funding-based guidance, carried out through established research institutions, such as those located within universities and supported through government funding. The Nuffield report promotes the concept of responsible innovation, particularly when contrasted with legislative approaches, self-governance, and market regulation. Responsible innovation becomes more about what it is not, rather than only procedural recommendations; RRI is described first as encompassing "stage gate review" (2016, p. 89), an interdisciplinary review with go/no-go authority used in clinical or field testing, and later as an approach that is integral to practice and doesn't rely on stages (p. 98). Central to the responsible innovation is a "moral imperative of greater public engagement with science at all levels" (p. 40).

The report draws on the concept of human dignity as the basis of the discussion of societal challenges of genome editing applications. Informed consent is presented then not as a form of governance, but as a small part of human subjects' protection regime that comes as a practical outcome of the human dignity discussion. The "opportunity to freely consent or refuse to participate," (Nuffield Council on Bioethics, 2016, p. 44) is taken alongside measures to protect dignity and rights, not as an individual calculation of risks vs. benefits. The clinical trials and human subjects' protection system is presented as "complicated," "refined," (Nuffield Council on Bioethics, 2016, p. 44) and generally able to handle the safety and efficacy of therapies based on genome editing. This focus on clinical trials also relies proof of concept and adverse results from 'basic' and 'translational' research, categories challenged by the Nuffield report. "Greater use of genome editing in biological research can also be expected to lead to greater understanding and refinement of the techniques themselves...As well as developing greater power to effect precise and reliable changes, development of genome editing tools may help to give greater confidence in their use in clinical conditions to treat disease by addressing safety concerns" (Nuffield Council on Bioethics, 2016, p. 36). Research funding is often contingent on social impact, while the governance of research is treated separately from technological innovation, obscuring "opportunities for the ethical governance of science"(Nuffield Council on Bioethics, 2016, p. 15). Reaching far beyond the human subjects' research protection regime, the Nuffield report is concerned with the direction and timing of research, distributive justice and human dignity.

Public input, and some type of consensus on these big questions is then seen as the starting point. By "exploring anew what it is we wish to avoid and what we hope to achieve" (Nuffield Council on Bioethics, 2016, p. 53), public input would drive research directions, and finally governance would follow. For the definition of the public and who, where, and when these discussions might take place the reader is referred to a separate report that discusses the timing of public dialogue for policy exercises on a national-level, problems with interest-group politics, and demand from scientists to look at changing policies proactively to "maximise social and economic benefits," (Sciencewise Expert Resource Center, 2016, p. 8). This report advocates an active approach using the RRI framework. Practically, this would look like a number of small participatory activities designed around specific policy questions, with an observatory group monitoring and potentially coordinating the different "micro-dialogues" (Sciencewise Expert Resource Center, 2016, p. 15). The conclusion of *Genome Editing: an ethical review*, is that these dialogues must be based around problems or challenges rather than technologies. The next step is to craft a follow-up report focused on one such issue looking at the existing governance and underlying assumptions, the interests involved, and different possible outcomes. The approach, based on the call for public input, is consistent with the writing of the report. The committee's

work can be viewed as a kind of observatory approach as recommended in the workshop report.

Jasanoff (2005) characterized the Nuffield Council as a group built on a contradiction of representing public insecurity and vulnerability, while tempering public anxiety to mitigate controversy that might challenge the autonomy of scientific research. The work of both the Nuffield Council on Bioethics and the report on genome editing then is to bring these tensions into the public sphere. With regard to inheritable genome modifications, the Nuffield does advocate the "muddling through" approach that Jasanoff describes: "the controversy remains unresolved. We do not believe, however, that this is the result of an intractable opposition of principled positions, but of complex judgements made in a changing context of relevant factors"(Nuffield Council on Bioethics, 2016, p. 116).

The number of individuals involved in the process so far is a small circle of insiders and interested parties[8]. The British approach, of relying on a wise council who can "see correctly for the people," (Jasanoff, 2005, p. 188) described by Jasanoff's (2005, 2011) comparative work in epistemic cultures fits well with the early steps taken by the Nuffield Council: A workshop with experts on public engagement, the bioethics report, and plans for a future report[9].

The Nuffield report presents the existing system of research and regulations as a variable, carefully raising questions about the current system of governance for basic research based on research funding and professional norms, while putting off concrete normative or policy statements for a future committee. At the same time, the report does make judgements with policy implications, such as moving to product-based assessment for Genetically-Modified-Organisms in plants (58, 62) and using a 'responsible innovation' phased governance model for the introduction of gene drives (93).

6.1.3 Containment and Governability

Even as the reports diverge in their assessment of science governance in general, with respect to cell-based therapies or somatic genome editing, they converge. Both reports find that the issues raised by genome editing in this regard are not new and recall decades of work dealing

[8] 8 Committee members, 11 staff, 28 workshop participants, 15 responses from individuals and 39 from organizations to the Call for Evidence, 33 presenters and 6 reviewers. But from 140 "contributions" there were 118 or fewer contributors due to people serving in multiple roles, such as staff working on both the workshop and report, presentations from a commenting organization, or presenters who also served as reviewers.
[9] The report was issued on July 17, 2018 during the review of this manuscript.

with safety issues and ethical challenges that have co-produced the governance structures in place today. The reports anticipate enforcement issues with any governance measures put in place, including, off-label prescriptions, 'regulatory havens' for medical tourism and research, and premature or unproven use. The NASEM report argues that prohibiting the FDA from reviewing proposals that involve germline modifications will "drive development of this technology to other jurisdictions, some regulated and others not" (2017, p. 136). In Europe, regulatory uncertainty in regard to genetic modifications in agriculture is associated with disinvestment, a loss of the research base, and failing international competitiveness (Nuffield Council on Bioethics, 2016). Research priorities and availability of public money, along with a more abstract notion of national competitiveness, are often part of a dialogue about getting practical or realistic about ethics and regulation.

A second appendix to the NASEM report focuses specifically on the laws and regulations of other countries, color coding based on whether germline modifications are illegal (red), prohibited by non-binding guidelines (pink), restricted (light grey), or ambiguous (dark grey) (p. 268). Parties to the Oveido convention (Council of Europe, 1997), are red and the UK and China are pink, whereas the US is depicted as light grey, due to funding restrictions. Russia, which has so far not been a part of the discussion is notably dark grey. According to the report, international agreements like the Oveido convention are, "difficult and time consuming to negotiate, and often present difficult enforcement issues" (p. 270). If regulatory havens and the potential for medical tourism exist, the logic is that there is no point in taking a moral high ground. At the same time, citing practical concerns is a way to negate the importance of ethics and bioconservativism. Arguments that a lack of regulation in one jurisdiction make enforcement difficult in another rely on the free movement of paying patients and medical practitioners who are willing to forego professional norms (an uncommon scenario). Neither the NASEM, nor the Nuffield Council have formal regulatory powers. The report's impact on policy and practice is largely projected through shaping the discourse within the international scientific community as much or more so than with publics and politicians. The reports diverge in their portrayal of the practitioners and site of genome editing work, leading to different conclusions about the appropriateness of self-regulation.

> *"Although human genome editing may be somewhat more difficult to control than traditional gene therapy because technical advances have made the editing steps easier to perform, the cellular manipulations and delivery of edited cells to the patient continue to demand high-quality laboratory and medical*

> *facilities, which generally will ensure that regulatory oversight is in place"(NASEM, 2017, p. 107).*

> *"Inasmuch as some may regard the researchers who reported human embryo genome editing experiments as 'mavericks' in relation to the responsible mainstream 'international scientific community', this may reinforce skepticism that such a community exists or is able to regulate itself effectively"(Nuffield Council on Bioethics, 2016, p. 39).*

Where enforcement challenges lead the National Academies Report to resort back to existing regulations based on institutional oversight and professional norms, the Nuffield Council advocates working in all the overlapping and contradictory layers of jurisdiction, rejecting both the basis and applicability of self-regulation. It is precisely because genome editing technologies are beyond the limits of professional self-regulation that it is transformative and requires reexamination of existing governance.

One way to look at the story is to focus on scientists' ideological work to set science apart (Gieryn, 1983), framing emerging technologies as a boundary struggle between science and state intervention. With the advent and spread of CRISPR-Cas9, researchers have found themselves in a quandary; namely, that governance focused on containment within the lab and strong distinctions between basic and clinical research now prevents translational research. Evans and Palmer (2018) might classify this as an anomaly handling strategy of deference and diversion (dating back to early fears about recombinant DNA). The biosafety regime established after Asilomar separated genetically engineered organisms from the general environment, creating a space protected from both danger and public inquiry into their research. Stretching the space beyond containment labs, both GMOs (Jasanoff et al., 2015) and gene therapy faced growing pains in the form of protest and distrust. New boundaries erected to protect research from intrusion focused on personal choice in the form of consumer labels and informed consent, that came hand in hand with prohibitions on making inheritable changes. Today, the number of people involved in making genetic manipulations has vastly outnumber the intimate community at Asilomar. "Beyond the class of elite academic research scientists there is a growing class of scientific professionals and technicians, and, beyond these, a demi-monde of scientifically literate but not scientifically socialised ('disciplined') amateurs and dilettantes, with a variety of interests in genome editing" (Nuffield Council on Bioethics, 2016, p. 107). This expansion of practitioners is met with many people who have had their genome sequenced or undergone genetic screening – which combined with a proliferation of public opinion surveys and participatory mechanisms has made tracing impacts on policy and practice unpredictable and

difficult. A 'public' discussion of the proper boundaries between science and the state must consider that the players have changed dramatically since existing regulations were put into place.

6.1.4 Moving toward a Public Discussion

Researchers and potential beneficiaries are experiencing uncertainty and ambiguity. The question isn't only can we try, but *may* we try? Not only the terms guiding the committees, but the recommendations and conclusions of both reports point to future public discussions about genome editing. This discourse isn't starting from scratch, there already is an answer to the question *may we try*, and the answer, at least in the UK, US and China, is no. The hard line against inheritable changes is an example of the co-production of governance, a decision reached through evaluating technical and social conditions at a place and time. CRISPR-cas9 has the potential to change the technical side of the balance, creating ambiguity as to whether social conditions have also changed.

A public process is envisioned by both reports as part of the negotiations about what should be allowed and how it should be governed. The concept of a public discussion is multiple (Mol, 2002), that is, it has different, overlapping context-specific meanings. A public process for the Nuffield Council might mean a process that requests input from interested parties, that is an open process,

> *"Much of the evidence we received pointed to the importance of having an open, effective and inclusive public sphere in which questions about genome editing could be raised and discussed, in which different positions and arguments could encounter each other, and the importance of democratic governance" (Nuffield Council on Bioethics, 2016, p. 31).*

While a public process in the American context might be webcast and include public representatives, this public process is transparent, with a more instrumental focus.

> *"In light of the technical and social concerns involved, the committee concluded that heritable genome-editing research trials might be permitted, but only following much more research aimed at meeting existing risk/benefit standards for authorizing clinical trials and even then, only for compelling reasons and under strict oversight. It would be essential for this research to be approached with caution, and for it to proceed with broad public input"(NASEM, 2017, p. 7).*

In the NASEM quote, broad public input can be seen as an extension of the existing governance for clinical trials, a way of bringing informed consent to a society level. In both cases, removing restrictions on inheritable modifications to the genome are presented as something for public discussion.

Additional challenges might come about from opening decisions about the direction and purpose of science to public input. There is a careful stalemate in the US: the national government and funding agencies have withheld funding for any research involving the destruction of embryos, without placing legal restrictions on embryos or legislative definitions of the beginning of life, while promoting a bioeconomy and GMO plants and animals. US forums for debate are limited in either access (i.e., FDA) or influence (RAC) (NASEM, 2016). Increased transparency in the US government has not been accompanied by public participation in the design or direction of regulation and private industry remains insulated from publics, with the exception perhaps of shareholders. The NASEM report writes,

> *Public input and engagement are important elements of many scientific and medical advances.* ***This is particularly true*** *with respect to genome editing for potential applications that would be heritable—those involving germline cells—as well as those focused on goals other than disease treatment and prevention. Meaningful engagement with decision makers and stakeholders promotes transparency, confers legitimacy, and improves policy making. There are many ways to engage the public in these debates, ranging from public information campaigns to formal calls for public comment and incorporation of public opinion into policy. (NASEM, 2016, p. 4, my emphasis)*

The methods described in this passage, public information campaigns and comment periods, would generally not be considered meaningful engagement by STS standards (Wynne, 2016). The caveat of, "this is particularly true," for controversial and prohibited research directions further diminishes the impact of the statement. True public engagement, with implications on the design, direction and limits on genome editing, could lead to legislative action against embryo research and manipulation as easily as it could open up federal resources to development research and therapeutics that generate inheritable changes.

The public process envisioned by the Nuffield Council is more immediate and ongoing. The Nuffield report refers to "the strength and unreconciled diversity of public opinion" (Nuffield Council on Bioethics, 2016, p. 116) as a good reason for upstream engagement, calling for urgent attention to inheritable edits in humans and the genetic manipulation of livestock.

The concept of diversity relates to a more socially robust knowledge (Nowotny, 2003) than the expert committee might make on their own. The National Academies report also refers to "diverse and informed viewpoints," (p. 10) to describe a diversity of opinions, rather than the more familiar definition of diversity, based on diversity of participants (p.168), which is also important. Public representatives, rather than publics, are responsible for drawing attention to the public good on the RAC, and institutional oversight committees in the US. National Academies reviewers were chosen for their "diverse viewpoint" (p. ix), and a culturally diverse group of members thanked for bringing their "diverse perspectives" (p. xi). Bringing diversity into the academy allows the appearance of public discussion, perhaps without the presence of uninformed or unreasonable views.

In the US, the call for public discussion, outlined below, comes at some time in the future, as a prerequisite to FDA approval for applications of genome editing aimed at enhancement. No timeline is given. A separate discussion on germline editing is "needed now" (p. 134), so that values can be incorporated into FDA-led risk/benefit calculations; however, the report emphasizes that this is neither a requirement, nor consistent with the FDA approach. At the writing of the report, the FDA was also legislatively prohibited from reviewing proposals for germline editing. The discussions on values are prescribed as part of ongoing future scientific research

> *For any consideration of applications of genome editing of the human germline, extensive, inclusive, and meaningful public input consistent with the principles of engagement outlined in this chapter would be a necessary condition for moving forward…agencies would need to consider funding programs...Experiences with the genome initiative's program for including considerations of "ethical, legal, and social issues" as part of its overall funding of scientific research, and experiences with the Centers for Nanotechnology in Society, funded by the National Science Foundation, might provide useful frameworks for structuring similar research agendas or funding programs for public engagement for genome editing(NASEM, 2016, p. 177).*

ELSI type program(s) have been criticized for their lack of authority over research design and close ties to the promotion of the research. In both the ELSI Program attached to the Human Genome Project (Hilgartner et al., 2016) and embedded social scientists working under the National Nanotechnology Infrastructure Network (Hilgartner et al., 2016; Viseu & Maguire, 2012) significant criticism came from both inside and outside. A similar arrangement delegating

public engagement to an add-on, social science driven program might leave the FDA free to consider the outcomes of other engagement exercises (or not).

The Nuffield report sets priorities for discussions, focusing first on an upstream discussion about whether inheritable human genome editing is worth pursuing at all, as well as a discussion about genome editing already taking place in livestock. Their "triage of issues for ethical discussion" (p. 115) is a practical guide for policy makers and RRI practitioners. The next discussions should be on editing of wild species, focused ostensibly on gene drives in mosquitos and xenotransplantation in humanized animals (probably pigs). Finally, cell-based therapies, plant science, and industrial biotechnology all require attention and observation, if not their own follow-up report. This triage also helps to keep in mind that there are many issues and applications beyond inheritable changes that tie genome editing to societal challenges today. The previous workshop (Sciencewise Expert Resource Center, 2016) recommends a global observatory to keep track of and coordinate individual public engagement actions already underway.

For the UK-based Nuffield group, the forum in which ethical debates might take place is less concrete: an aspirational "historically and geographically defined site where social and technological conditions interact" (Nuffield Council on Bioethics, 2016, p. 115). Although the "nature and force of the public interest" (p. 117) are unknown and unpredictable, the conclusions of the Nuffield Council rely on a future process, where "governance is informed by public discourse" through a "difficult" (Nuffield Council on Bioethics, 2016, pp. 115, 116) process, where complex judgements come together and are capable of reaching consensus. This notion of a discernable single public interest is at odds with the characterization of diverse opinions and long-standing controversy; the report creates a paradox of public engagement for a future report to resolve.

6.2 Societal Challenges and Debates

Genome editing is often referred to as an emerging field, and the reports describe both continuity and change in the technical development of genome manipulation. Much of the excitement about CRISPR is the technical understanding, adaptation, and redeployment of bacterial defense system. It is in relating this to society that this knowledge becomes powerful, in making promises and naming challenges. Approaching technological power with humility reminds us that not everyone will benefit equally, that some may be harmed, and that technologies shape who we are and how we live together. In naming one goal, such as reducing the burden of genetic disease, biotechnology achievements may exacerbate another, such as the

societal challenge of respecting individual dignity and free will. As outlined in the state of the art (Chapter 2), controversy has often attended biotechnology, co-producing the governance regimes in place today. In attaching to certain promises and challenges, the reports contextualize issues and give references to orient the reader, framing certain issues as resolved and others as open to debate. In naming ethical questions, the reports take a normative stance about what is desirable and reasonable. The analysis in this thesis looks at human development, gene therapy, distributive justice, transhumanism and GMO's – societal challenges that stood out from the texts during the coding process.

6.2.1 Human Embryos and Understanding Human Development

The NASEM report begins a discussion about the "understanding of Human Development" in the chapter on basic research. CRISPR-Cas9 can knock out genes in zygotes (fertilized eggs) and then study the effects increasing knowledge about human development, at least at very early stages. The report outlines differences between mouse and human embryos and mentions that research is permitted up to 14 days in many countries, together with the prospect of "improved culture systems that allow human embryos to develop in culture during the implantation period" (NASEM, 2017, p. p. 76), without explicitly explaining that this research would be outside of the international norms and laws currently in place. The report argues that embryo research will improve IVF and stem cell therapies, as outlined in the table below.

TABLE 3-1 Reasons for Laboratory Studies of Human Embryos

In Vitro Studies	Clinical Outcomes
Studies of fertilization in vitro	Improvements in in vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD) Possible improvements in contraception
Improved culture of early human embryos	Improvements in IVF and PGD Insights into reasons for miscarriages and congenital malformations
Development of extraembryonic tissues (yolk sac and placenta)	Insights into reasons for failures in implantation and for miscarriages
Isolation and in vitro differentiation of pluripotent stem cells	In vitro models for human diseases for experimental testing of drugs and other therapies Improved cells for somatic gene/cell therapies and for regenerative medicine
Investigations of sperm and oocyte development	Possible novel approaches to infertility

Figure 4: Table of Reasons for Laboratory Studies of Human Embryos (NASEM, 2017, p. 78)

The NASEM report notes that embryo studies are also an important step on the way to clinical applications that would involve human pregnancies and the birth of a genome edited human. Still under the heading of basic research, the report outlines technical challenges to clinical applications of genome editing in humans and how this research could address them (p.78).

Later, in the section on ethical and regulatory issues in basic research, it becomes clear that this research is controversial and faces restrictions on funding and review. The oversight proposed would be non-binding and limited to ensuring transparency, responsibility and justifying the use of human embryos (p. 81), without discussion of the desirability of the outcome and alternative approaches.

This contrasts with the Nuffield approach;

> *If the objective is to produce a healthy child for a couple at risk of passing on a serious genetic condition to any child they conceive naturally, the alternative of adoption, surrogacy and egg donation, as well as PGD may be available…It is reasonable, in most cases, to question whether the focus is on genetic solutions just because the problem is conceived as a 'genetic' one and genetic technology is what is in view (Nuffield Council on Bioethics, 2016, pp. 48, 49).*

Another way of looking at studying human development by manipulating embryos is to focus on the way that it brings basic and clinical research closer together. The significance of genome editing on research using human embryos was that,

> *in some cases, alteration of a genome sequence could, in principle, serve both to discover the function of the gene and to enable treatment… the proof of concept of the research technique may equally constitute a proof of concept for a prospective treatment" (Nuffield Council on Bioethics, 2016, p. 38),*

speeding up development and eliminating space for deliberation about the social desirability of pre-implantation modifications to embryos. The Nuffield report criticizes calls for a second Asilomar, or self-regulation by the community, questioning the effectiveness of regulations, the existence of a coherent community, and the "narrowness of the debate process and the dominance of scientific interests within it" (2016, p. 40). Even when societal challenges, impact and economic value are brought into the discussion, science may not have responded to political and economic controls. The "moral imperative" identified is not for or against embryo research

to understand human development, but for "greater public engagement with science at all levels" (p. 40).

In neither case do the reports use this as an opportunity to re-open ethical questions about embryo research in general. The NASEM report expresses that the moral status of the embryo and how embryos are used in research is outside of the scope of the report (p.45). However, as these issues are central to the ethical and social implications of genome editing, they have anyway to be addressed. The NASEM report anchors it's understanding of the debate to discussions about stem cells, frequently citing the NIH 1994 Human Embryo Research Panel as a way of referring to the ethical questions without expressing an opinion. In the following passage, the NASEM report distances itself from one side of the debate, both through rhetorical 'othering' and by citing a previous committee report:

> *'Some of those opposed to making embryos in research argue that fertilization brings a new, morally significant human being into existence, and that making embryos for research purposes is inherently disrespectful of human life and potentially open to significant abuses' (NIH, 1994, p. 42). (NASEM, 2017, p. 43).*

However, in choosing a referent that is not only outdated, but was directly challenged by congressional action in the form of the Dickey-Wicker Amendment (which has prohibited federal funds that involves creating or destroying embryos since 1996), they do in effect take sides.

This discursive marginalization is also used in concluding the chapter, establishing that current regulations, even while they differ by jurisdiction, could be expanded to genome editing, for they note that "while there are those who disagree with the policies embodied in some of those rules, the rules continue to be in effect" (NASEM, 2017, p. 81). Using the designator "while there are those who disagree" dismisses any arguments to reconsider the rules, without addressing them directly. This is followed directly by a recommendation that existing systems "should be used" (NASEM, 2017, p. 82) to govern basic research on human genome editing.

The Nuffield report doesn't hide the controversy:

> *…of all the potential applications of genome editing that have been discussed, the one that has consistently generated the most controversy is the genetic alteration of human embryos in vitro and the possibility that altered embryos*

> *could be transferred to a woman who would give birth to a human being with a unique, altered genome (Nuffield Council on Bioethics, 2016, p. 115).*

The moral status of the embryo is a principally unknowable thing. Where the Nuffield report acknowledges that the Roman Catholic Church consistently holds that the moral status of human life begins at conception; the evaluation is that if research that discards embryos is morally reprehensible, a genome editing treatment that saves a life is a moral imperative (2016, p. 48), in effect asserting that the moral status of the embryo is negative knowledge, something we don't need to know to move on. In the UK, where the Human Fertilisation and Embryology Authority (HFEA), a special regulatory body, is concerned with embryos, decisions are made based on a variety of criteria concerned with safety, purpose, and types of cells. The Nuffield report focuses on current studies, noting the HFEA license

> *…granted to the Francis Crick Institute in London for research to understand embryonic development and developmental problems that might contribute to implantation failure and miscarriage [and how..] two Chinese research groups have modified embryos in order to edit genes involved in human disease, although in each case tripronuclear embryos were used, as these are thought to be unable to develop into a baby (Nuffield Council on Bioethics, 2016, p. 36).*

These practical, moral distinctions about the prospects of a viable pregnancy and birth frame the ethical question posed for discussion.

6.2.2 Gene Therapy and Regenerative Medicine

Whereas the embryo represents embroiled controversy, anchoring to gene therapy is strongly associated in the NASEM report with extending the existing regulatory framework to govern genome editing in humans. Gene therapy is tied to promises, informed consent and the clinical trial regime. Gene therapy is a story of dedicated scientific research through ups and downs, attended by regulatory hurdles and bioethics review. The death of a trial participant in 1999 is recalled to stress the differences and coordination between the RAC and FDA (NASEM, 2017, p. 56), stressing improvements since that time. Genome editing is invoked as a renewal of the promises of Gene Therapy:

> *With these distinctions in mind, there appears to be broad international consensus, derived from decades of research and clinical trials for gene therapy, that a somatic intervention undertaken to modify a person's genetic makeup for purposes of treating disease is not only permissible but encouraged, provided it proves to be safe and effective (NASEM, 2017, p. 147)*

The Nuffield report also promises that genome editing will break down "roadblocks" (2016, p. 40) in gene therapy, grouping it together with the prospect of xenotransplantation, particularly prospects for replacement organs grown in personalized pigs.

One key difference between the reports is whether disease prevention is considered together with therapy (NASEM, 2017), or together with enhancement (Nuffield Council on Bioethics, 2016), a distinction that extends and deepens the divide between individual choice and social justice. Where the National Academies report tells us that

> *It is important to note, for example, that one can use genome editing to achieve enhancement of a cellular property (e.g., secreting supernormal amounts of protein or resisting a viral infection) with the intent of curing a disease. Such cellular enhancement with intent to modify disease course needs to be distinguished from the concept of enhancement aimed at creating a desired or novel organismal feature in humans (NASEM, 2017, p. 91)*[10].

The Nuffield report identifies "a large grey area before one arrives at the threshold of enhancement" (2016, p. 50).

Complicating the already dense ethical question of what is normal, and therefore therapeutic, or enhanced, genome editing is also sometimes related in the NASEM report to regenerative medicine/stem cell therapies (p. 56), particularly when discussing clinical trial oversight and therapeutic applications (see Figure 4: Table of Reasons for Laboratory Studies of Human Embryos (NASEM, 2017, p. 78)). Gene therapy is distinguished from regenerative medicine – with perhaps higher stakes, noting the death of a clinical trial patient (p. 56), and more oversight, distancing gene therapy from problems of unregulated use in regenerative medicine (p. 107). The Nuffield report does not refer to regenerative medicine, and references to stem cells are mainly related to research (p. 35). Steering more towards gene therapy, rather than regenerative medicine focuses the issue more on future, more permanent and potentially inheritable modifications, rather than more immediate uses of genome editing in regenerative medicine. As envisioned by the reports, and perhaps fueled by their endorsement, clinical trials using genome editing are already underway. As these treatments become realities, the question becomes: Who benefits?

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[10] The possibility of a middle ground is also briefly mentioned in the enhancement chapter: "Such alterations could be viewed as enhancements or as leveling the playing field for those not fortunate enough to have these traits at birth, and they also complicate the distinction between therapy and enhancement unless one includes prevention as an intermediate concept" (NASEM, 2017, p. 148).

6.2.3 Societal Impact and Societal Challenges: Working at Cross-purposes

"Society's investments in science and technology" (Jasnaoff, 2004, p.16) call for research to have some kind of societal impact. Societal impact might be conceived in terms of products and services, with or without reference to a larger societal challenge. Although the complicated economics of genome editing is not a major focus of the reports, money does play a major role in research design & development directions. The Nuffield report posits that due to intellectual property regimes, only major corporate biotechnology firms are in a position to bring genome editing products to market, with "consequences for access, distribution and distributive justice" (2016, p.17). The NASEM report includes "cost" (2017, p. 103) as one of the factors at play in evaluating different gene therapy approaches. In the short term at least, gene therapy is only directed at a limited population. In a webcast follow-up of the National Academies report, committee member, John H. Evans indicated that perhaps 300 couples with genetic diseases who desired a genetic-related child, were at stake. Evans explained that genome editing investments would do nothing to alleviate health problems for the poor, and that the applications supported would have no social impact, stating that publics committed to "radical justice" or "opposed to the destruction of embryos" "should stop here"(J. H. Evans, 2017). While this view may not have fit the consensus building atmosphere of the report writing process, more subtle discussions of tradeoffs between individuals and society are included. The report is reflexive not only about the harms, but the difficulty of weighing more concrete and immediate "benefits that accrue primarily to individuals (such as prospective parents and children) against not only risks to the individuals, but also against possible harms at a social and cultural level [that…] are necessarily more diffuse" (NASEM, 2017, p. 119). Returning to xenotransplantation, the Nuffield report raises questions of "privacy and of equity (e.g. who should have, and who not have, a personalised animal model, and under what conditions?)" (2016, p. 38). Public health come in only later, in discussing gene drives to control insect-borne diseases (p. 80).

Sometimes it isn't the limited impact of potential cures, but the cure itself that creates a societal challenge. The Nuffield report relays that genome editing promises to overcome an important technical problem in xenotransplantation, which would lead to more experiments on large non-human primates, potentially raising animal welfare issues. Finding societal challenges in opposition is certainly the case for disabilities, as pointed out in both reports.

> *Disability justice and rights scholars have made a range of moral arguments against selective technologies, from individual rights based arguments such as the right to life of people with disabilities, to arguments for the social and*

> *emotional value (e.g. vulnerability to contingency) of biological difference, to the value to humankind of conserving disability cultures, and the importance of the visibility of disability in establishing social attitudes, behaviour, and structures (Nuffield Council on Bioethics, 2016, p. 28)*

The NASEM report points out that these are complex, overlapping, and contested values, and that "any step toward the use of genome editing to eliminate disabilities must be carried out with care and open discussion" (2017, p. 127). There may be many other forms of indignity that are exacerbated through genome editing, but don't have sophisticated advocates or eloquent positions and examples for an expert committee to grasp. Other publics, such as transhumanists, are overrepresented for argumentative purposes.

6.2.4 Transhumanism

Transhumanism is the "belief or theory that the human race can evolve beyond its current physical and mental limitations, especially by means of science and technology" (Oxford English Dictionary, 2018). Disproportionate space is given to transhumanism in both reports.

"As a species facing a number of potential environmental catastrophes Darwinian evolution may just be too slow." (Nuffield Council on Bioethics, 2016, p. 51).	"Whether to improve the species, and if so, in what way was the core of the ethical debate until the early 1970s. A discussion then—one continuing today among some transhumanists—is whether human evolution should be left to processes of natural selection, which are random and occur very slowly." (NASEM, 2017, p. 155)

Mastery of discourse may explain in part why transhumanism is given such serious consideration within the reports. Transhumanism is not an institution with leaders and membership, but rather a "loosely defined movement," or a "class of philosophies that seek that seek the continuation and acceleration of the evolution of intelligent life beyond its currently human form and human limitations by means of science and technology"[11]. Although transhumanism does not have the coherence, recognition or following of many of the other groups of people cited in the reports, such as the Roman Catholic Church or Greenpeace, their

[11] Definitions retrieved October 21, 2018 from https://whatistranshumanism.org.

positions are often named within the text as opposed to being relegated to the notes or receiving generic terms of 'some' or 'many'.

Take for example this passage in the NASEM report,

> *Some contemporary transhumanists point out that the human body is flawed in that it easily becomes diseased, requires a great deal of sleep, has various cognitive limitations, and eventually dies. They suggest that it would make sense to improve the human species by making it more resistant to disease, more moral, and more intelligent. Some, such as philosopher John Harris, say that in certain cases there is a moral obligation to enhance ourselves genetically (2017, p. 142).*

Compare this to the vague and sweeping generalizations that lump Christian traditions with diverse religions, secular culture and belief systems among some Native American nations together as bioconservative and set them against Jewish, Muslim and Buddhist traditions commitment to relieve suffering as if all the diversity of beliefs boil down to pro-nature or pro-medicine (see NASEM, 2017, p. 125). The inclusion of transhumanist ideas, particularly when set against bioconservative and religious concerns acts to move inheritable genomic modifications to the middle as a reasonable course. In doing so, a preference for natural processes is depicted as unreasonable, because nature is dangerous, unpredictable, random and slow (p. 125). In a veiled reference to transhumanist writings, the report refers to "people holding the unwarranted believe that the past processes of natural evolution have optimized humans for the current environment" (2017, p. 144). What beliefs must people have for their arguments to be reasonable and considered in ethical debates? If a belief in evolution is unwarranted, what then of those who don't believe in evolution at all?

The Nuffield Report also lists religions to support the claim that although sometimes moral perspectives coincide,

> *There is often no orthodox and generally accepted source of ready-made moral judgments," Footnote: "We received responses from the Church of England; the office of the Chief Rabbi; Hindu Council UK; the Sikh Missionary Society UK and the Muslim Council of Britain, as well as various Christian professional groups and NGOs (Nuffield Council on Bioethics, 2016, p. 31).*

The conclusion is that current governance is based on "norms derived from nature or established by convention," the result of which is "conservatism that seeks to restrain the

ebullience of biotechnology" (Nuffield Council on Bioethics, 2017, p. 31) while, "Other approaches would direct the development of biotechnology according to principles of welfare maximization, and control it in accordance with principles of justice" (p. 31).

6.2.5 Genetically Modified Organisms

There is one significant area where concern with human intervention in nature took the scientific community seemingly by surprise, that is, in the ongoing controversy over genetically modified (GM) foods. Here concerns about wider cultural changes in food production, as well as specific suspicions about health effects of transgenic foods combine with an unease about the degree and nature of human intervention. Although the prospects for genome editing in food is outside of the scope of this National Academies report, the "irreparable damage to the emerging scientific field of genetic engineering" (NASEM, 2017, p. 164) is recalled in setting up the importance of meaningful public engagement. The Nuffield Council takes up the subject in much more detail in the chapter, "FOOD", stressing a few points:

1) organisms modified using genome editing may be indistinguishable from techniques that rely on breeding using available laboratory equipment and knowledge. (p. 59)
2) Regulations, including labeling requirements, shape the means, methods, and economic relationships of how food is grown and the overall food supply. (p. 67)
3) existing GMOs have not demonstrated an exceptional risk to health. (p. 67)
4) the controversy is not really about risk. (p. 65)

The Nuffield report questions the place of meat in our diet and food system and shifts the debate from how plants are grown to the importance and role of plants – as feed, food security, and economic strength. While the framing of human health and intervention in livestock is relatively open, specific ideas about what is reasonable and good seem to be pushed in the discussion of plant-foods. This speaks perhaps to the Nuffield's conflicting mission to both promote discussion and avoid controversy, which is taken up again in the discussion section. This chapter, more than any other section of the report, references STS concepts, such as "contending imaginaries," (Nuffield Council on Bioethics, 2016, p. 69), meaning conflicting ideas about what is good and what the future should look like. Along with opportunity costs and unpredictability, the report writes that choices about biotechnology should, "involve people in collective acts of evaluation and moral reasoning, leading to societal choices" (2016, p. 65). In turn, "People may have concerns, but not be able to express their concerns in the precise language that lends itself to expert discourse" (p. 65). The report goes on to argue that "Meaningful public engagement depends on finding a common language" (p. 66) and should avoid framing technical subjects in terms of natural and artificial. These arguments are then

turned against non-governmental organizations (NGOs) who want to extend regulations of GMOs to genome edited crops.

In the GMO debate, NGOs have co-opted the language of risk assessment to join the policy conversation. The Nuffield report employs STS arguments about moving beyond risk assessments to discredit NGO's for these discursive tactics.

> *A number of NGOs nevertheless, continue to mount arguments for products developed by genome editing to be regulated as GMOs, and separately from other foods, on the basis of a putative risk to health or to the environment…They suggest that biotechnology researchers are being misleading when they describe genome editing as 'precise' in order to emphasise its difference from first generation GM (Nuffield Council on Bioethics, 2016, p. 67).*

Even as STS concepts are used, the effect is far from parallel; the committee intervenes (Hacking, 1983) through their characterizations of early observations in the debate on edited plants.

6.2.6 Human Dignity & Respect for Persons

A small but important difference between the reports lies in the concepts: "respect for persons" and "human dignity." The National Academies report refers to

> *overarching principles for human genome editing, adopted by the committee for this study, which are informed by those international instruments and national rules and which in turn inform the conclusions and recommendations presented in this report" (NASEM, 2017, p. 29),*

essentially using the rules to define the ethics, rather than vice versa. Here the report defines bioethics as "applied ethics" (p. 30) and sets human rights as a starting point, but promotes a concept of "reflective equilibrium" that balances utilitarian and virtue ethics. The result is avoiding the infliction of harm, accepting a duty of beneficence, and maintaining a commitment to justice. Respect for persons is the fifth principle, following 1) promoting well-being, 2)transparency, 3)due care, and 4)responsible science. The principle of respect for persons is followed by 6) Fairness and 7) Transnational cooperation (p. 33).

By Contrast, the Nuffield Council contextualizes human rights and dignity as the "valorization of natural order" (2016, p. 28) tied to natural law philosophies, post-enlightenment concept of

moral duty, and a contemporary turn to human rights after the abuses of the second world war. "It is argued by many that dignity and rights discourse is, in fact, insufficient to ground socially just action and that a specifically social justice perspective is called for (Nuffield Council on Bioethics, 2016, p. 30).

The respect for persons is tied strongly to the Belmont Report and resulting human subjects' protection regime discussed earlier. By invoking respect for persons instead of human rights, the NASEM report ties human dignity to consent and choice, rather than to justice and fairness. This focuses on not compelling people to undergo genetic changes (eugenics). The Nuffield report warns of a different kind of eugenics, the "'consumerisation' of human biology, and the spread of 'consumer' or 'liberal' eugenics, driven by the choices of parents rather than by state policy, but with possibly similar, socially divisive results" (2016, p. 52).

6.2.6.1 Eugenics

Eugenics is defined as "the control of reproduction to increase the occurrence of desired heritable characteristics in a population" (Nuffield Council on Bioethics, 2016, p. 49). The National Academies report first recalls "eugenics of the past" more as an example of how issues beyond safety and efficacy might matter, citing "faulty science" and "discriminatory political goals" (2017, p. 24). It is also used in a very literal way, "a commitment to preventing recurrence of the abusive forms of eugenics practiced in the past" (2017, p. 34). This refers to involuntary medical procedures or state-sponsored or coercive measures aimed at populations, public health statistics, the gene pool. Because "genome editing consolidates, at a genomic level, the choices of some in the possibilities open to others" (p.49), eugenics again becomes a concern. Projecting a future where genome editing is widespread, concerns about a "selection society" (Nuffield Council on Bioethics, 2016, p. 49) or "parallel populations" (NASEM, 2017, p. 128) are a way to build consensus around undesirable outcomes or futures. Where the Nuffield report mentions eugenics in relation to social justice, the NASEM report discusses eugenics in more detail throughout the report.

There is a sort of boundary work happening in the National Academies report. The first distinction is whether a modification is or isn't eugenics. Referring to an NIH RAC discussion that called enhancements that go beyond normal function as eugenics (NASEM, 2017, p. 146), anything restoring so called normal function would not be eugenics. Within the category of eugenics there is a further division between negative eugenics and positive eugenics. While the report acknowledges that "purely voluntary, individual decisions can collectively change social norms regarding the acceptance of less serious disabilities" (2017, p. 126), it doesn't take a

stance against genetic screening or genome editing. Positive eugenics are affiliated in the report with transhumanist arguments. Concerns about changing relationships between parents and children, as well as threats to equality and human dignity that positive eugenics pose, are presented as religious arguments.

Religious View	Transhumanist View
"… begetting, (i.e. nondesign) is critical to human dignity and human rights because "we are equal to each other, whatever our distinctions in excellence of various sorts, precisely because none of us is the 'maker' of another one of us" (citing Meilanender, 2008, p. 264). These concerns about objectification might possibly apply to germline conversion to genes associated with ordinary health, but would more likely be raised by enhancements, health-related or beyond." (NASEM, 2017, p. 157)	"One might say that making choices about our genetic future --- whether or not they increase the perception that humans are more like objects --- is precisely human (p. 158). As Joseph Fletcher, one of the founders of bioethics, wrote in 1971: "Man is a maker and a selecter and a designer, and the more rationally contrived and deliberate anything is, the more human it is. . . . [T]he real difference is between accidental or random reproduction and rationally willed or chosen reproduction" (citing Fletcher, 1971, pp. 780-781). (NASEM, 2017, pp. 157-158)

These two characterizations of the debate seem to cancel each other out, leaving room for a compromise position on germline editing for treatment and possibly prevention.

The characterization of eugenics of the past in the NASEM report goes along with the concept of respect for persons; the practice of eugenics is condemned because of the methods, coercion, racism, and subversion of individual rights to utilitarian views of burden or public health. In contrast, the concept of human dignity upheld by the Nuffield Council is challenged by the underlying deterministic view of genetics that privileges some over others. Where the Nuffield report talks about eugenics in the past, it is to point out the origins of current prohibitions covering germline intervention (2016, p. 49). Although the methods are different, in both cases, these prohibitions are called into question.

6.3 Argumentative Practices

Perhaps the most difficult task of a bioethics report is establishing credibility with both technical and non-technical audiences. *Independence* and *expertise* are central to the self-presentation of both bodies, but where the National Academies of Sciences, Engineering and Medicine also stakes a claim to objectivity, the Nuffield Council focuses on anticipation. This comes out in the way the NASEM report describes the importance of framing and the how objectivity can be constructed in contrast to the Nuffield Council report's call to anticipate how framing might impact the discussion:

NASEM	Nuffield Council
"Fairly minor differences in how scientific techniques are described in meeting materials or the examples that are chosen for particular applications can significantly alter initial attitudes among participants, as well as the overall nature of discussions …written meeting materials or presentations by experts during public engagement exercises …need to be systematically pretested using empirical social science to ensure that they minimize a priori biases and allow for inclusive, broad discussions that are not constrained artificially to the technical or scientific aspects of the subject" (NASEM, 2017, p. 176).	"The danger of the metaphor lies not in the fact that it is a metaphor, and therefore a non-reducible way of referring to complex realities; it lies in the possibility that the metaphor might either dissemble significant ethical questions through the use of euphemism, or lead reasoning astray by overstretching the power of analogy" (Nuffield Council on Bioethics, 2016, p. 20).

In both cases, social science expertise is called for in protecting the public discussion, a claim which says something first about how this discourse is envisioned, but also asserts the expert authority of the reports in being the ones to say how the discussion should and should not be framed.

The reports make statements that order the world in a specific way, bringing new relationships between people and medicine into focus. As a glimpse into the methodology behind the analysis presented in this thesis, we can start to take apart a statement we've seen before using grounded theory coding.

Text from NASEM Report	Coding the text – looking for actions and framing
"With these distinctions in mind,	Making distinctions – between disease and enhancement

there appears to be	Representing public opinion
broad, international consensus	Making judgements about reasonable arguments Drawing attention to jurisdictions Building consensus
derived from decades of research	Projecting long term Building authority
and clinical trials for gene therapy,	Clinical trials as governance Anchoring to other debates
that a somatic intervention undertaken to modify a person's genetic makeup	Making distinctions – between somatic and germline Defining genome editing
for purposes of treating disease	Naming societal challenges
is not only permissible but encouraged,	Naming governance issues Defining ethical questions
provided it proves to be safe and effective"	Acknowledging Non-knowledge Under conditions Using Risk Benefit in clinical trials

(NASEM, 2017, p. 147)

The argumentative strategy is to make somatic gene editing seem self-evident; this is based on claims of internationality, research and clinical testing focused on a specific intervention to treat disease. This draws attention away from the uncertainty and perhaps towards a moral imperative to help, stipulating a more permissive regulatory atmosphere that accounts for harm only to individual volunteers participating in clinical trials.

This thesis started with the premise that we live in a complex society, and the way we live is deeply intertwined with science and technology. The Nuffield report begins with the statement, "There is a concern that genome editing science and innovation are moving ahead of public understanding and policy" (Nuffield Council on Bioethics, 2016, p. 1) this characterization of a race between policy and science fails to consider how social technologies, like the HFEA and NIH grant-making bodies, have co-produced the state of genome editing along with scientific work. The "law lag" argument depicts these processes as hurdles to scientific progress by focusing narrowly on the 14-day rule and Dickey-Wiker amendment rather than the subtle ways in which scientific proposals follow funding and avoid paperwork. Both reports look to authorities on genome editing and bioethics to inform decision makers and the public alike. In this section, we look closely at the argumentative practices of the authorities tasked with narrowing the gap,

focusing on uncertainty, projections, distinctions, and framing. To begin, there are areas that the authorities aren't sure of, don't know, or didn't think of – using the concept of non-knowledge the analysis unpacks how uncertainty in dealt with and used as a rhetoric strategy in the reports.

6.3.1 Non-Knowledge

Undesirable outcomes of science and technology have led to distrust of expert authorities and questions about the distribution of benefits and harms. Genome editing is an emerging technology. Many of the applications under discussion are speculative and may not be possible; genome editing tools and practices described are also changing. The reports must deal with the unknown to do their work in informing publics and other policy makers. In a traditional risk/benefit analysis, foreseeable risks are compared to known alternatives. Without data, these analyses are highly speculative. Alternatives, such as gene therapy are only marginally better understood and not at all in generational or cultural impacts. The NASEM report concedes, "First-in-human trials make compliance with these provisions difficult, given that by definition, it is very difficult to assess the degree of uncertainty that pertains when research is moving from preclinical models to human interventions" (p. 47). As a result, many of the risks discussed are presented as (temporary) problems for research to solve.

6.3.1.1 Not-yet knowing

The Nuffield report acknowledges that there may be new ways "that have not yet been described or even envisaged" (2016, p. 4), and is careful to start with the current state of genome editing, based largely on CRISPR-Cas9 work in the laboratory before moving to projected applications. The technical description focuses on what has already been done and the challenges and problems researchers were working on. The Nuffield report is upfront about how much is unknown about how CRISPR-Cas9 might perform outside the laboratory: "So young a technology has nevertheless, yet to be fully delineated" (2016, p. 10).

In contrast, the National Academies report focuses on applications from the beginning. The state of current research is included as an appendix. Non-knowledge is often framed as technical challenges and plays a strategic role in the National Academies report, particularly in identifying legal or funding restrictions to research. In the following example, two technical challenges, 1) maintaining a stable spermatogonial stem cell (SSC) line and 2) generating spermatozoa from these stem cells are presented as separate research aims that do not present an anomaly to the existing bioethics regime.

> *"stable human SSC lines have not yet been reported, but would clearly be an important tool for understanding male infertility" (p. 79).*

> *"human gametes have not yet been generated successfully from pluripotent stem cells, although two recent papers report the generation of early germ cell progenitors from human ES cells" (p. 79).*

The report mentions that similar research in mice has been successful, creating both a reasonable assumption of success for the stem cell and spermatozoa research, and a motivation for doing the research.

> *Stages of spermatogenesis in mice may not always be applicable to the same process in humans (NASEM, 2017, p. 80)*

> *If human haploid gametes could be generated from human pluripotent cells, as they can be in mice, it would open up new avenues for understanding gametogenesis and the causes of infertility. It would also open up possibilities for using heritable genome modifications to address health problems that originate from genetic causes (NASEM, 2017, p. 80).*

What is unclear from the NASEM report is that the next step, combining the two lines of research in creating laboratory generated spermatozoa, crosses an ethical barrier: involving inheritable changes to the germline. Conflating existing governance for stem cell and embryo research with ethics, the next paragraph indicates that "few new ethical issues are raised," with the exception that "research with embryos is more controversial" (NASEM, 2017, p. 80). The knowledge gained from this research is a precursor for human genome editing. There are many unknowns in getting to a point where SSC generated spermatozoa could technically be combined with oocytes, or egg cells, to create an embryo. The proposed governance measures, self-regulation through institutional oversight committees would only apply if these technical challenges were met. The impact of all this 'not-yet' knowing, is that it gives the report space to ignore ethical issues in upstream research, while pressing for self-regulation downstream.

This same technical challenge is described in the appendix quite differently:

> *In the mouse, this is achieved by transfer into the germ cell-depleted testis - not an easy solution in humans. Alternate approaches include generating a "reconstituted testis" with mixed SSCs and supporting cells of the testis and transplanting this under the testis capsule. This approach would also be ethically challenging in humans. The possible use of interspecies reconstitutions*

> *and transplants into immune-deficient mice would bring its own scientific and ethical challenges(NASEM, 2017, p. 242).*

These ethical issues are neither explained in the appendix, nor mentioned in the body of the report. It draws the reader into a paradox of scientific authority – it is difficult to grasp the ethical issues without some framing of the technical information, and yet these explanations often judge whether something is ethical without providing a cultural or political frame of reference.

6.3.1.2 Off-target effects

One type of non-knowledge in genome editing has acquired its own term: Off-target events or effects. Off-target events "…could have consequences, many unnoticeable but others damaging, depending on their location and their effects" (NASEM, 2017, p. 24). As implied by the name, these are effects that are not intended. In STS circles, terms such as unintended consequence and side effect (Beck, 1997) have been criticized for their pejorative use and shift from consequences to intention. The term off-target effect also refers to intention, rather than effect. Off target effects present a significant challenge to applications of CRISPR-Cas9 where adverse events must be minimized, as well as to the metaphor of genome editing and description of genome editing tools as precise, efficient, or effective.

One of the tasks for the NASEM committee was to respond to the question: "Can or should explicit scientific standards be established for quantifying off-target genome alterations and, if so, how should such standards be applied for use in the treatment of human diseases?" (NASEM, 2017, p. 17). The report answered, that "because off-target events will vary with the platform technology, cell type, target genome sequence and other factors, no single standard for somatic genome-editing specificity (e.g., acceptable off-target event rate) can be set at this time" (NASEM, 2017, p. 110). This response is framed as not-yet knowing. The Nuffield Report provides essentially the same answer: "The difficulty of each of these challenges will vary with a large number of factors, including the characteristics of the technique used, the method and timing of delivery, and the characteristics of the target cells"(p. 41). The difference is that the way this latter description is framed creates more non-knowledge, without anticipating that there would ever be a solution.

6.3.1.3 Negative Knowledge

Non-knowledge isn't always problematic. One way to address non-knowledge is to present it as having little or no impact on the outcome, in effect negating it. Negative knowledge, is presented

as something not to worry about. In the case of the human embryo debate (see 6.2.1), the report negates the question of the moral status of an embryo by the possibility of 'saving' an unviable embryo through genome editing. In other cases, this discursive technique is a way of dismissing risks or costs that cannot easily be calculated. "Despite these limitations, *ex vivo* genome editing has the advantage that cells with the desired alteration can be selected and the accuracy of the alterations validated before transplantation to the patient" (NASEM, 2017, p. 97). The risk of mutation, tumorigenesis, and failure to integrate functionally are minimized by screening. Consequentially, anything that fails to be screened would be an unintended side effect. Another example is the suggestion that men could be successfully monitored for accidental germline transmission from somatic genome editing techniques, while women cannot because "there are currently no noninvasive means of monitoring women for germline transmission," (NASEM, 2017, p. 19), leading to different individual risk/benefit analyses for women than men, as well as an assumption of the ability to maintain a strict distinction between somatic and germline editing.

Negative knowledge can also be used to disregard social impact such as in the summary for the National Academies report, "Germline genome editing is unlikely to be used often enough in the foreseeable future to have a significant effect on the prevalence of these diseases" (NASEM, 2017, p. 6). In other cases, negative knowledge emerges from principally unknowable things, such as when life begins: "This report does not address those ethical arguments (embryos in research), and accepts as given the current legal and regulatory policies that apply in each country" (NASEM, 2017, p. 45).

This other category of non-knowledge – principally unknowable things - encompasses much of the value-driven, metaphysical issues that do not lend themselves well to quantitative assessments or consensus processes. Other unknowable questions are turned into matters for philosophical and theological reflection: "The question will always be how much human-directed intervention in nature and in humans themselves is appropriate or even permissible" (NASEM, 2017, p. 125). Referring to germline or potentially inheritable changes, the Nuffield suggests facing the unknowable head on.

> *Despite the amount of consideration that these questions have received, the controversy remains unresolved. We do not believe, however, that this is the result of an intractable opposition of principled positions, but of complex judgements made in a changing context of relevant factors (Nuffield Council on Bioethics, 2016, p. 116).*

Beyond not-yet knowledge, negative knowledge, and principally unknowable things, there also lies unknown unknowns, or nescience-- that which we don't expect and haven't thought of, such as cultural and environmental impacts. Jasanoff reminds us that "Social science has made visible the social problems of modernity – poverty, unemployment, crime, illness, disease and lately, technological risk – often as a prelude to rendering them more manageable" (2003, p. 240), without changing the underlying issues, and calls for frame analysis and the humble acknowledgment of the inability to predict.

6.3.2 Projecting: Making Promises and Challenges

Genome editing, like stem cells and gene therapy is often presented as the promise of a cure for genetic diseases (Thompson, 2013), and as the CRISPR patent battle shows, genome editing also promises economic rewards. Where this National Academies report focuses on biomedical applications, the Nuffield report draws on a diverse set of opportunities. In invoking opportunity, something else is problematized, a societal challenge framed in a way that delivers a particular solution. Earlier in the analysis we looked at how genome editing relates to complex societal challenges: genetic disease, disability, food production, inequality and injustice. This section covers discursive practice of projection within the reports.

The NASEM report begins with projections, based on the efficiency and precision of CRISPR/Cas9, including germline editing to prevent genetically inherited disease and personal genomic enhancement. In the chapter on basic research, the report states that "controlled genetic changes in any DNA" has enabled research on gene function, developed models for studies of human diseases using stem cells or laboratory animals, created modified plants and animals to improve food production, and developed therapeutic uses in humans. Genome editing is presented as an "invaluable core technology" (NASEM, 2017, p. 23). While enhancement raises "questions of fairness, social norms, personal autonomy and the role of government," current applications raise no new issues. The Nuffield report takes a different approach to upstream research, arguing that "the factors that act to attract and consolidate investment may also have the effect of confirming a course for innovation" (2016, p. 18). Challenges, such as genetic disorders and their burden on families, are also entangled in these upstream research justifications. The NASEM report argues, "although examination of past technological innovations can help in making predictions about social and cultural changes, these predictions remain necessarily speculative because any such changes resulting from a new technology take time to develop" (2017, p. 199).

Genome editing research promises better genetic understanding and genome editing tools that could be used in clinical settings. In the Nuffield report, projected applications are presented together with projected societal impacts, or in the language of the report, the focus is on "problems or challenges (and the potential diverse framings of those challenges), rather than technologies" (2016, p. 115). It is almost as if in the NASEM report, genome editing solves societal challenges; in the Nuffield report, it creates them. An imaginative litany of possible applications includes enhanced nightvision or sense of smell, human photosynthesis (p. 51), xenotransplantation, gene doping in competitive sports, novelty pets and glowing sushi, gene therapy for pets, and performance-focused edits for soldiers; all raise more questions than they answer (Nuffield Council on Bioethics, 2016). While perfecting astronauts and athletes and in-utero editing do appear in the NASEM report (2017), the focus is largely on a small (American) population of potential parents who both carry recessive genetic variants associated with disease. Neither report mentions the much higher rates of recessive genetic disease in cultures where consanguineous marriages are accepted Tadmouri et al., 2009). Instead, the NASEM report projects a rather imaginative scenario to envision genome editing's future in reproductive medicine.

> *As the survival of people with severe recessive diseases like cystic fibrosis, sickle-cell anemia, thalassemia, and lysosomal storage diseases improves with advances in medical treatments, the possibility cannot be dismissed that there will be an increase in the number of situations in which both prospective parents are homozygous for a mutation. The societal and medical pressures faced by these people often bring them together in social groups where they are more likely to interact and develop close relationships (NASEM, 2017, p. 114).*

The NASEM report projects adverse effects as well. Technical challenges such as adverse immune system responses, transgene toxicity, and delivery procedures are discussed at length. Successful projections of human genome editing rely on being able to not only successfully translate work done in mice to humans, but also find better ways to direct homologous repair, and avoid or control for unintended edits. Projections for edits in fertilized human eggs would also need to eliminate mosaicism, as the success rates in mice are much lower than would be acceptable even in compassionate use cases for humans.[12] Early trial results show that many people are resistant to the bacteria housing the CRISPR/Cas9 system(Charlesworth et al., 2018). Presenting uncertainties as technical challenges makes it a problem of resources, talent, and

[12] An example from a mouse model generated to study MERS, "Five of 66 live animals produced showed evidence of both the 288 and 330 modifications" (Cockrell et al., 2016, p. 9).

research freedom. The Nuffield report points out that, "Whereas scientific knowledge is international, science funding is often national, and researchers are constantly embroiled in direct competition for resources, jobs and recognition" (2016, p.14). Whether intentional or not, funding priorities are political decisions about desirable futures, which often come without much public input. It's hard to say just how many researchers and resources are currently devoted to working on these problems worldwide; however, even with the funding restriction on embryos, the US National Institutes of Health has awarded over 1 billion USD to active projects that mention CRISPR in the description.[13]

6.3.2.1 Time to Talk

The time for public discussions is often framed in relative terms of urgent, in the near future, or long term rather than specific references to time. Relative terms such as soon or long-term are often used to narrow or open up possibilities for debate. This section looks at what these modifiers do discursively to our understanding of the issues and how they are used to set-up public discussions of genome editing. The Nuffield report triages the issues into those needing urgent attention, that which should be discussed in the near future, and that which can wait. The Nuffield report promotes upstream discussions of genome editing, to the extent possible, so that societal challenges can drive the selection and direction of solutions, which may include genetic technologies, but may not. Reproductive issues are urgent, because ideally the discussions would have already started. This is also the case with the issue of editing livestock, which is already being field tested. Sometimes, soon is then a way of saying now, while giving some room to the report process – the writing, review, edits, printing and launch that come between the committee debate and public discussion.

The NASEM report actually doesn't use the word soon, choosing instead 'near future,' 'foreseeable future,' 'and, 'not yet'. "The committee calls for continued public engagement and input (see Chapter 7) while the basic science evolves and regulatory safeguards are developed to satisfy the criteria set forth here" (2017, p. 135), which suggests a concurrent process, rather than an upstream one, and removes the urgency from the discussion. Short-term projections, such as solving technical challenges related to delivery, mosaicism, and immunity mentioned in the previous section avoid mentioning specific units of time. Three to five years, the standard project lengths for sponsored research is one way researchers think about time, but projects may focus on one aspect of one challenge. There is no way to predict how long (in years) the

[13] Data Source: https://projectreporter.nih.gov/ 23 May, 2018 Search result for active projects using text search "CRISPR" sorted by project funding and fiscal year.

development of applications beyond disrupting gene function would take. NASEM also uses longer passages such as, 'These dramatic improvements in efficiency have enabled scientists and clinicians to consider using genome editing for a greatly expanded range of applications, including application to the treatment of diseases" (2017, p. 88), that don't refer to any timeline at all.

Long term projections however, do sometimes have a time signifier – the decade.
In the discussion, a decade, 10 years, is a significant marker of whether something is short term or long term: "from the current stage of development of genome editing-enabled gene drives, large-scale release is likely to be at least a decade away. However, this does not mean that ethical examination is currently not required."(Nuffield Council on Bioethics, 2016, p. 118). The NASEM report moves in the other direction, arguing that "Heritable genetic engineering has been the subject of public and academic discussion for decades" (20178, p. 132), using the decade to show something that is well established.

Drawing on gene therapy (p. 83) and regenerative medicine (p. 69), the NASEM report emphasizes that basic research takes decades to reach the clinic. "The idea of making genetic changes to somatic cells, referred to as gene therapy, is not new, and considerable progress has been made over the past several decades toward clinical applications of gene therapy to treat disease" (NASEM, 2017, p. 83). This image of a steady progression from stem cell research to gene therapies and regenerative medicine doesn't reflect the uneven pace and bumps in the biotechnology sector (Birch, 2016) and implies that applications in genome editing will also take decades of steady work, despite repeated references to the speed of development (NASEM, 2017, pp. 4, 23, 25, 67, 68, 95, 133, 181, 188). This focus on speed is also central to the Nuffield report, although more emphasis is placed on the relationship between speed and social pressure.

> *Whatever the optimum form of governance, the major consideration for this report has been the speed of development and diffusion of the techniques of genome editing relative to the social processes by which normative frameworks, such as those of law, regulation and public acceptance evolve. The possibility of attenuation or fracture of this relationship between the scientific and normative knowledge warrants further examination (Nuffield Council on Bioethics, 2016, p. 108).*

Time is used particularly to separate technological from ethical issues, and set them against each other in a race. "Alarmed by the direction of the research, the U.S. Congress… [prevented]

the FDA from using any of its resources to even consider an application to proceed with clinical trials involving germline modifications" (NASEM, 2017, pp. 131-132). Calling for time is a way to call for more consideration of ethical and legal issues, but is often characterized as being at the expense of progress. The term "law lag" is often used to depict boundary work with time as the main reference, Jasanoff criticizes that "To see law and public morality as always lagging, however, leads us into the trap of technological determinism. It suggests that technology sets its own moral codes, and public values simply catch up later" (2016, p. 144). Jasanoff continues, "confronted with novel ways of characterizing and manipulating the stuff of life, people have striven with energy and ingenuity to rearticulate their fundamental moral commitments: the preservations and protection of life; to upholding human dignity; and to maintaining institutions such as motherhood and fatherhood, albeit with a wider range of possibilities and imaginations than before" (2016, p. 144). This understanding that moral commitments should both precede and be rearticulated together with technical work, rather than after, is reflected by the NASEM committee in adopting principles, rather than specific rules.

Time can also work for patients burdened with genetic disorders, as pointed out by the Nuffield report

> *The pace of genome editing advances may result in special considerations for clinical translation, just as in basic research, there may be arguments in favour of delaying clinical implementation until the rate of progress has slowed given that any application of genome editing today may turn out to have been better if done tomorrow (Nuffield Council on Bioethics, 2016, p. 44).*

Even with this understanding, both reports present public discussions and ensuing regulations as countering the fast pace of development. NASEM report notes that public consultation could alter the "speed of biotechnology innovation" (2017, p. 262), and that preventing antisocial uses of technology might be accomplished by placing "speed bumps on the slippery slope" (2017, p. 129).

Within the informed consent paradigm, long-term follow up is presented as central to evaluating the risks and benefits of early genome editing clinical trials. This draws on gene therapy as a precedent. In this case, long-term is defined as a period of 15 years (2016, p. 104). Seeing only 10 or 15 years into the future also makes impacts on generations or evolutionary impacts impossible to see. This allows the NASEM report to claim that "Changing a disease-causing mutation to a known existing nonpathogenic sequence would be the case in any currently envisioned therapeutic applications, and thus the effect of any such heritable genome-

editing changes for therapeutic purposes is expected to have minimal effect on the gene pool" (2017, p. 118). The NASEM report notes the incommensurability of individual-level benefits, which are projected before clinical trials, with societal-level risks, which are judged after a technology or treatment, is established through lawsuits in the risk/benefit paradigm currently in place in the United States. "Individual benefits and risks are more immediate and concrete, whereas concerns about social and cultural effects are necessarily more diffuse" (p. 119).

Decisions about timing and quantification in risk/benefit analyses have normative impacts, despite attempts at objectivity, in this case by leaving society out. Limiting the scope to future offspring and their descendants allows the NASEM report to look further into the future, "By definition, those affected by the edits (future offspring) did not make the decision to be subjects of research or attempts at therapy, adverse effects might be multiplied by reverberation across generations" (2017, p. 122). This recommendation stays within the human subjects' paradigm. Contributors to the Nuffield report advocate "tracking social justice outcomes over time," (2016, p. 30) presumably for much longer than decades. The Nuffield characterization of genome editing as a transformative technology capable of disrupting incumbent technologies in reproductive medicine and agricultural biotechnology, with societal impacts that go far beyond the participants in clinical trials, is based on a look farther into the future, whereas the NASEM report focus is more on foreseeable tension between biotech companies, funders and regulators, and publics in the next 10-15 years.

6.3.3 Making Distinctions and Classifications

The NASEM report is straightforward about its role in setting the terms of the debate. The report makes distinctions deliberately, explaining the boundaries and arguing for their importance in discussing and building consensus. A section heading reads: Drawing lines, therapy versus enhancement, and is followed by Box 6-1, Making Distinctions (NASEM, 2017, pp. 145-146). Distinctions are also instrumental in the passage on page on page 147, explored in detail at the start of the section.

> *With these distinctions in mind, there appears to be broad international consensus, derived from decades of research and clinical trials for gene therapy, that a somatic intervention undertaken to modify a person's genetic makeup for purposes of treating disease is not only permissible but encouraged, provided it proves to be safe and effective (NASEM, 2017, p. 147).*

The purpose of all this distinction making is to prepare us to accept the premise of the report, that somatic genome editing does not require a public discussion.

Distinctions order ideas. Although it doesn't come through as an official recommendation, the report also endorses an idea that "as genome-editing technologies and applications develop, the need for ongoing public discussion about how regulatory bodies should draw distinctions between such concepts as therapy and enhancement or disability and disease" (NASEM, 2017, p. 165). This argument is attributed to STS scholars Jasanoff, Hurlbut, and Saha (2015) and Sarewitz (2015), but misses their main points about thinking beyond risk/benefit assessment and finding ways to direct scientific efforts towards consumer demand, ideas that bring the public in as equal participants in guiding applications of genome editing.

The performativity of categorization comes through in Nuffield report's reflection that, "Such distinctions include that between 'germ line' and 'somatic' cells, which is required to do so much normative work, and between genomic and epigenomic changes, in view of the potential of each for reversibility and their relation to personal identity" (2016, p. 53) and important for making laws or detailing ethical positions. These distinctions should be "consistent with the current state of scientific knowledge" (Nuffield Council on Bioethics, 2016, p. 53). As in the embryo debate, scientific observation provides clues that are interpreted through value judgements. An ethnographic study of stem cell laboratories for plants and humans at Brown university (Wilson, 2015) deconstructed the idea of germline cells as a distinct inheritable cell type, following research on gametogenesis (the formation of germline cells) in mammals and plants. The germline distinction is not purely scientific fact, but socially constructed, something that seems to be at least tacitly understood by the committees.

The NASEM (2017) report starts from a premise that there is a continuum of acceptability in genome editing. This continuum is also referred to as a slope.

> *Many of the attempts to introduce speed bumps or friction on the slippery slope in the evolution of genetic modification of humans have focused on the easily grasped linguistic/cognitive difference between a body/individual and offspring/society, thereby establishing the distinction between editing of somatic and germline cells (NASEM, 2017, p. 128-129).*

By introducing the germline as a human construction, it takes away the moral stance and turns it into a regulatory one. The following passage further shifts the discussion from the moral basis of prohibitions on germline edits to regulatory issues: "proponents of slippery slope arguments raise the question of whether and how society can develop regulations that are sufficiently

robust to quell the fear of a progressive move toward less compelling and more controversial application" (NASEM, 2017, p. 129).

This type of work in making distinctions based on scientific facts, which are then challenged by exceptions and revelations about their construction, and shift accordingly, is more of a demonstration of the slippery slope concept than a reflection of it. The Nuffield deals with how forces of coproduction change regulations and norms,

> *The technologies in use in any society are often the result of both moral and technical co-evolutions that function to embed the characteristics of a given technology in a set of normative conditions in a way that might make genome editing the 'technology of choice' for a variety of applications (Nuffield Council on Bioethics, 2016, p. 48).*

The distinction between therapy and enhancement, discussed in the previous section in regard to gene therapy is also pertinent. One potential application of genome editing is "engineering resistance to HIV" (NASEM, 2017, p. 93). Here engineering resistance is included in a chart, "Table 4-1: Examples of Potential Therapeutic Applications of Somatic Cell Genome Editing" and the stage of development is listed as "clinical trial" (NASEM, 2017, p. 93). The designations of therapeutic, somatic, and clinical trial all act to fit this intervention into existing governance, without mentioning that the Chinese project involving non-viable embryos would not have been characterized as a clinical trial or allowed in the US system. The Nuffield discussion of this same project leads to a discussion of transhumanism and aspects of prevention as enhancement, introducing the concept of "'consumer' or 'liberal' eugenics, driven by the choices of parents rather than by state policy, but with possibly similar, socially divisive results" (2016, p. 52).

Making distinctions is a subtle way of drawing attention away from the category being distinguished against. When the NASEM report says, for example, that the distinction between "mutant and normal" is "worth keeping in mind" (2017, p. 139), it reinforces the argument for considering enhancement separately from prevention. In rejecting the categories of somatic/germline, risk/benefit, and enhancement/prevention established in the 1970s to protect research freedom, the Nuffield report leaves room for a much broader discussion.

> *Genome editing is a potentially transformative technology, not merely in an economic sense but also in a moral sense, in that it has the capacity both to produce new differences in the world and to provoke new ways of thinking*

> *about differences in the world. There is a need for normative judgements to respond to the world as it is presented in the current state of scientific understanding (Nuffield Council on Bioethics, 2016, p. 26).*

Genome editing might alternatively be categorized into applications in reproduction, genetic disorders, sports, military and anti-aging as ways to produce differences. The 'new ways of thinking about differences' might be acceptance for genetic disorders, those with or without access to genome editing interventions, 'naturalness' or other differences that have meaning to lawmakers, participants in public engagement exercises, candidates for genome editing, and wider publics.

6.3.4 Transformative?

The categorization of genome editing as transformative by the Nuffield Council is performative, in that it attempts to re-order how science and science governance are organized. It is the transformative nature of genome editing that allows us to re-open settled debates that separate scientific discourses from normative discourses. This has two consequences for inheritable genome editing– first, "normative judgements enshrined in moral and legal codes" (p. 27) can be revisited, as in, allowing germline editing, and second, promising technologies, regardless of safety, should not move forward without a "publicly coherent solution," that satisfies "different thoughts about the nature of morality and different ways of valuing" (p. 32).

Where the Nuffield report does not consider genome editing to be transformative, such as in destroying embryos in research (p. 38), gene therapy (p. 44), and plant modification (p. 60), new discussions are not called for. The Nuffield report is one forum where scientific and normative discourses meet and different positions and arguments encounter each other, however it is not subject to, nor a form of democratic governance. The "inclusive public sphere" (Nuffield Council on Bioethics, 2016, p. 31) where open and effective discussions about genome editing occurs is yet to come.

Where the Nuffield's characterization of CRISPR-Cas9 as transformative clashes with the National Academies assessment that the ethical challenges of genome editing are 'not new,' it reflects the differences in the definitions of genome editing as a practice (Nuffield), or as a tool (NASEM). The premise that genome editing is instrumentally "not new," serves as an endorsement for the status quo. The technical descriptions of CRISPR-Cas9 however, describe a "game-changing advance" (NASEM, 2017, p. 23) that has "revolutionized the field of genome editing" (p.65), and "has lent new urgency to calls for a broad public dialogue about these

technologies and their applications" (p. 163). The appendix also describes a "completely novel system" (p. 218) leading to an "explosion in the application and refinement of Cas9-mediated cleavage" (p.224) and dramatic changes in generating mutant animals. What is not new is the idea of genetic manipulation. The report argues that human genome editing is still largely a promise, and one that we've imagined already for decades.

Even though both reports present a similar picture of dramatic changes in research practice with uncertain consequences for society, the difference in policy implications is stark. Despite the caveats presented, the National Academies report is an endorsement for pursuing almost all applications of genome editing, including research on inheritable genome editing. The Nuffield report on the other hand is an endorsement of the deliberative co-production of governance. Tacitly, this still opens the door for inheritable genome editing, but it raises many more issues for consideration and discussion and broadens the scope of issues that can be considered.

7 Discussion

This section brings literature and concepts from Chapters 2 and 4 into the analysis, contributing to ongoing discussions on reflexivity, justice and STS engagement. As a bridge between the text-grounded analysis in Chapter 6 and conclusions in Chapter 8, this chapter highlights significant areas for further discussion and research.

7.1 Authority and Humility

Returning to the paradox of scientific authority and the call for "technologies of humility"; how do these assessments, that is the reports, assert authority and contend with *framing*, *vulnerability*, *distribution*, and *learning* (Jasanoff, 2003) about the complex topic of genome editing? The NASEM report draws on many technical experts from around the world as well as several professional bioethicists with backgrounds in law – skilled at debate. Individual credentials are de-emphasized, while strength in numbers and degrees is projected. For the Nuffield council, the strength comes from the process and bringing in wise outsiders. These practices reinforce past observations about US and UK cultures of regulatory science (Jasanoff, 2006 & 2011). In both cases the committees speak with authority and purport to provide background information for an informed and reasoned discussion. However, although the scientific and even STS literature reviewed are the same - the resulting material reads very differently from one report to the next. The Nuffield (2016) report speaks of a transformative technology affecting food, health, reproduction and the environment which needs to be observed and guided, while the NASEM (2017) report focuses on biomedical breakthroughs and transparency. The section on argumentative practices has touched on some ways in which the

reports have framed and reflected on the framing of time, off-target rates, significance and second order ethical concerns. One thing that distinguishes these reports from technological assessments of the past is an acknowledgement that values are an indisputable part of technological assessment - judging whether genome editing applications are good, or at least acceptable. Public discussion is made accomplice to the authority of these institutions, and the reports act as an agenda for the discussion. This section opens a discussion about how the reports reflect on this performative aspect. The role of STS concepts and researchers in the reports is also discussed.

7.1.1 Reflexivity

Reflection is not merely part of the discussion, but used as a sort of methodology of how to approach genome editing. Where classifications in the NASEM report are presented as evidence-based and objective, the Nuffield report deconstructs these categories and shows how, for example, separating basic science from applications often precludes public engagement, or focusing on humans draws attention away from animals and ecosystems. These reflections call for earlier and more open discussions about research design and coordination, such as incorporating RRI practices in basic research and instituting an observatory for genome editing projects. In this way, the document also works to expand reflexivity in policy and research organizations.

> *Scientific discovery and technological innovation is important but not inevitable. Most important among the factors shaping technological development is human agency. It is human agency, in terms of decisions that are made about directions of research, funding and investment, the setting of legal limits and regulatory principles, the design of institutions and programmes, and the desire for or acceptance of different possible states of affairs, that will determine whether, and which, prospective technologies emerge and, ultimately, their historical significance (Nuffield Council on Bioethics, 2016, p. 112).*

At the same time, the Nuffield report asserts that its own methodology is 'analytic' and that normative assessments are being held in reserve for a future report (Nuffield Council on Bioethics, 2016, p. 112). This is one way of claiming objectivity. This analytical distance is accompanied by extensive challenges to the organization and funding of research made by the

report.[14] In being reflexive about science, they are not so reflexive about the Nuffield Council's place within the constellation of science institutions, a point which I will pick up later in discussing how STS is making an impact.

The Nuffield report gives great weight to how conceptual issues matter, and the consequences of categorization and distinctions, speaking about how plants were categorized would have consequences not only on their regulation and labeling, but would have the potential to define the "moral and social significance of genome editing procedure itself" (2016, p. 106). Where technical aspects of genome editing make distinctions more difficult to make, it's important to reflect on what values are embedded in reaffirming distinctions. One approach in STS is to study scientific practice as a cultural activity, often using ethnographic methods, these result in a focus on the social hierarchies and rituals, as well as decision-making practices. Reflection on science as a cultural activity appears in the reports, possibly through exposure to STS studies or because of personal experience and observation, such as this passage

> *In addition to the intrinsic features of the technique, the rapid development and diffusion of genome editing techniques to date has been driven by both demand from researchers and high profile advocacy by the developers and early adopters, and enabled by the conditions and culture of research in the biological sciences (Nuffield Council on Bioethics, 2016, p.14)*

In the NASEM report a quote in French by Pasteur about the communal ownership of knowledge, "La science n'a pas de patrie, parce que le savoir est le patrimoine de l'humanité" (Science has no homeland, because knowledge is the heritage of humanity) (2017, p. 30), followed by a rebuttal about the political systems and cultural norms within which science operates, could have come from a lecture at the STS Department in Vienna. This passage is used to make a point about the inexistence of universal truths and situated and constructed process of bioethics. While the eventual point is about a pragmatic "reflective equilibrium" (NASEM, 2017, p.30), which is not so different from a "publicly coherent solution" (Nuffield Council on Bioethics, 2016, p. 32), there are two ways to see this type of reflection. The first is to say that at least some members of the committee have taken some STS concepts to heart and have carved

[14] For example, rejecting the idea of an "international scientific community," and its ability to self-regulate pose a significant challenge not only to human subjects reviews, but would also have implications for other aspects of science that are largely self-regulated, namely animal welfare, biosafety, equipment sharing and subcontracting practices which presuppose similar narrow institutionally bound practices.

out some voice in the paper; the other is to say that the language of STS has been co-opted argumentatively, but does not penetrate the surface of the writing.

One distinct feature of the NASEM report process, is that committee members themselves do the actual writing, rather than the staff, as is the case in the Netherlands (Bijker et al., 2009). Within this context, the explanation seems more likely that one committee member introduced ideas into the body of the text that might not penetrate the summary. These traces of authorship are found throughout the report: the focus on regenerative medicine in the chapter on basic research, but distancing from regenerative medicine in the chapter on somatic; and in references to a committee members' specific work on genome editing (Belmonte), on slippery slopes (Evans) or comparative stem cell law (Charo). Although these personal contributions lengthen the document, the summaries and recommendations lose these nuances and project a unified, institutional voice. The question then is not whether the document is reflective, but what the reflection does. One way the documents act on this constructed nature of bioethics is to expand access to the construction process to the public. Public engagement is then in turn reflected on and these reflections feed back into the bioethics institutions and practices. In other places reflection is used more instrumentally to avoid the appearance of subjective or arbitrary positions.

In the following passage, a reflexive and open statement, is followed with a dismissal:

> *Resistance or skepticism may be an outgrowth of concerns about the degree to which an innovation affects cultural identity or may distort socioeconomic patterns in a fashion that is harmful to at least some part of the population. If and when these concerns are either addressed through remedial measures or shown to be unwarranted, innovations that are needed or perceived as desirable become widely accepted (NASEM, 2017, p. 144).*

Which authority decides whether concerns about cultural identity and social justice were warranted, and if responsibility can even be traced, who has standing to make claims? The body of the report is reflexive about the limited scope of review in the context of human subjects' research by IRBs and IBCs, as well as the difficulty in "balancing individual-level benefits and societal-level risks" (NASEM, 2017, p. 119), subtleties lost in the executive summary and recommendations that somatic applications should continue under existing governance.

7.2 Disability Justice and Rights

Within the discourse on disability justice and rights there are multiple layers, conflicts and interdependencies, and traces of political and sociotechnical developments over decades. The debates offer a place to explore the complexity of societal challenges by unravelling these strands. The reports' technique resembles co-production based analyses in the way cultural and value distinctions are drawn out. In the first place, the reports give space and voice to advocates of persons with disabilities, in particular, those who are opposed to genome editing and genetic screening.

> *Disability justice and rights scholars have made a range of moral arguments against selective technologies, from individual rights based arguments such as the right to life of people with disabilities, to arguments for the social and emotional value (e.g. vulnerability to contingency) of biological difference, to the value to humankind of conserving disability cultures, and the importance of the visibility of disability in establishing social attitudes, behaviour, and structures (Nuffield Council on Bioethics, 2016, p. 28).*

For the Nuffield Report, reflecting on the tension between genetic screening and disability rights moves into a discussion of human dignity, intergenerational and social justice in general and shortcomings of democratic procedures in considering these second order questions. The conclusion, that a "publicly coherent solution" (p.32) which allows genome editing to eliminate disability is possible, does not necessarily negate the concerns about preserving disability cultures, the importance of visibility of disabilities, and the value of difference, but seems inconsistent with an assessment based on vulnerability and distribution. Reflections on cultural differences and contending values vis-à-vis biotechnology come back to key concepts in STS, but where this is understood in the disability discourse, these same lessons don't seem visible for other publics.

Both reports make the same move from disability to human rights and human dignity, but the NASEM report reads as if there should be a tradeoff between policy success and treatment, "the decades that saw the explosion of prenatal diagnosis (accompanied by selective abortion of affected fetuses) and preimplantation diagnostics (accompanied by selective implantation of nonaffected embryos) are the same as those in which public attitudes toward disability became far more accepting" (2017, p. 127). Here the limitation of thinking of long-term in terms of decades instead of generations, blocks learning. Focusing on political gain, that is that accommodations for disabled communities have increased, subtle or unknowable population shifts due to abortion become negative knowledge.

Although concerns about preserving disability culture remain, in the cost/benefit analysis style of the report, the "not monolithic" (p. 126) disability rights community presents a problem for the NASEM committee in seriously taking these voices into account. The report captures the complexity of conflicting values in preventing disability: judgements about distress, negative experiences and the burden of disability on families and public health systems that do not match lived experience of high satisfaction with life, but are used to justify medical intervention. While the NASEM report is able to reflect on these complicated issues in the past, it appears to have difficulty in applying these lessons to the present, using instead reflection as a tool for moving past unresolved, value-laden issues. The inclusion of "a commitment to destigmatizing disabilities" (NASEM, 2017, p. 34) in the general principles, tied to human dignity and preventing eugenics of the past, leaves second order concerns unaddressed. As much as these second order issues of distribution and vulnerability are discussed, the forum for considering them in a meaningful way falls short. The concept of "reflective equilibrium" (NASEM, 2017, p. 30) is introduced as a way of *doing* ethics, involving high theory and case studies, geared toward acceptance by a multicultural audience. It requires a commitment to finding consensus that may not be possible or even desired in a public discussion (Horst & Irwin, 2010). Public discussion is invoked to settle questions of value, which are set within the framework of specific questions about inheritable genome editing and enhancement via genome editing. In preparing for the public, experts have already gone through a process of selecting theories and case studies, such as those presented in the report. Finding equilibrium is then more of an exercise in finding the middle of the selected material than a reflection on the topic. Where some participant engagement methodologies exist that seek to minimize the presentation and ordering of material (Felt, Schwarz, Strassnig, 2013) it is not uncommon to encounter carefully structured and presented expert advice like the NASEM report.

7.3 Science, Technology and Society in the Reports

It is possible to disregard the appeals for meaningful public engagement based on communication and consultation as lip service, that is, without fundamental changes to the process, and, in fact, the follow-up activities of both committees might support this conclusion in the short term.[15] The Nuffield report, with a subheading entitled, "competing imaginaries" and an entire chapter devoted to "science in context," reflects the inclusion of key STS concepts.

[15]NASEM Follow on activities include a sparsely attended discussion on ethics for academic theologians, briefings for industry, and discussions about how to use CRISPR for epigenetic environmental research. The Nuffield Council issued a follow up report on Human Reproduction in July 2018 and is working on a report on livestock editing.

The participation of STS scholars in the production of these reports raises questions about what contributions STS can make to the organization, funding and governance of science and technology.

Over the decades, there has been a movement from STS as outside critic, to critically engaged, to embedded insider. Within the genome editing discussion, Shiela Jasanoff has been critical of both the December 2015 International Summit on Human Gene Editing and of the attention toward CRISPR, as seen in her presentations at the University of Vienna's symposium, symposium, Editing Genomes with CRISPR: between scientific breakthroughs and societal challenges[16] and a meeting about the Oveido convention both in October 2017. On the other hand, Benjamin Hurlbut and Sarah Hartley are more engaged, having been involved in the reports as commentators and reviewers. Charis Thompson, on the other hand is embedded in the process, serving on the Nuffield Committee and having presented in Washington at the Genome Editing conference.

That critical scholars are welcome and invited at the table reflects the growth and success of STS, however participation does not come without cost. Downey and Zuiderent-Jerak point out the perils to STS practitioners: "expertise will be misunderstood, will be judged to be threatening, or will not resonate sufficiently with the concerns of actors involved" (2016, p. 232) with implications for the credibility of STS expertise and identities. Institutional procedures and credibility performances matter. The Nuffield Council on Bioethics does not require or aspire to consensus in committee reports, limiting the risk to STS scholars' reputations for participating in something that may not ultimately reflect STS scholarship.

For example, STS Scholar, Sarah Hartley is very involved in the Nuffield Report. She is a contributor to the "Call for Evidence," presented as an expert to the committee, and served as a reviewer, but is not involved in decisions or writing. Within the final report, a quote from Hartley's research, "…experts make decisions when policy-makers fail to acknowledge the limitations of science for risk decision-making." (2016, p. 279), is brought to bear on a discussion about the limitations of the precautionary principle as a tool for governance, rather than its original context as a missed opportunity for public discussion about genetically modified animals. As a reviewer, she would have had the opportunity to comment on, but not rewrite how her work was used. Hartley's focus on livestock is however picked up in the final

[16] See https://rri.univie.ac.at/aktivitaeten/workshopconferences/crispr-symposium/

recommendations, and a separate, normative report for 2018 is reported on the Nuffield website.

On the other hand, Charis Thompson is on the Nuffield Committee. A Gender and Women's Studies scholar, her books "Making Parents" and "Good Science" are widely read in STS, and ideas from her work permeate the report. The idea that some aspects of biotechnology, such as human embryonic stem cells "have ethics" (Thompson, 2013) before any applications, issues, or publics are raised finds its way into a discussion about Basic Research on page 13 of the Nuffield (2016) report and furthers the STS discussion about issue and public formation (Asdal, 2008; Marres, 2005). Here, a line about the co-production of ethical orientations with public trust (or protest) provides reference to Thompson's (2013) book, Good science: the ethical choreography of stem cell research: "public trust…is sensitive to events and to narratives that celebrate the achievements of science, on the one hand, or draw attention to its failures, limitations and historical perversions, on the other" (Nuffield Council on Bioethics, 2016, p. 25).

Critical voices from STS are also picked up in the literature review – Jasanoff et al. (2015) and Sarewitz (2015) both wrote about CRISPR just as the committees were forming. The Nuffield report takes seriously the ideas that self-regulation is insufficient and impossible, and that public discussion is possible and necessary. The NASEM text acknowledges the critiques and raises them for discussion: "Some scholars have argued that human genome editing has raised, and will continue to raise, ethical, regulatory, and sociopolitical questions that go well beyond discussions of technical risks and benefits identified by biologists (Jasanoff et al., 2015) or even philosophical and sociopolitical concerns raised by social scientists and ethicists (Sarewitz, 2015)" (p. 165). If we unpack this quote, it's basically saying human genome editing is beyond the grasp of science, and professional ethics, which is rather ironic in a report written by scientists and professional ethicists about human genome editing. This is not the discussion that follows. The report misuses the STS critique to support a much more limited form of public engagement that is instrumentally summoned to relieve the committee of responsibility for unanswerable questions: "This argument suggests, as genome-editing technologies and applications develop, the need for ongoing public discussion about how regulatory bodies should draw distinctions between such concepts as therapy and enhancement or disability and disease" (NASEM, 2017, p. 165).

Benjamin Hurlbut, an STS scholar focused on biotechnology and bioethics, and author on the paper, CRISPR democracy: Gene editing and the need for inclusive deliberation (Jasanoff et al., 2015) served as a reviewer for the NASEM report. This visible and open peer review is a

demonstration of legitimacy and credibility, consistent with Jasanoff's (2011) assessment of the US 'practice of objectivity' as well as Hilgartner's (2000) depiction of National Academies' reports as a staged performances. His involvement didn't assure that his own ideas were meaningfully implemented in the report. Particularly where STS shcolars and concepts are involved, it is important to separate the performance of credibility from humility in technological assessment.

7.3.1 Ripples

By focusing on the upstream, before a technology is locked-in and committed to, as in germline editing and livestock, the Nuffield report makes a big gamble aimed at institutional change. Charis Thompson uses a more extreme formulation of the stakes of the debate, "who lives at whose expense through which technics?" in describing how the stem cell debate was framed in terms of curing genetic diseases (Thompson, 2013, p. 45). At other times, it seems that the language and deep insight of STS is turned against itself, "while it is important to recognize the limits of human understanding and proceed with all due care, this does not necessarily mean that society should forswear any human intervention at all" (NASEM, 2017, p. 125).

The Nuffield Report embraces RRI and critiques ELSI consistent with trends in STS literature (Hilgartner, Prainsack, & Hurlbut, 2016). The focus on methodology, and conclusion that upstream engagement should be focused on challenges, rather than technologies, is consistent with the *The Handbook of Science and Technology Studies, Fourth Edition* (2016). Research administrators and policy makers looking to understand human genome editing may question their own assumptions about science and its governance after reading the Nuffield report. The report takes an active and normative stance on the organization and governance of science, using the transformative character of genome editing technology to advocate system change. In doing so it defers taking a normative stance on genome editing applications. Both of these anomaly handling strategies – system change and deference (Evans & Palmer, 2018) acknowledge that genome editing is an anomaly, the differences being whether it can be addressed in the current system. Notably, by extending the deliberations and including support for genome editing in gene therapy, they affirm the HFEA's authority in the present. The NASEM's performed consensus that genome editing is *not new* and narrow focus on inheritance and enhancement, removes the question of how to change the system. At the same time, the report calls for public discussions and provides practical examples and illustrations of ways to proceed that will serve as a resource for administrators and assistants working on implementation.

There is an appeal within the NASEM report, perhaps a lone voice on a committee of 23, to expand public engagement, to somatic applications as well. For while in the executive summary and Chapter 3, the consensus is that

> *laboratory research involving human genome editing … raises issues already managed under existing ethical norms and regulatory regimes…while there are those who disagree with the policies embodied in some of those rules, the rules continue to be in effect (NASEM, 2017, p. 81),*

in Chapter 7 there is polite dissent, "Engagement mechanisms built into current regulatory infrastructures in the United States are sufficient to address somatic applications of human genome-editing techniques, but this does not mean they cannot be improved" (NASEM, 2017, p. 176). The text goes on to set the RAC as not the best forum, for discussing ethical issues, but the least, setting a higher bar for "true public *participation"* (NASEM, 2017, p. 176, emphasis in original). In effect, the document allows for pre-clinical scientific work to continue as if nothing is different, while providing resources for administrators of clinical trials to turn to for public engagement methods that could lead to an incremental expansion of engagement activities, resulting in the broader engagement, raised in the report on enhancement issues. This point is almost lost on the 195th page[17] of a 329-page document, and is contradicted by the summary. It is also followed by an endorsement of the ELSI program in nanotechnology, despite critiques that it reinvented a model that educates rather than listens to public concerns (Viseu & Maguire, 2012).

Fifteen years ago, Jasanoff (2003) wrote about 'unknown ripples' that technologies of humility might have. What impact do these successful insertion of STS concepts into the reports have on the general discussion and discourses that come next? Part of the answer depends on returning to the question: How are societal and technical challenges in Genome Editing co-produced in official bioethics reports? Or more simply what are these reports and what is it that they do?

8 Conclusions

This thesis began with an anecdote about researchers using a bioethics report (NASEM, 2017), to justify crossing an ethical line: editing the genomes of human embryos, where existing laws left room for interpretation. Building on the body of knowledge from Science, Technology and Society (STS), the thesis presented an in-depth examination of the NASEM report, *Human Genome Editing: Science, Ethics, and Governance* alongside the bioethics report from the UK

[17]Pagination begins only after 19 pages of front material, so this is page 176 in the report.

Nuffield Council on Bioethics, *Genome Editing: An ethical review*, to understand how these reports bring together important aspects of genome editing, some more technological, others more societal to suggest a reasonable path through ethical and regulatory uncertainty. The state of the art in this thesis looked first at how emerging biotechnologies and public hopes and fears within legal and ethical contexts coproduced the stem cell debate, genetic testing and identities, and the GMO controversy, and next at STS literature on navigating an acceptable course in the governance of emerging technologies, focusing on institutions and experts, publics and public engagement. Understanding the coproduction of social and technical challenges in human genome editing will contribute to both important lines of STS research. The reports were coded and analyzed using qualitative methods investigating the text and context through a comparative lens. This cataloging of what the reports are doing, defining, distinguishing, debating, citing, assuming, downplaying and recommending provides the basis for the analysis and conclusions. This thesis doesn't assess the impact of the reports, only how they position themselves, however this is no small thing. The following conclusions reflect what I've learned both through the STS program at the University of Vienna and through analyzing the reports.

There are different ways of creating credibility. The NASEM procedures create credibility thorough demonstrating consensus; while some meetings are available by video for transparency, debates between committee members are kept 'backstage' (Hilgartner, 2000). The conclusions on somatic editing are claimed to be made based on a "broad international consensus" (NASEM, 2017, p. 147), a reference perhaps to the International Summit on Human Gene Editing: A Global Discussion (National Academies of Sciences et al., 2015), but potentially a self-reference to the international, interdisciplinary 23 member committee Consensus is required; all 23 committee members associate their name, institutional affiliation and professional reputation with the report and its recommendations. Horst and Irwin identify consensus processes as "closing down complexity, building collective identity, and reducing social opposition" (2010, p. 122). The NASEM committee achieves consensus around a major shift in bioethics allowing for possible germline (inheritable) genetic interventions. Although this moves against the Oveido Convention (Council of Europe, 1997) and prohibitions against changes to the human germline, the other recommendations from the committee are conservative, in that they reinforce the authority of existing governance, including self-regulation in human subjects and biosafety protections by institutions that promote research.

The Nuffield Council's procedures require neither consensus nor recommendations. This allows social science scholars to engage while maintaining a critical stance, and for all committee members to be reflexive. The credibility of the report is built on a call for evidence; public input

forms the basis for the challenges and promises discussed in the report. The open submission process and inclusion of diverse viewpoints is another way of demonstrating objectivity (Jasanoff, 2011). Like the NASEM report, credibility also comes from the reputation of the institution and committee members, but at Nuffield the reputation is for "advising policy makers and stimulating debate[18]," opening up questions for discussion, whereas the NASEM stakes its reputation on "high-quality, objective advice on science, engineering, and health matters.[19]", providing evidence for a decision.

Institutions matter – not only does the institution responsible for the report set the scope and invite the committee, they also make the rules. One important outcome of these very different ways of exercising scientific authority is that consensus-making practices make it difficult for STS scholars, whose work requires asking questions about framing, vulnerability, distribution, and learning (Jasanoff, 2003), to participate on a committee and sign off on conclusions and recommendations. In contrast procedures that invite difference and reflexivity greatly benefit from such participation.

Proposed applications of genome editing could exacerbate some societal challenges, like healthcare disparities, even while working towards alleviating others, like the burden of disease; discussing the societal impact of genome editing applications requires looking beyond individual health benefits. Genome editing research is often justified by potential applications that may relieve the burden of genetic disease and disability from patients and their families. Governance institutions such as the Food and Drug Administration (FDA) and Human Fertilisation and Embryology Authority (HFEA) weigh the prospect of a therapeutic against the risk to individuals directly involved in the research, warranting that public funds will have a net-positive societal impact. However, they don't consistently assess the impact of prospective future therapeutics such as the distribution, exacerbation of differences for vulnerable communities, or ecological changes. This leaves ethical, legal and social issues underexamined, while public funding appears to condone such research.

The bioethics committees were convened (NASEM, 2017, p. 17; Nuffield Council on Bioethics, 2016, p. 6) because issues of justice and morality, embedded in existing governance, are brought into tension by these applications. Eugenics and human dignity, access to care, and fairness are challenged, rather than served by genome editing. These projections are based on

[18] http://nuffieldbioethics.org/about
[19] http://www.nationalacademies.org/about/whatwedo/index.html

contemporary analogies; as cures in gene therapy become available, the price of therapies can also be a burden and barrier. Outside of prohibitions to inheritable genetic modification, such as the Oveido Convention (Council of Europe, 1997), laws and regulations related to biotechnology do not always take justice or moral questions into account. The NASEM report brings the moral challenges mentioned above to the forefront for applications of genome editing that involve inheritable changes or could result in human enhancement, while other applications of genome editing are sidelined from these discussions. Ethical issues for non-inheritable and treatment uses of genome editing are relegated to existing IRBs, which by regulation do not look at societal impacts[20]. Scope also comes into play in the NASEM report, which engages with a narrow set of issues in human genome editing. Xenotransplantation – which involves editing pig genomes to partially match a patient's genome for organ transplant is not included. The Nuffield report raises many more issues across many envisioned applications, driven by public input and endorses both an observatory to track research trends and long-term monitoring of society-level impacts. Although envisioned differently, both reports conclude that a public discussion is necessary to reconcile the tension of these societal goals set in opposition.

Not all publics are equally relevant. The report process seeks to incorporate different views and values by both reaching out to organized groups and scholars and by inviting comments and questions at different parts of the process. General ambivalence and distrust are difficult to represent, while publics with official positions, evidence, and spokespeople are featured in the reports. By mastering bioethics language, networking with committee and institutional representatives, and staying attuned to time-sensitive submission processes, one voice can stand out over others. In both reports, disproportionate space is given to transhumanism. Other publics, for example, creation-centered Christian ideologies are not mentioned, a move that shifts the middle-ground of the debate on genetic manipulation toward a more interventionist stance. While values and to a lesser extent, morality, are central to bioethics, and in this regard, bring religious ideas into the discussion, religion itself is treated as taboo because it does not lend itself to a consensus process. Instead, religions are set against each other and contrasted with transhumanism to arrive at a middle ground. Voices from disability justice and rights, are presented in the report as reasonable and as an allegory for different ways of valuing. This reasoning contrasts with the focus of the NASEM report on risks and benefits, but fits well with the Nuffield accounting of values and opportunity costs. Public submissions are qualified before

[20] Code of Federal Regulations - 21 CFR 56.111(a)(2): "The IRB should not consider possible long-range effects of applying knowledge gained in the research" available at https://www.ecfr.gov/cgi-bin/text-idx?SID=6e16f822e695d343a72b02bbdac96bbd&mc=true&node=se21.1.56_1111&rgn=div8

inclusion; designators such as *some, others* or "controversialists" (Nuffield Council on Bioethics, 2016, p. 115) are used to frame inputs that might not support the conclusions of the report. In considering the role of publics in the reports, it's important to remember that they are used as a reflection of ethical questions, not as a stand in for the public discussions that are to follow.

Whether genome editing to prevent disease and disability is considered treatment or enhancement has significant implications for governance recommendations.
When prevention of genetic disorders is included with treatment, as in the NASEM report; it generally follows a first order, individual choice logic and is governed through the clinical trials system (through the FDA in the U.S.). When prevention is grouped with enhancement, as in the Nuffield Council report; it's generally focused on second order, social justice concerns. The report advocates that there should first be consensus on "what it is we wish to avoid and what we hope to achieve" (Nuffield Council on Bioethics, 2016, p. 53), that would inform distinctions, as well as governance. While this could potentially problematize somatic genome editing, it does not seem to within the scope of the Nuffield report.

Before birth, interventions are simultaneously prevention and treatment, owing to the question of when life begins, a principally unknowable thing. A couple with a high chance of passing on a genetic disease, could frame genome editing as treatment, anchoring to established practices of IVF and less established PGD, or, when considering the possibility of adoption or not having a child, genome editing could be framed as enhancing both the future child and the population. As outlined in the section on human embryos and understanding human development (6.2.1), the reports accept current arrangements that deal with the embryo question; in the UK, the HFEA and in the US the prohibition on public funding, even as researchers and publics continue to test the boundaries.

On a personal note, these questions cannot and should not be resolved. It is a fundamental paradox of bioethics that in protecting life, there is no consensus on when life begins. Although difficult for governance, the range of responses and beliefs about life are important for a diverse, vibrant society, and this exchange of ideas is particularly what makes democracy so powerful.

Public discussion is not informed consent
The Nuffield Council report acknowledges that experts alone should not be responsible for ethical decisions and maintains that deadlock in public debate over embryo research is not "intractable" (Nuffield Council on Bioethics, 2016, p. 116) and input would be beneficial to

policy outcomes. Based on the analysis in the section on moving toward a public discussion (6.1.4) there seems to be an idea that public discussion can determine the proper balance between risk and benefit on a societal level, almost in the way that informed consent has been used to reconcile harms and benefits in clinical trials. The Nuffield report refrains from making recommendations (except in the case of GMO regulations), but promises to do so in a future report. Both reports describe potential methods and pitfalls in engaging publics through surveys, workshops, focus groups and consensus conferences and are a good resource for policy makers and regulators, such as the FDA and HFEA. However, where an individual is readily identifiable and autonomy of decision making constructed (with accommodations for language and reasoning abilities), the bounds of the 'public' are difficult to draw. The 'public' is often a black boxed entity – we have to ask, who are the participants and who gets a voice? A discussion group, no matter how large and diverse cannot deliver consent in the way that an individual patient might in a clinical trial. Nor can it be treated as an open agreement. Shifting difficult and possibly impossible questions onto the 'public' through public engagement activities may help ensure that developments in science and technology serve society, but these discussions are not necessarily representative and unlikely to result in consensus.

The analysis highlighted that there are two distinct ways of navigating the complicated terrain of risk, hope and controversy in genome editing; a scientific frame that fixes CRISPR on a biotech trajectory with origins at Asilomar, and a social frame that sees a potential disruption in scientific practice as well as relationships with our children, food and environment. How these reports construct societal and technical challenges will continue to shape the discourse and course of genome editing development. The paradox of scientific authority (Bijker et al., 2009) remains –understanding technical information for critical inquiry into emerging technologies requires reflection on the knowledge production context. Conversely, opening decisions about the direction and purpose of science to consider responses from public engagement and public discussion is perhaps more complicated, and requires an even greater degree of reflexivity.

Overlapping jurisdictions and movement of researchers and patients make nation-based policies only one element in the governance of emerging technologies. Boundary work to preserve the self-regulation of basic research has led to a proliferation of institutional oversight committees, funding based guidelines and professional credos. Many DIY Bio labs also have elaborate codes of conduct (Meyer, 2014). This system of tacit governance is easier to change, and less subject to democratic processes. The statement in the NASEM summary that "the committee concluded that heritable genome-editing research trials might be permitted" (2017, p. 7), overshadowed the more nuanced evaluation that "a re-evaluation might be justified in the

light of technical developments" (Nuffield Council on Bioethics, 2016, p. 49). In both cases, re-opening the germline question can be seen to undermine non-binding and tacitly understood boundaries of acceptable and unacceptable genetic modifications. With the fast pace of developments, the reports' recommendations that germline editing be discussed, could be taken for the discussion itself.

Final Thought

Research using genome editing technologies may change our understanding of what it means to be human. The promise of overcoming genetic disease is a powerful idea that disrupts what we thought was determined or destined. Acknowledging the complexity of these science-society relationships and following them over time is part of reflecting on who we are and where we are going.

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Appendix A: Deutsch Abstract

Bei der vorliegenden Arbeit handelt es sich um eine vergleichende Studie zweier Berichte über Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) und andere Genomeditierungs-Technologien: Untersucht wurden zum einen der Bericht der US National Academies of Science, Engineering and Medicine (NASEM) „Human Genome Editing: Science, Ethics and Governance" aus dem Jahr 2017 sowie der Bericht des Nuffield Council on Bioethics "Genome Editing: an ethical review" aus dem Jahr 2016. Beide Texte wurden geschrieben, um öffentliche Debatten anzustoßen und sind daher an der Grenze zwischen Politik und Wissenschaft zu verorten. Die vorliegende Arbeit stellt die Fragen, wie gesellschaftliche und technische Herausforderungen der Genomeditierung ko-produziert werden. Jeder Bericht entwickelt eine Geschichte über Governance, welche eng mit den Herausforderungen und Debatten zu Gentherapie, Foruschung an menschlichen Embryonen, sowie Behindertenrecht und damit verbundene kulturelle Fragen verknüpft ist. Durch den Vergleich zweier unterschiedlicher Herangehensweisen an das Verfassen eines wissenschaftlichen Berichts – einer basierend auf evidenzbasiertem Konsens, der andere auf der Ergründung ethischer Fragen – soll die Performativität solcher Berichte sowie die Rolle von ExpertInnen aus dem Feld der Science and Technology Studies diskutiert werden. Der Bericht der National Academies verweist darauf, dass Genomeditierung nicht neu sei und beschreibt CRISPR als besonders effektives Werkzeug, während der Nuffield Council dies als transformative Technologie bezeichnet. Basierend auf diesen Rahmungen schlussfolgert der Bericht der National Academies, dass bestehende regulative und ethische Vorgaben, die für Gentherapie und Stammzellforschung gelten, auch für neue Genomeditierungs-Technologien grundsätzlich angemessen seien. Der Nuffield Council hingegen empfiehlt, existierende Governance-Strukturen zu überdenken.

Appendix B: English Abstract

This thesis is a comparative study of two policy reports addressing issues related to Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and other genome editing technologies: the 2017 US National Academies of Science, Engineering and Medicine (NASEM) report "Human Genome Editing: Science, Ethics and Governance" and the 2016 Nuffield Council on Bioethics report, "Genome Editing: an ethical review." Written to promote public discussions, these reports are at the boundary of politics, science and society. The thesis asks how within these reports societal and technical challenges in genome editing are coproduced. Each report creates a story about governance that ties into societal challenges and debates, like gene therapy, research on human embryos, and disability rights and culture. Contrasting two approaches to writing reports, one based on evidence-based consensus, and the other the open exploration of ethical questions, the performativity of the reports and role of STS trained people is discussed. The National Academies report establishes that genome editing is not new, describing CRISPR as a particularly effective tool; while the Nuffield Council report finds that CRISPR is a transformative technology. Based on these framings, the National Academies report advises that the regulatory and ethical frameworks established for gene therapy and stem cell research will be generally adequate for new genome editing technologies, while the Nuffield Council report recommends revisiting governance structures.