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# The division of advisory labour: the case of 'mitochondrial donation'

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**Abstract**
The UK-based deliberations that led up to the legalisation of two new 'mitochondrial donation' techniques in 2015, and which continued after that time as regulatory details were determined, featured a division of advisory labour that is common when decisions are made about new technologies. An expert panel was convened by the Human Fertilisation and Embryology Authority (HFEA), charged with assessing the scientific and technical aspects of these techniques. Meanwhile, the Nuffield Council on Bioethics addressed the ethical issues. While this division of labour was undertaken in the name of thoroughness, I argue here that it can have the unintended consequence that hybrid questions that simultaneously involve ethical and technical aspects—especially questions about where to set evidential thresholds for the acceptance of new technology—do not receive enough attention.

**Keywords** HFEA · Inductive risk · Maternal spindle transfer · Mitochondrial 'donation' · Nuffield Council on Bioethics · Pronuclear transfer · Value-Ladenness

## 1 The division of advisory labour

When regulatory agencies evaluate new technologies, it is not unusual for advisory labour to be divided. Salient questions are split into those that are alleged to be 'purely scientific' on the one hand, and those that are of a broader legal, ethical or social variety on the other. Different advisory groups then tackle these different domains. This article subjects this division of labour to philosophical scrutiny, via a detailed investigation of UK-based deliberations over a new set of experimental IVF procedures that were legalised in 2015.

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They are often referred to as 'mitochondrial donation' or 'mitochondrial replacement' techniques.

An expert advisory panel was convened by the Human Fertilisation and Embryology Authority (HFEA) in 2011 to review the state of evidence concerning 'mitochondrial donation'. Several features make these techniques ethically contentious. They are widely regarded as germline interventions. They involve three different individuals providing genetic material to the embryo. The clinical rationale for using them presupposes the importance of genetic connectedness between parents and offspring. The HFEA panel duly noted that, '…it is important to note that issues other than *purely scientific* need also to be considered' (2014: 3, emphasis added). These issues, according to panel, fell outside its remit. The implication was that the HFEA's own deliberations *were* 'purely scientific', and that it was leaving consideration of ethical and legal matters to other bodies.[1]

It seems that in writing of 'purely scientific' issues, the HFEA meant to highlight technical matters it considered to be free of ethical evaluative content. Philosophical research on the relationship between science and values raises the question of whether any piece of scientific work—especially when that work is presented in policy contexts (Elliott and Richards 2017, p. 6)—should be wholly free of ethical values. This research thereby questions the wisdom of dividing advisory labour between deliberation over matters of ethics and law on the one hand, and deliberation over matters that are 'purely scientific' on the other. In this paper I use this philosophical work—in particular debates over the argument from inductive risk—as a framing device for the establishment of three broad claims about the division of advisory labour.

First, and most important, I show that the HFEA panel did not conduct a 'purely scientific' evaluation of these new IVF techniques. Here the direction of argumentation is from the inductive risk framework to the mitochondrial case. Philosophers such as Douglas (2000, 2009) have used the argument from inductive risk to claim that ethical values should be used in the setting of evidential thresholds. I draw on this argument to expose a variety of moments at which the HFEA's deliberations were indeed informed by ethical considerations.

The descriptive claim that the HFEA panel did not succeed in deliberating in a value-free manner leaves open a normative response that this was a failure on their part. Perhaps their reports would have been better if their deliberation had been free of ethical values? In order to block this response I make two further claims that complement the first, but in a manner that reverses the argumentative relationship between case study and philosophical framework. Rather than using philosophical work on inductive risk to illuminate unnoticed features of the HFEA's deliberations, I draw on features of these deliberations to respond to Betz's defence of the value-free ideal (2013). My second main claim in this article concerns his suggestion that scientists can avoid making value-laden claims by asserting hedged statements about risk. I argue that it fails to take account of pragmatic communicative issues regarding what is conveyed by logically weak claims.[2] My third main claim is that a value-free evaluation would

[1] Just such a review of ethical and legal issues was undertaken by the Nuffield Council on Bioethics in 2012 (NCOB 2012). This division of labour was not explicitly planned by the UK government. The Nuffield Council is an autonomous and independent body that sets its own research agenda. The government explicitly requested a technical evaluation from the HFEA, which then opened up an opportunity for the Nuffield Council to focus in a complementary manner on ethical issues.

[2] This point is made in passing by John (2015a). It receives vivid practical illustration in the case of the HFEA's reports, and is important enough to be developed at greater length.

have been of little use to the parliamentarians who were relying on it (see John 2015b; Steele 2012; Frank 2017; Havsted and Brown 2017).

Some bodies have expressed admiration for the rigour with the UK mitochondrial investigations were conducted. For example, the International Society for Stem Cell Research (ISSCR) indicated that the discussions should possibly serve 'as a model for deliberations on germline nuclear genome editing technologies' (ISSCR 2015). While I share this admiration, my argument reveals further room for improvement in advisory governance. Questions about whether sufficient evidence has been collected to proceed in some novel technological direction have a hybrid character straddling the ethical/technical boundary. I argue that an unintended effect of dividing advisory labour is that these questions can receive insufficient scrutiny. This is because of the risk that bodies assigned the job of ethical evaluation regard them as 'scientific', hence outside their remit. Meanwhile, bodies assigned the job of technical evaluation regard them as 'ethical', hence outside their remit. The result is that no deliberative body addresses them properly. If these hybrid questions are to be tackled in full, then the intermingling of ethical and technical themes needs to be explicitly recognised. Interdisciplinary teams whose expertise stretches beyond medicine, engineering and the natural sciences should be assigned to address them.

It has been a commonplace over several decades for researchers working in science and technology studies (STS) to claim that, in the domain of science and policy, there are forms of 'interpenetration' of fact and value (e.g. Owens 2015).[3] The general claim that science and values are enmeshed in policy contexts is not new. This paper uses a detailed case study to show one specific set of ways in which this 'interpenetration' can occur. It focuses very specifically on the risks of dividing advisory labour between ethical and technical domains, and it offers recommendations for better organisation of deliberative governance. It achieves this using a different, albeit complementary, approach to most STS scholars: it brings the argument from inductive risk into contact with an analysis of deliberation over PNT and MST in the UK.

## 2 Overview

This paper is organised as follows. Sections three to six give, in turn, a primer on the nature of mitochondrial disorders; an account of the two new interventions designed to combat these disorders; a summary of the regulation of these interventions in the UK; and an overview of the deliberative processes that gave rise to these regulations. Section seven then summarises Douglas's (2000, 2009) version of the argument from inductive risk. This argument purports to show the legitimacy of value-ladenness in scientific work, at least when there is potential for errors to have morally weighty consequences.

In sections eight and nine I move on to argue, consistent with Douglas's argument, that the HFEA did not bracket off ethical issues in its technical assessment. This claim draws on a close reading of the HFEA panel's reports, and on additional comments made by HFEA panel members. Section ten then illustrates the risk that the division of

[3] A list of illustrative references would be impractically long. The first chapter of Owens (2015) gives a good sense of some important landmarks in this body of work. Highlights in this tradition include Jasanoff (1990); Ezrahi (1980); Fischer (2000); Funtowicz and Ravetz (1985); Wynne (2002) and many others.

advisory labour, even when made in the hope of thoroughly addressing both technical and ethical issues associated with new technologies, can lead to neglect of important hybrid questions relating to evidential thresholds.

The descriptive claim made in the first three-quarters of the paper—namely that the HFEA's reports were not value-free—is consistent with Douglas's views about inductive risk and the legitimacy of value-ladenness. It is also consistent with opposing views suggesting that even if the HFEA's reports were laden with value, they would have been better if they had been free of values. Section eleven uses the HFEA's reports to close off a possible response to this article; namely that had the HFEA used hedged claims about risk, it could have avoided taking contentious stands on evaluative matters (see Betz 2013). I claim that the HFEA did use hedged claims about risk, and yet this did not enable it to elude issues of inductive risk. Section twelve makes the case that the panel could not have offered the sort of advice that would have been of value to parliamentarians without taking stances on contentious ethical issues. This makes it even more important that these ethical issues are explicitly recognised, and that they are considered by more diverse groups of experts than was the case in the UK.

## 3 Mitochondrial disorders

The majority of an organism's genes are found inside the cell nucleus. That said, a small number—the figure usually given for humans is 37, around 0.1% of the total number of genes—reside within the mitochondria (NCOB 2012). The mitochondria are small structures—'organelles'—found within the cytoplasm of animal cells. Their primary known function relates to the production of energy. Defects in the mitochondrial genome can result in a range of diseases that are systemic, progressive, and that sometimes result in death in childhood of the individuals affected.[4] These mitochondrial genetic disorders can be inherited across generations, but because the genes in question are not located within the nucleus, inheritance follows an unusual pattern. The disorders can be passed only by mothers—not by affected fathers—to their male and female children.

## 4 Maternal spindle transfer and pronuclear transfer

In February 2015 the United Kingdom became the first country in the world—and still the only country in the world—to pass legislation that explicitly permits the clinical use of two new forms of in-vitro fertilisation (IVF) designed to limit the inheritance of mitochondrial diseases. They are known as Maternal Spindle Transfer (MST) and Pronuclear Transfer (PNT).[5] The same broad approach underlies both treatments. They begin with a woman who wishes to have children, but whose mitochondrial genes are defective. I will sometimes refer to this individual as the 'intended mother'. Nuclear chromosomal genetic material deriving from one of her eggs is transplanted into either an enucleated egg, or into an embryo with nuclear genetic material removed, that comes

[4] Mitochondrial disease can also arise from defects in the nuclear genome (NCOB 2012).

[5] There is a third, new, and potentially valuable technique called Polar Body Transfer, which was discussed by the HFEA Panel in their reports, but which was not made legal in the UK. (Greenfield et al. 2017 give details.)

from a donor with healthy mitochondria. The intended mother then carries the fertilised embryo, with healthy mitochondria, to term.[6]

The differences between the two techniques derive from differences in when, precisely, the medical team intervenes. MST makes use of an egg from a healthy donor. The 'spindle' of nuclear chromosomes is removed, and replaced with the spindle of chromosomes from the intended mother. This egg—which now has the intended mother's nuclear material in a healthy mitochondrial context—is fertilised in vitro. The embryo is placed in the intended mother. If the technology works as envisaged, the child will develop free from mitochondrial disease.

PNT instead begins with the fertilisation of a healthy donor egg. The two chromosome-containing 'pronuclei' (one deriving from the donated egg, the other from the fertilising spermatozoon) are removed. They are replaced with two pronuclei from a second fertilised egg, deriving from the intended mother and the intended father. Again, the result is an embryo that has nuclear material from the egg of the intended mother in a healthy mitochondrial context. Fig. 1 below gives a schematic illustration of PNT, produced by the Newcastle Fertility Centre.[7,8]

## 5 Recent regulatory developments

The UK parliament's decision to legalise MST and PNT did not result in a free-for-all, allowing any fertility clinic to perform these procedures for any individual. Instead, the new regulations require a two-stage process of approval by the HFEA whenever PNT or MST are to be used in the clinic (HFEA 2017). First, a fertility clinic must earn an HFEA licence that recognises its competence to perform the procedures. Second, each patient must also be approved by the HFEA to receive treatment. The HFEA waited until 15th December 2016, following a fourth scientific report from its expert panel, before announcing that it was ready to accept applications for clinic licences.

The Newcastle Fertility Centre immediately applied for a clinic licence, which the HFEA granted in March 2017 (HFEA 2017). The Newcastle centre announced, on receipt of its clinic licence, that it planned to start using PNT for treatment at some stage later in 2017. The HFEA then confirmed on 1st February 2018 that it had issued the Newcastle centre with a PNT treatment licence for two women with MERRF syndrome, although it was not clear at the time of the HFEA's confirmation whether the

[6] The presentation in this paragraph is based on NCOB (2012) and HFEA (2014, 2016).

[7] For the purposes of this article PNT and MST are sufficiently similar to make a second diagram illustrating MST otiose.

[8] At this point I can explain why I have placed the terms 'mitochondrial donation' and 'mitochondrial replacement' in scare quotes in this article. They are widely used as labels to pick out this family of new treatments, but they have the potential to mislead (Lewens 2015; Baylis 2017). They suggest that with both PNT and MST, the donor contributes nothing more than healthy mitochondria to the intended mother, or that the intended mother's defective mitochondria—and nothing more—are replaced. Consider, in support of this, that phrases like 'kidney donation' imply that the donor gives a kidney—and only a kidney—to the recipient. It would be misleading to describe someone as a 'kidney donor' when she gives her entire torso (kidneys included) to someone with renal failure. In the case of PNT and MST, while it is true that the donor contributes mitochondria to the intended mother, she does this by virtue of contributing *all* embryonic cellular structures to the intended mother, with the sole exception of nuclear chromosomal material.

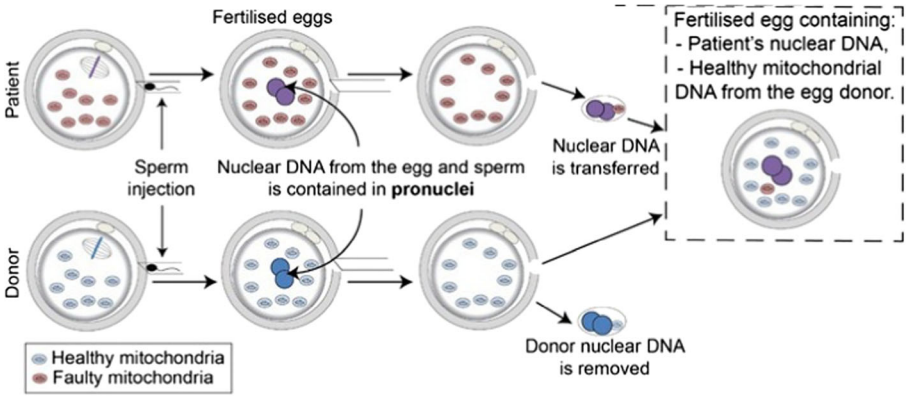


**Fig. 1** Pronuclear Transfer, diagram reproduced with permission from http://www.newcastle-hospitals.org.uk/services/fertility-centre_mitochondrial-treatment_mitochondrial-donation.aspx

women had already received the treatment (Sample 2018). The upshot is that the first babies may be born from this treatment in the UK some time in 2018.

In spite of the legality of these techniques in the UK, their first reliably documented clinical use took place elsewhere. On 27th September 2016, the magazine *New Scientist* reported that a healthy baby had been born in Mexico, through the use there by a US-based team (headed by Dr. J Zhang) of MST (Hamzelou 2016). I noted above that the UK remains the only country to *explicitly* permit the use of MST and PNT. Zhang's team chose Mexico because, as Zhang put it to the *New Scientist*, 'there are no rules' there.[9] The HFEA expert panel was able to take Zhang's first comments on the baby's health into account when it composed its December 2016 report on safety and efficacy.

## 6 Scientific versus ethical review

In February 2011, the UK Secretary of State for Health asked the Human Fertilisation and Embryology Authority to convene an expert panel that would conduct 'a scientific review of the safety and efficacy of mitochondrial replacement techniques' (HFEA 2014). In the end, the panel produced four reports, in 2011, 2013, 2014 and 2016, each of which reviewed the state of evidence as it developed across that period. There was never any suggestion that these scientific reviews would suffice to determine the acceptability of PNT and MST. In particular, the HFEA panel drew attention to a 2012 report analysing ethical, legal and social issues produced by the Nuffield Council on Bioethics (NCOB 2012). The many-faceted nature of the issues raised by PNT and MST was always explicitly recognised.

The job of this article is not to analyse the ethical issues raised by PNT and MST in detail. Readers need only to have a feel for what some of those issues are (Appleby et al. 2017). Two of the most obvious concern what is sometimes called 'three-person

[9] What Zhang meant by this, presumably, is that he took the view that PNT and MST were legal in Mexico because they were not explicitly outlawed. In contrast, Palacios-González and Medina-Arellano (2017) have argued that, according to their interpretation of Mexican law, Zhang's team 'broke federal regulations regarding assisted fertilisation research'.

IVF', and the question of germline interventions. First, PNT and MST both involve the creation of children with genetic material from three individuals. The child's nuclear genes derive from the intended mother and father, but the child also has mitochondrial genes that derive from the egg donor. The involvement of a third individual in the provision of genetic material raises potential moral concerns about disrupting the natural order of reproduction. Children may also suffer from stigma or confusion if they feel their parentage is aberrant (Scully 2017).

Second, PNT and MST have the consequence—if they work as intended—that women with mitochondrial disorders can have children, grandchildren and great-grandchildren who are likely to be free of mitochondrial disorders. Had they not used PNT or MST, these women would have faced significant probabilities of passing their diseases on over several generations. PNT and MST achieve this multi-generational effect via effects on germ cells; i.e. those cells with specialised reproductive function, which ultimately give rise to gametes (Wylie and Anderson 2002). For these reasons, PNT and MST are widely viewed as germ-line interventions (Lewens 2015; Newson and Wrigley 2017). Interventions in the human germ-line are often regarded as ethically dubious. The US National Institutes of Health (NIH), for example, have commented that, 'The concept of altering the human germline in embryos for clinical purposes has been debated over many years from many different perspectives, and has been viewed almost universally as a line that should not be crossed' (NIH 2015).

These ethical issues were 'not within the scope' of the HFEA panel's review, which, in its own words, 'focuses exclusively on the science and the safety and effectiveness of these techniques; it does not consider the ethical and legal issues that are raised by such techniques except when these are directly relevant to proposed research' (HFEA 2014, p. 3). The stated brief was that the HFEA panel would only comment on matters of ethics insofar as they concerned the ethics of research one might wish to do to determine the safety of the techniques in question. The report announced that it would be silent on all more general questions about the ethical acceptability of PNT and MST.

I mentioned above that the third HFEA panel review referenced the Nuffield Council on Bioethics' (2012) report on these ethical issues. Just as the HFEA panel distanced itself from addressing contentious matters of ethics, so the Nuffield Council distanced itself from pronouncing on contentious technical matters. For example, the Nuffield Council summarised its main conclusions thus:

> We believe that if these novel techniques are adequately proven to be acceptably safe and effective as treatments, it would be ethical for families to use them, if they wish to do so and have been offered an appropriate level of information and support. (NCOB 2012)

The approach taken by the Nuffield Council implicitly repeats the division of labour indicated by the HFEA panel. The Nuffield Council assessed questions relating to '3-parent babies', effects on identity, germline interventions and so forth. It then announced its verdict that none of these ethical issues was serious enough to impede the use of the technologies. Hence all that remains is for some *other* body to give a favourable technical evaluation of PNT and MST before the techniques can be made available. The Nuffield Council thus refrains from adjudicating on the technical issue of whether the techniques are 'adequately proven to be acceptably safe and effective as treatments'. That is a

question for groups like the HFEA panel to address. The result is a reciprocally endorsed picture. It acknowledges that 'mitochondrial donation' raises technical and ethical issues. It then divides these issues into those that are (in the HFEA panel's terms) 'purely scientific' on the one hand, and those that are of an ethical nature on the other.

There are similar divisions of labour in other contexts where new technologies are evaluated. For example, the UK Royal Academy of Engineering and the Royal Society jointly published a report in 2012 on hydraulic fracturing. This is a technique for the extraction of shale gas that is more widely known under the name of 'fracking' (Royal Society/Royal Academy 2012). In the summary notes at the beginning of the report, the authors note that they have 'analysed the technical aspects of the environmental, health and safety risks associated with shale gas extraction'. They do not explicitly contrast these questions with ethical ones. They do point out that there are issues of 'public acceptability' that they have not addressed. They also note that they have not 'attempted to determine whether shale gas extraction should go ahead'. They regard this as 'the responsibility of Government'. So while the precise place of ethics remains unclear, the report indicates that its role is not to intrude in this area. It will address solely 'technical aspects' of questions around fracking. The result is that its analysis leaves open the more general question of whether fracking should proceed across the country. This article focuses on the division of advisory labour as it occurred in the mitochondrial donation case, but its general message has broader interest for how to deliberate about technology policy.

## 7 The argument from inductive risk

The preceding sections have outlined the general nature of PNT and MST, and they have shown how advisory labour was divided when assessing them. Sections eight and nine establish the first main claim of this article in detail, namely that the HFEA did not, in fact, deliberate in a value-free manner. It is helpful to preface this argument by summarising recent discussions of inductive risk, especially as presented by Douglas (2000, 2009).

Douglas follows Rudner (1953) in using scientific uncertainty as the basis for an argument that science frequently is not—and should not be—'value-free'. Consider the following highly stylised example that illustrates the basic argument from inductive risk. Suppose a scientist is trying to determine whether a piece of fragile coastline will collapse and fall into the sea in the next five years. The scientist cannot be certain that it will happen, nor can she be certain that it will not. Even so, she may be forced to choose one or the other hypothesis to use as a basis for action. Whichever claim she accepts, there is both a probability that she will err, and there is also a cost associated with her potential error.[10] If she accepts the claim that the coastline will collapse, when

[10] Both Rudner (1953) and Douglas (2000) frame the argument in terms of what the scientist 'accepts', and I follow them here for the purposes of exposition. I take it that in 'accepting' a hypothesis, the scientist makes a commitment to that hypothesis as a basis for action. Examples of such actions may include giving advice, pursuing further inquiry, or specifying the construction of some technical artefact. Jeffrey puts it like this: 'It is commonly held that although we have no certain knowledge we must often act as if probable hypotheses were known to be true. For example it might be said that when we decide to inoculate a child against polio we are accepting as certain the hypothesis that the vaccine is free from virulent polio virus' (1956: 238). Nothing in this article turns on whether 'acceptance' is the best way to frame inductive risk considerations.

in fact it will not, then this may have adverse consequences in terms of needless relocation of the local population, and so forth. If, instead, she accepts the claim that it will not collapse, when in fact it will, then the costs may instead felt in terms of injury, loss of life and damage to property. It seems to follow, then, that in deciding which claim to accept the scientist must also take into account the relative *ethical* weights of these different errors. This decision to accept one hypothesis or another involves a value judgement, because it requires the scientist to weigh up, for example, lives lost against unwarranted relocation. Douglas (2000) argues that a full appreciation of Rudner's argument has implications for what she characterises as the 'internal' stages of science. In particular, she argues that reflection on the costs of error should affect scientific decisions over which data sources to rely on, and which methodologies to use.

There is a significant *prima-facie* difference between the concerns of Douglas and Rudner on the one hand, and the case of mitochondrial donation on the other, which should be acknowledged before proceeding further. Recall that the HFEA panel was asked to determine the safety and efficacy of PNT and MST. Questions of 'inductive risk' concern the potential practical consequences (both positive and negative) that arise from decisions to accept or reject hypotheses, given the possibility of error. But questions of safety, for example, immediately and explicitly concern whether a given technology presents a sufficiently low risk profile. In other words, the HFEA panel was asked to comment on matters concerning 'plain' risk, not inductive risk. One might therefore think it obvious that the panel could not have commented on purely scientific matters. Questions of safety can only be established by combining an assessment of what the effects of technologies are likely to be with an assessment of the severity of those various consequences. Determining severity, hence determining safety, involves making an ethical judgement.

How can the HFEA panel's claim to address purely scientific matters plausibly be squared with its brief to offer an assessment of safety? The most obvious response looks, once again, to a division of labour. Perhaps the HFEA panel does nothing more than report, in a value-free manner, the state of evidence concerning likely effects of PNT and MST on the course of mitochondrial disease over generations, and on the potential for disruption to the development of maturing embryos. Questions of social or ethical value—how good or bad these various outcomes might be—can be handled by other groups, with different responsibilities.

In the sections that follow I argue that the HFEA panel did not, in fact, purge their reports of ethical evaluation in this way. I do so, in the first instance, by asking the sorts of questions encouraged by Douglas's version of the argument from inductive risk. In particular, her version of the argument encourages us to examine how ethical considerations regarding the costs of error should be used to set evidential thresholds.

## 8 The benefits of mitochondrial donation

In the opening remarks to its third report, the HFEA panel notes that, 'From a medical or scientific point of view all novel treatments pose essentially the same question: when is a treatment safe to offer?' (2014: 5). It is impossible to formulate a well-grounded view on this question without paying due attention to scientific research relevant to PNT and MST. Even so, this question is not 'purely scientific'. It also has an ethical dimension. That is because, as I will illustrate in this section, it is not possible to say whether

*sufficient* evidence has been gathered to pronounce on the safety of a procedure without also taking into account what the benefits of the procedure are supposed to be.

One might think that this focus on *benefit* signals a departure from the standard presentation of the argument from inductive risk, whose proponents usually focus on the *costs* of error. This apparent difference is illusory, for in considering the problem of inductive risk it is important to consider benefits that might be foregone. Douglas, for example, reminds us to consider how an overly pessimistic assessment of the toxicity of an industrial chemical might have negative consequences in terms of overly restrictive regulation (Douglas 2000). The degree to which such restrictive regulation is costly will depend on the degree to which the industry's work is beneficial.[11]

PNT and MST have the potential for effects that are significantly detrimental—via their potential to disrupt developmental processes—in additional to having the potential for beneficial effects. Even so, this section focuses on their benefits because, as I will show, the nature of those benefits is especially contentious. If they were entirely uncontentious then the HFEA panel could perhaps claim that it did not need to deliberate over ethical matters. It might claim that questions of ethical value were obvious enough that an overall assessment of safety would arise from a combination of an evaluation of technical facts, set in the context of a set of ethical evaluations antecedently accepted by all.

What, then, are the benefits that come from PNT and MST? When Dr. Zhang first announced the birth of the baby using MST he commented that the intervention was proper because 'To save lives is the ethical thing to do' (Hamzelou 2016). Zhang's rationale is implausible. PNT and MST do not aim to save the lives of the women who might make use of these interventions. Instead, the techniques are focused on reducing the transmission of mitochondrial diseases to the next generation.

Few would claim that PNT and MST save the lives of children in the next generation. The difficulties associated with this claim can be understood by imagining that a woman with mitochondrial disease has intercourse with her partner, with the result that she later gives birth to baby Susan. Susan inherits the disease, and she dies at a young age because of it.

Would Susan probably have been healthy, if her mother had taken advantage either of PNT or of MST? Regardless of which technique is contemplated, the woman in question would have had a baby originating from an entirely different egg; namely, one that came from a donor with healthy mitochondria. Unlike the egg that actually gave rise to Susan, this alternative egg would then have been subjected to IVF. Given the elaborate nature of this procedure it is hard to maintain that the fertilising sperm used would have been the very same one as that which was the actual originator of Susan. Moreover, the resulting child—free of debilitating disease—would have had markedly different life experiences to Susan's actual experiences. These differences with respect to the actual Susan's origins, experiences, memory and character are significant enough for many commentators to suggest that the child issuing from PNT or MST is not a

[11] Later in the article discussion will move beyond this basic presentation of the argument from inductive risk, for it will address not merely the role of ethical values in deciding how to act against a static body of limited evidence, but also the role of ethical values in determining whether to seek more evidence (see also Steele 2012).

healthy Susan, but a wholly different child who is free from mitochondrial disease (e.g. NCOB 2012; Liao 2017).[12]

PNT and MST are not the first technologies to give women with mitochondrial disease the opportunity to have healthy children with confidence (HFEA 2014; Baylis 2017). Such women can adopt. Adoption would not offer them the possibility of gestating and giving birth to their child, but these processes are also possible without PNT and MST. Women with mitochondrial disease can use conventional IVF with donated eggs. The prime benefit of PNT and MST, then, is that they offer women with mitochondrial diseases the prospect of having healthy children to whom they have transmitted nuclear genes.

This feature of PNT and MST was very clearly noted by a US report on what they call 'Mitochondrial Replacement Techniques' (MRT), their generic label for PNT and MST. As they put it, 'MRT could satisfy a deeply held desire on the part of these mothers to have a child who bears an nDNA [nuclear DNA] connection to them.' They go on to conjecture that, 'Having a child genetically related to both prospective parents may be part of one's conception of traditional family formation' (National Academies 2016).

The value of genetic connectedness or relatedness—the key benefit that PNT/MST afford—is contested. One way to argue in favour of it might invoke evolutionary considerations regarding heightened concern for genetically related others, perhaps drawing on classic work in sociobiology by the likes of Hamilton (1963). Alternatively, and considerably more plausibly, an argument might try to show that there is value in respecting individuals' desires to reproduce in whichever ways they see fit. This would indicate that there is good reason to enable individuals to reproduce in ways that give them genetic links with their children, if this happens to be something that the people in question regard as important (see O'Neill 2003 for criticism).[13] I raise these issues here not in an effort to establish or undermine the value of (nuclear) genetic relatedness, but merely to make clear the disputed nature of this putative value.

The argument from inductive risk predicts that the stance taken on this contested issue informs the question of how much evidence is required before pronouncing PNT or MST adequately safe. At one extreme it is possible to imagine an individual who argues thus: 'There is no significant value in a mother sharing nuclear genes with her children: a woman who uses donated eggs is in no worse position than a woman who uses PNT/MST, except that she may erroneously feel some form of misplaced disappointment. This sense of disappointment carries no serious moral weight, because it is misguided.' Such an individual will tend to oppose the introduction of both PNT and MST, even if the apparent risks are comparatively low, on the grounds that the benefits are trivial. Such an individual might eventually approve the use of these technologies if she becomes

[12] Some bioethicists have rejected this view (e.g. Bredenoord et al. 2011), and it is not my intention to imply that it is univocally endorsed (see Newson and Wrigley 2017). By changing the terms of this example it is possible to find cases where PNT, in particular, does not seem so obviously identity-affecting. Take the case of a woman with both mitochondrial disease and infertility who uses traditional IVF to produce a fertilised embryo. At *this* point, the medical team asks whether she would also like to make use of PNT. In such a case it is more plausible that PNT is identity-preserving, by virtue of preserving chromosomal nuclear materials. I am grateful to Andy Greenfield for this suggestion.

[13] Hendriks et al. (2017) have recently produced evidence suggesting that 'nearly all infertile men and women prefer genetic parenthood' over non-genetic parenthood. See Greenfield (2018) for an account of the significance of genetic relatedness.

convinced they can do no harm (or that they harms they can inflict are negligible), but only when their safety is established with a very high degree of confidence.

At the opposite extreme, it is possible to imagine a different individual who argues as follows: 'There are obvious forms of value attached to genetic relatedness. PNT and MST therefore offer clear advantages over egg donation, and they respond to urgent problems by virtue of that.' This individual will say that once a reasonably large body of evidence points in the direction of safety, it is irresponsible to further delay the introduction of these valuable technologies by insisting on gathering more evidence.

When dealing with technologies that intervene in basic developmental processes of growing children, one can never dismiss the possibility that they might have significant detrimental effects on health. The question of whether it is time to stop seeking further evidence of safety and to move ahead with release of a technology, or whether instead further evidence is required before a new technology is made available, depends on an ethical evaluation regarding the benefits the technologies in question offer. This is how ethical evaluation and technical evaluation become entwined.

## 9 Ethics and the HFEA panel

The previous section established in broad terms that the benefits of PNT/MST are ethically contentious, and that the answer to a question that might appear purely technical, 'When is a treatment safe to offer?', is affected by that ethically contentious evaluation. In this section I establish in some detail the implicit ethical stance adopted by the HFEA panel in its reports. My claim is that the HFEA panel took the view, in 2014, that a suitable evidential threshold had very nearly been reached to justify offering PNT/MST. It took this view because it regarded the technologies as answering fairly urgent medical needs. I establish this contention by reflecting on the panel's responses to technical concerns about mitochondrial-nuclear interactions.

### 9.1 Mito-nuclear interactions

In 2013 Edward Morrow and colleagues argued that it might be 'premature' to make PNT and MST available in the clinic (Reinhardt et al. 2013). They worried that placing nuclear genetic material in the cellular context of distantly related mitochondria might disrupt normal healthy functioning. They argued, based on a variety of pieces of experimental evidence, that this healthy functioning relies on finely tuned mito-nuclear interactions:

> …energy production critically hinges on extensive cross-talk between genes dispersed across the nucleus and the mitochondria. Because phenotypes with less-than-ideal cross-talk are disfavored by natural selection, coordinated mitochondrial-nuclear interactions become highly specific over evolutionary time. If MR [Mitochondrial Replacement] disrupts such specific, highly coordinated mito-nuclear allelic interactions, adverse health outcomes might occur. (Reinhardt et al. 2013: 1346)

The HFEA panel reflected on Morrow's work in their third report. Some of the panel members were asked about their response to Morrow's concerns when they appeared before the UK House of Commons Science and Technology Committee in 2014. These responses to the committee were made by individuals expressing matters in their own terms after the third report was produced. It must not be assumed, then, that they give an indubitable picture of the panel's collective position, or of the reasoning that informed that position. Even so, it is reasonable to assume that they provide some insight regarding these matters.

Peter Braude, one of the panel members, said the following to the Commons Committee:

> There are three pages in a separate box in the [2014] report specifically dealing with mitochondrial interactions. We spent an inordinate amount of time on it—too much as far as I was concerned; we spent a long time on it—and wrote about it. (House of Commons 2014)

Braude's remark that 'too much' time had been spent dealing with mito-nuclear interactions suggests that, as far as he was concerned, Morrow had raised worries that did not put the clinical use of the technologies into genuine doubt.

In the HFEA panel's published remarks on Morrow in their third report, the panel characterised Morrow as raising 'hypothetical problems', which were 'based on evolutionary arguments' (2014: 32). Morrow had empirical data, drawn from experimental work on animals, which suggested that sometimes there could be disrupted mito-nuclear interactions caused by mitochondrial donation. The panel responded that the animal models Morrow was relying on probably had little relevance for human populations. A letter that the HFEA panel chair, Andy Greenfield, wrote to the *Guardian* gives a good sense of why they were sceptical:

> Among other things, the panel felt that the data he submitted related to inbred mice and *Drosophila* [fruitflies] in a way that did not materially contribute to an understanding of a predominantly outbred human race, and also noted that data obtained in large-scale human genome projects looking for disease associations have not found any consequences due to the exchange of mitochondrial DNA (mtDNA) haplogroups by reproduction. The panel also consulted other scientists with expertise in evolutionary biology, who, while also raising the hypothetical issue of mismatching, assessed the situation differently from Dr Morrow. (Greenfield 2014)

Greenfield was suggesting that the very fact of inbreeding in the lab had made Morrow's animal models less able to cope with their nuclear DNA being placed in a modified mitochondrial context. In other words, the troubling data from these animal models were products of the specific ways in which the animals had been treated for experimental purposes. For humans who are not restricted to labs, and who regularly reproduce with unrelated individuals scattered all over the world, such models were not relevant. Even so—and this explains Braude's later hint that they had probably given too much credence to Morrow—the panel indicated that it might potentially be worth using 'haplotype matching' of donor and recipient mitochondrial DNA as a

precautionary measure, in case Morrow's concerns should turn out to have some foundation after all.

Morrow also appeared before the Commons Committee, and his remarks indicated that, in his view, the panel's proposed precautionary measure was inadequate.

> Haplotype matching may reduce the risk, so you have a more closely related mitochondrial genome that you are swapping in; but it may not work, because we know that it needs only one change, one single nucleotide in the mitochondrial genome, for an effect. Haplogroups—haplotypes—vary in many different loci. There are lots of differences. It is more closely related, but it is not identical. (House of Commons 2014)

Morrow took the view that it was unwise to proceed with PNT and MST, on the grounds that there was a possibility that haplotype matching would not sufficiently reduce the risks of adverse mito-nuclear interactions. The HFEA panel took the view that haplotype matching might well be an excessively cautious response to what were highly speculative safety concerns, grounded in work on animal models of dubious relevance.[14]

The full resolution of this standoff partly turns on technical empirical issues. It also turns on ethical evaluation. It is telling that when Braude cast doubt on the practicality of haplotype matching in his remarks to the Commons Committee, he did so by drawing attention to patient suffering:

> At the end of it, the panel recommended that consideration is given to mitochondrial, mtDNA, haplogroup matching with selected donors, bearing in mind the practicality of doing it. It all depends where you get your donors from. It is all very well to say, 'We want type A donors,' or whatever it happens to be, but what happens if they are not there? Do you say, therefore, 'You will suffer with your disease because we cannot find the right donor,' or do you say, 'We'll take the theoretical risk and go ahead without haplotype matching'? (House of Commons 2014)

There is no guarantee that a donor will be found with a similar mitochondrial haplotype to the intended mother. In these circumstances, what is one to do? Braude suggests that delaying treatment in order to find a close enough haplotype match—a delay that could be endless if one were to take Morrow's worries about the broad-grained nature of haplogroups seriously—cannot be justified given the urgent needs of the patient.

Concerns about whether to gather more evidence in the face of risk, are here assuaged by appealing to the immediate need to reduce suffering. I have indicated that the form of suffering involved carries ethical weight of a contentious nature. Women with mitochondrial disease will not be cured themselves by PNT/MST. PNT and MST do not allow them, for the first time, to have healthy children with confidence. These women's suffering derives from their uncertainty regarding the prospect of having healthy children who also share a nuclear genetic link with them. Let me stress once

[14] Some of the panel members had familiarity with scientific work on mice. Andy Greenfield, for example, is a specialist in molecular genetics with a track-record of working with mouse models: https://www.har.mrc.ac.uk/research/whos-who/andy-greenfield (accessed 16th July 2018).

again that my claim here is not that Braude was wrong in his appraisal of the situation. My claim is merely that his position regarding the significance of Morrow's technical argument derived, in part, from an ethical standpoint that one might challenge. It was not a purely scientific judgement.

The same can be said for Andy Greenfield's concluding comments in his letter to the *Guardian* about nuclear-mito interactions. While Braude pointed to the welfare of mothers, Greenfield pointed to the welfare of children:

> [The] panel is satisfied that the conclusions of the report represent a balanced view of the progress being made towards safety in this area – progress that could offer children lives free from severe and debilitating illness. (Greenfield 2014)

I established above how difficult it is to argue that either PNT or MST, 'offer children lives free from…illness' in the sense of curing the illnesses of individual children. They do offer the prospect of a world where children do not have to suffer from these serious illnesses, but egg donation also enables this outcome.

### 9.2 Germ-line interventions

The HFEA panel's exchange with Morrow offers probably the strongest evidence for my contention that ethical evaluation informed its deliberations regarding technical matters. A second example concerns the HFEA's implicit stance on the ethics of germ-line interventions.

There are wide variations in the proportions of unhealthy mitochondria in the cells of women with mitochondrial disease. Women with 'homoplasmy' have close to 100% defective mitochondria in their cells. Some women instead have varying degrees of 'heteroplasmy'; i.e. their cells contain lower proportions of defective mitochondria. The comparatively well-established technique of preimplantation genetic diagnosis (PGD) potentially allows clinicians to select eggs that happen to have low levels of defective mitochondria. These could then be used for conventional IVF. But the third HFEA report notes that PGD is of no use to women with 'homoplasmy', or with very high degrees of 'heteroplasmy'. When a woman is homoplasmic it is quite possible that all of her eggs contain too many unhealthy mitochondria for a healthy baby to develop. Hence the report concludes that MST and PNT, unlike PGD, offer 'the prospect of eliminating, and not just reducing, the risk of disease due to mtDNA mutations' (HFEA 2014, p. 13).

The situation is made more complex by the possibility that neither PNT nor MST will fully eliminate these risks, as the HFEA panel explains. This is because of a phenomenon known as 'reversion'. The process by which the nuclear material from an affected mother is placed in a new cellular context involves a potential risk of 'carry-over'. This occurs when a small number of defective mitochondria are transferred into the healthy donated egg or embryo.[15] Very low levels of defective mitochondria normally bring no clinical symptoms. Even so, a variety of processes make it possible for defective mitochondria to amplify in numbers during iterated cycles of cell division

[15] The diagram of PNT reproduced in Figure 1 indicates the possibility of carry-over by showing a mitochondrion transferred along with the intended parents' pronuclei.

as the embryo matures into an adult. This gives rise to a risk that an apparently healthy girl born via PNT/MST might find, when she grows up, that her own eggs contain a newly magnified load of unhealthy mitochondria. How can this woman avoid the risk of transmitting mitochondrial disease to her children?

The HFEA panel responds by suggesting that a girl born by MST or PNT could later use PGD to assess the health of her own embryos' mitochondria. At this point, the woman born from MST/PNT could be far more certain of the permanently eliminated risk of passing mitochondrial disease to children and grandchildren. The HFEA panel indicates that the combination of MST/PNT and PGD, '…would guarantee that subsequent generations would be free from disease' (HFEA 2014, p. 27).

Here the HFEA panel expresses the view that a germline intervention is an attractive proposition. In contrast to this, some have suggested using PGD in a very different way to ensure that only male embryos—and not female embryos—created by PNT/MST are chosen for reimplantation. Since it is females, and not males, who pass on their mitochondria to offspring, this measure would reduce worries about the long-lasting effects of PNT and MST. In particular, the measure would reduce concerns about unanticipated effects of the techniques, which might adversely affect health, and which might be transmitted down the generations. This was precisely the stance taken by the US National Academies' report:

> Because of the scientific uncertainties associated with these novel techniques and because MRT in female embryos would result in heritable genetic modification, the committee believes that a cautious approach to MRT in the U.S. research context is required, including a restriction to male embryos in initial clinical investigations. (National Academies 2016, p. 10)

The HFEA panel had considered this measure too, but rejected it:

> [The panel] did not support any proposal to select only male embryos for transfer after MST or PNT, even though this would avoid these issues as well as circumvent objections made by some that the methods are a form of germ line genetic alteration. Selecting only XY embryos for transfer would require PGD, an additional step that is likely to compromise early development of already manipulated embryos; moreover, it would on average immediately reduce by half the number of embryos available for transfer. This would decrease the efficiency of the techniques and make it likely that patients would have to undergo repeated cycles of treatment. (HFEA 2014: 27)

Remember that the HFEA panel recommended PGD for women born using PNT/MST. Here, it opposes using PGD on the grounds of a double insult to embryos, beyond the initial use of PNT/MST. This position is consistent. For a woman with mitochondrial disease, the US proposal would require that her embyros are first manipulated via PNT/MST, then subjected to PGD. The HFEA rule out this double manipulation. Instead, they propose that PGD is used only to assess the embryos of women who are themselves born via PNT/MST. Those second-generation embryos will not have been subjected to the additional insult of PNT/MST.

One plausible way to interpret the HFEA panel's position credits it with a sceptical attitude towards ethical worries about germline interventions. Suppose the HFEA panel

had regarded 'germline' interventions as crossing an important ethical boundary. This negative prospect would have acted as a far more significant counterweight to its concerns about the reduction in efficacy brought about by the double insult of PGD plus MST/PNT.[16] Once again, let me stress that my aim is not to argue that the HFEA panel acted inappropriately here. My aim is simply to show that the panel's reasoning on technical matters was not independent of background ethical concerns. In spite of addressing 'purely scientific' matters, the HFEA panel took an ethical stance.

## 10 The risks of dividing labour

The preceding three sections established that the HFEA panel's reasoning was influenced by ethical evaluation. In this section I draw some normative lessons for advisory governance from this intermingling of ethical and technical matters. On the face of things, by dividing advisory labour between ethical evaluation on the one hand, and scientific/technical evaluation on the other, all contentious aspects of a new technology are guaranteed to receive expert attention. Here I suggest that the division of advisory labour can have the unintended effect of shielding important questions about the ethics of risk from scientific scrutiny.

Recall that in the case of MST/PNT, the Nuffield Council concluded that 'if these novel techniques are adequately proven to be acceptably safe and effective as treatments, it would be ethical for families to use them.' The Nuffield Council did not attempt to determine whether the techniques were 'adequately proven to be acceptably safe and effective'. That job would remain for a more technical body such as the HFEA panel. The HFEA panel did make an assessment of whether the treatment was 'safe to offer'. I have argued that a good answer to this question involves both ethical and technical reflection. This is because the question of whether the level of evidence in favour of making a new technology available is 'adequate' turns on an ethical assessment of its benefits.

It is now possible to state the risks of dividing advisory labour more clearly. In the PNT/MST case, reflection on where to set evidential thresholds was not undertaken in any detail by the Nuffield Council, on the grounds that this was a technical problem that lay outside their remit. The HFEA panel did come to views about evidential thresholds. They did so by bringing an implicit ethical stance into contact with a large body of scientific work. That evaluation remained hidden from view (perhaps even hidden from the panel members themselves) by the panel's stated goal of coming to a verdict on 'purely scientific' matters.[17] The result was that, because of well-intentioned division of advisory labour, neither the Nuffield Council nor the HFEA panel explicitly reflected on crucial ethical dimensions of evidential threshold-setting.

[16] This is not to say that the US panel regarded all germ-line interventions as impermissible in principle: it is consistent with that panel's comments that they simply took a different (ethical) evaluative stance to the HFEA on the contingent costs and benefits of interventions with effects that persist down generations.

[17] See also Havsted and Brown (2017).

It is worth noting the composition of the HFEA panel, compared with that of the Nuffield Council working party. The latter involved individuals from a diverse group of disciplines: medicine and science, but also philosophy of science, science communication, bioethics and so forth.[18] The former was composed exclusively of technical experts, and its evidence-gathering exercises also involved experts with purely scientific and clinical backgrounds. Some technical scientific and clinical specialists—Peter Braude, Frances Flinter—were on the HFEA and Nuffield Council groups. The sort of ethical deliberation undertaken by the Nuffield Council needed to involve technical scientific experts alongside experts in social, ethical and legal domains. If I am right that the questions addressed by the HFEA panel also rested on ethical considerations, then the HFEA panel should also have featured experts from outside the strictly technical scientific and clinical disciplines.

In making this recommendation I do not mean to suggest that these technical scientific experts should offload reflection regarding evaluative questions onto those with expertise in (for example) legal, ethical and social domains (see also Havsted and Brown 2017). As Douglas puts it, 'scientists have the same moral responsibilities as the rest of us' (2000, p. 563). My claim is simply that a mixed panel is likely to be better able as a whole to deal with a series of intertwined evaluative and technical issues.

There are risks of dividing technical and ethical labour, but we should not lose sight of the benefits. There are, for example, good practical reasons to refrain from trying to answer all of the questions raised by new technologies simultaneously. In the case of PNT/MST, one group might reflect on questions about (for example) the likely wellbeing of people born using these new technologies, and on broader issues about precedents set in terms of germline interventions. Another group might burrow into great detail into the current state of evidence regarding safety and efficacy. Even so, while it may be wise to continue to divide the *topics* addressed by advisory groups in a way that does not depart greatly from current practice, there are good reasons to depart from current practice by broadening the *composition* of all of these groups beyond scientific and medical disciplines.

The fact that evidence regarding safety and efficacy needs to be assessed in detail may have the result that some non-scientists will struggle to contribute effectively. But just as scientific and clinical experts can learn to make valuable contributions to ethical discussion, there are grounds for thinking that individuals from philosophy, social sciences and other humanities disciplines will be able to make valuable contributions to technical safety assessments. My argument shows, simply, that because questions that address safety in technical detail are answered in part by recourse to ethical considerations, it is important not to exaggerate the independence of these two realms of inquiry.

## 11 Science and values: The hedged claims response

Up until now, I have tried to establish the first overall claim of this paper: the HFEA panel reports did not succeed in avoiding taking stands on contentious matters of ethical evaluation. This claim is consistent with Douglas's argument that science should be informed by ethical values. It is also consistent with a variety of views that support

[18] I was a member of this working group. Just as I do not intend this paper as a criticism of the HFEA panel, neither is it intended as a criticism of the Nuffield Council's deliberations.

the 'value-free' ideal. The proponent of value-freedom might concede that the HFEA reports were not free of value, while adding that they would have been better reports if they had been free of ethical value.

In this section I consider what I call the 'hedged claims' response. Betz (2013) has suggested that considerations of inductive risk can be avoided if scientists make claims that carry no salient possibility of error. I argue that he overlooks important elements of the pragmatics of scientific communication, which resurrect concerns about inductive risk even when scientists make near-certain assertions. These features are nicely illustrated by the case of mitochondrial donation.[19] This is the second main claim made in this paper overall.

Betz (2013) has argued that Douglas's position relies on the premise that in coming to conclusions, scientists run significant risks of being mistaken.[20] He counters that there are some claims that scientists are entitled to make with degrees of confidence that approach certainty. They can do this by making highly hedged claims about risk. Since they can be practically certain of the truth of these hedged claims, the question of error is irrelevant. That means that no consideration of the value or disvalue of the consequences of error is needed.

In order to illustrate Betz's argument, let us begin with a bold proposition: 'Babies born from PNT and MST will experience severe developmental anomalies as a result of the use of these technologies.' Call this proposition P. Betz claims that Douglas focuses solely on epistemically risky claims like, 'P is false', 'P is true' or even 'P has only a 5% probability'. There is a significant chance that every one of these claims will turn out to be false. Betz points to the availability of more hedged claims. He gives the examples, 'It is possible that P' and 'We have not been able to refute P' (2013: 214). These last two claims are, logically speaking, exceptionally weak. The more a claim is hedged, the more certain one can be of it. To the extent that scientists can be certain of these hedged claims, they have no need to contemplate the consequences of errors before accepting them.

To see why Betz's comments overlook pragmatic elements of communication, consider some more remarks made by HFEA panel members to the House of Commons Science and Technology Committee. Robin Lovell-Badge told the Committee that the panel's overall conclusion was 'that there is nothing unsafe' about PNT and MST. In summarising the overall thrust of the HFEA panel's third report, Peter Braude said that:

> [We have tried to] look at the evidence to see whether there is anything that says to us fundamentally that this is not safe. We have not been able to find that. There have been some theoretical concerns, and we have tried to find ways of getting around those, but at the end of the day we have had to report that *it is not unsafe*. [Emphasis added]

As I will now show, the HFEA panel did not, strictly speaking, report that PNT and MST were 'not unsafe', although this may be what the panel intended to convey to the report's readers.

[19] These issues relating to the pragmatics of communication are rarely considered in detail in the literature on inductive risk: an exception is John (2015a).

[20] As Elliott and Richards put it, the argument from inductive risk begins with the observation that, 'There is always the chance that we have drawn the wrong conclusions from evidence we have' (2017, pp. 1–2).

The precise words the report used were that, 'the evidence [the Panel] has seen does not suggest that these techniques are unsafe'. There is a legitimate sense of the term 'suggest' according to which some of Morrow's animal data did indeed 'suggest' lack of safety. The panel took the view (explained above) that what these data may have 'suggested' to some eyes was in fact misleading. So, if the panel's remarks are to be interpreted charitably, they must be understood as intending something reasonably robust with their notion of what evidence 'suggests'. The panel's claim was that the evidence it had reviewed did not give significant support to the conclusion—as Braude put it, it did not 'say to us fundamentally'—that the techniques were unsafe.

Braude and Lovell-Badge's spoken words to the Commons Committee asserted a strong and epistemically risky conclusion: it is not the case that the techniques are unsafe. The panel's written wording instead made a more cautious claim: the panel had not *seen* any *strong* evidence pointing in the direction of lack of safety. This does not deny that future research (or even extant research the panel had not been made aware of) might show that there are significant safety concerns. So the panel's actual assertion is one that can be made with a high degree of certainty. In other words, the panel's actual assertion was of precisely the hedged kind that Betz highlights.

The panel could have made a very different hedged claim about risk. It could have said that it 'has not yet seen enough evidence to determine with certainty whether the techniques are safe.' That claim would also have evaded concerns about error, because it is a truism that the finite body of evidence the panel saw leaves open the possibility that further studies might put the safety of the techniques into doubt.

These two claims are both highly probable, and both bring with them very small chances of error. Their pragmatic effects on readers are entirely different. Had the panel reported that its limited body of evidence did not allow it to determine safety with certainty, this would not have been interpreted by parliamentary readers as a bland statement of the fallibility of science. It would have been understood as a signal that considerable further research was required before placing PNT and MST in the clinic. Conversely, the actual formulation used conveyed the panel's view that only a few further pieces of evidence would be required before the techniques could be used in the clinic. In other words, the panel was convinced that a suitable evidential threshold had very nearly been reached for the techniques to be made available. While this is not what it strictly asserted, there is evidence that it is what the panel conveyed in the Gricean sense. Braude's and Lovell-Badge's comments to the Commons Committee suggest that the panel intended to communicate this positive message, via its negative assertion that the evidence seen did not point to a lack of safety.

Scientists make assertions in their advisory capacities, and those assertions convey various messages to their readers and listeners. There is evidence that the HFEA panel used a comparatively certain assertion to convey a less certain message about safety. A responsible scientist needs to consider not merely the possibility that what she asserts might be in error, but also the possibility that what she intentionally conveys might be in error. Scientists can, as Betz shows, make near-certain hedged assertions. Even when they do so, a concern for the practical consequences of those assertions should affect their choice of communicative actions.

## 12 Science and values: The pure evidence response

In its simplest articulation, Rudner's version of the argument from inductive risk assumes that scientists accept hypotheses in a 'binary' manner. In the toy illustrative example used at the beginning of this paper a scientist accepts either that a piece of coastline will collapse, or that it will not. It is because both of these hypotheses are epistemically risky—in the simple sense that the evidence gathered leaves open the possibility of their falsehood—that the scientist must also consider the practical costs of her potential errors. On the face of things, scientists are not restricted to binary options. They can record the evidence as it stands, they can note when different pieces of research point in different directions, and they can state conclusions in probabilistic terms. Following Jeffrey (1956), one might then wonder whether the HFEA could have reported such evidence in a manner that did not require them to take a stand on ethical issues.

Here I will simply assume for the sake of argument that the HFEA panel could have written a report in the form of a value-free account of the state of evidence. This would summarise the likely consequences of PNT and MST for various physiological and developmental processes in donors, intended mothers and maturing embryos.[21] In this section I establish the third broad claim of this article. I argue (following Steele 2012 and John 2015b) that such a report would have been of little direct use to the parliamentarians ultimately responsible for deciding on whether to make the techniques available. These individuals are not usually technical experts themselves. They need a report that is more actively curated than a straightforward collection of claims about the current state of evidence.

A mere statement of current evidence leaves open the question of whether we know enough to decide whether PNT/MST should be used in the clinic, or whether more evidence should be sought before coming to a decision. I argue here that the HFEA panel took a stand on this further question. It is a question that has an ethical, evaluative dimension in addition to a technical dimension. I also argue that if the HFEA had not taken a stand on this question, the value of their report would have been limited.

The HFEA panel has observed that, 'Research can never answer every question before a new treatment is offered, nor can it be expected to guarantee safety or efficacy when applied for the first time in the clinic' (2014, p. 5). This remark is correct, but its significance should not be inflated. It would indeed be impossible to require that safety is guaranteed by evidence. It would also be reckless to use this truism as a justification for putting technology into the clinic when it has only a scant basis of evidence to support it. Judgement needs to be used to determine whether a body of evidence that falls short of giving certainty is nonetheless adequately supportive of a decision to proceed along some technological pathway.

Consider the worry that the efficacy of PNT and MRT might be undermined by 'reversion'. This is the phenomenon whereby an embryo containing overwhelmingly healthy mtDNA from the donor mother reverts to the intended mother's unhealthy mitochondrial type. Considerable work is still needed before scientists understand the circumstances under which reversion occurs.

[21] Douglas (2009) gives grounds to suspect this is not feasible. On the complexities of trying to untangle evidence and ethical evaluative input, especially in policy contexts, see Frank (2017) and Havsted and Brown (2017) among many others.

In its fourth report of 2016, the panel noted that reversion was:

> …a potential risk that the panel takes seriously and hence it recommends restricted application in the first instance. An alternative for the panel was to recommend that clinical application should not proceed until there was better understanding of the causes of the reversion and approaches designed to reduce or eliminate it. However, *the panel felt that this approach was too cautious, especially when the need is real*, and the risks may be small and manageable to some extent via prenatal testing, an option that may be acceptable to some patients. (HFEA 2016, emphasis added)

Here, quite explicitly, the panel invoked the notion of a real need to justify the decision to move ahead with placing PNT and MST in the clinic. In other words, it appealed to an ethical evaluative claim about the medical needs of patients in order to come to a judgement about whether to wait for further evidence to accumulate. Had the panel laid out the evidence in a manner that was entirely free of such evaluative considerations, it could not have come to any recommendation surrounding what might be a suitable level of caution in the face of uncertain evidence.

Imagine an alternative HFEA panel report that presented the rather complex and equivocal evidence on reversion, with no further synthesising indications regarding prudent action. The parliamentarians reading it would then need to convene another expert advisory group to offer interpretative suggestions on what might be a suitably cautious response. That group would need to draw on scientific and ethical expertise. A report that is wholly value-free, assuming such a thing were possible, necessitates a further value-laden report that interprets this value-free evidence, and aligns it with the deliberative needs of government. Such an interpretative report would be of just the sort recommended in section ten. It would be a synthetic evaluative statement of relevant technical considerations jointly composed by experts drawn from the sciences, medicine, and also from disciplines associated with ethical evaluation.

## 13 Conclusion

My primary goal in this paper been ameliorative. The expert panel convened by the HFEA aimed to provide a purely technical, scientific assessment of concerns regarding PNT and MST. I have argued that it took a series of implicit ethical stances as it reached its conclusions. I have not argued that the HFEA panel was blameworthy here. My concerns have rested instead on unintended consequences of dividing advisory labour. In attempting a strict separation of technical issues on the one hand, and ethical issues on the other, the result is that hybrid questions about where to set evidential thresholds—questions with ethical and technical aspects—receive insufficient attention. Deliberation would be more effective if the hybrid character of these questions were explicitly acknowledged, and if the groups assigned to address them were not drawn exclusively from technical scientific and medical disciplines.

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