This is a pre-copyedited, author-produced PDF of an article accepted for publication in *Internal Medicine Journal* following peer review. The definitive publisher-authenticated version [**Lipworth W**. **2007**. Managing scientific uncertainty in health legislation. *Internal Medicine Journal,* 37**,** 119-123] is available online at http://onlinelibrary.wiley.com/doi/10.1111/j.1445-5994.2007.01243.x .

Managing scientific uncertainty in health legislation

Wendy Lipworth, Centre for Values, Ethics and the Law in Medicine, University of Sydney

Keywords: Legislation, ethics, peer review, discourse

Acknowledgments: I am grateful for the assistance provided by John McPhee and Miles Little.

Legislation and regulation are one means of controlling biomedical research and its clinical applications. This is seldom a one-off process since biomedical science evolves rapidly, dynamically and often unpredictably, and legislative and regulatory reviews are often required in response to the emergence of apparently new ethical and legal issues.

In recent years, there have been several reviews of Australian biomedical legislation including the Australian Law Reform Commission's "Inquiry into the Protection of Genetic Information in Australia" ("the ALRC Inquiry") released in 2003 [1], and the Legislative Review of the *Prohibition of Human Cloning Act 2002* and the *Research Involving Human Embryos Act 2002,* ("the Lockhart Review") which was released in December 2005 [2]. The ALRC Inquiry was a response to developments in genetic research, particularly genetic epidemiological research involving powerful new techniques such as microarrays (gene chips). The Lockhart Review was concerned with developments in stem cell research, including the use of embryos produced in the course of assisted reproductive technology (ART) and through cloning.

These two reviews, when juxtaposed, highlight the key elements—both recurring and review-specific—of biomedical legislative review.

In terms of recurring elements, the ALRC Inquiry and the Lockhart Review had much on common. Both were concerned with biomedical technologies that have the potential to both improve health and cause harm. Both were faced with the need to consider divergent views from experts and the general public. And both considered ethical issues to be central to their terms of reference. The ALRC Inquiry took the unprecedented step of forming a formal partnership with the Australian Health Ethics Committee while the Legislative Review Committee in the Lockhart review included two "ethicists" (one of whom is also a lawyer) and four scientists one of whom is also a "community advocate."

While there was much common ground between the ALRC Inquiry and the Lockhart Review, there were also important differences, particularly in relation to the manner in which they responded to uncertainty regarding the likely clinical benefits of genetics and stem cell science respectively.

While genetics (the subject of the ALRC Inquiry) is often assumed to provide a simple and definite answer to questions regarding the diagnosis and management of disease, in fact there are a number of epistemological, epidemiological/ methodological and technical issues that limit the ability of genetic science to deliver definitive benefits to the community. Epistemological issues relate primarily to the low likelihood that the vast majority of diseases are primarily "genetic" (as opposed to environmental or degenerative) and the small number of "genetic" diseases that can be attributed to single genes (as opposed to the accumulation of multiple genetic abnormalities). Epidemiological/ methodological issues relate to the difficulty in interpreting large-scale genetic epidemiological results, uncertainty regarding the importance of so-called "junk DNA" and difficulty translating genetic epidemiological results into meaningful genetic tests (including pharmacogenomic testing), preventive strategies and therapies. [3-11] Technical issues relate primarily to the difficulties associated with delivery of gene therapies to individuals. [12]

In the ALRC Inquiry, the likely merit of the science (predominantly genetic epidemiological research involving gene chip or micro-array technology) was not open to debate. These scientific developments were seen, essentially unquestionably, as "breakthroughs" promising better medical diagnosis and treatments, and as a route to improved law enforcement. The issue in the ALRC Inquiry was not whether "the march of science" (in this case genetic technology) was likely to lead to medical breakthroughs, but rather how law could keep up with the science [1: 4.18] and, more specifically, how legislation could deal with the: "*general fear about uncontrolled or 'mad science', the spectre of eugenics, threats of biological warfare, reports of xenotransplantation (transplants from one species to another), the loss of privacy, and the increased possibilities for genetic discrimination.*" [1: 4.12] Whilst scientists were involved significantly in the ALRC Inquiry, their input related primarily to whether these fears should outweigh the unequivocally imminent medical benefits of genetic science.

The Lockhart Review, on the other hand, had among its central questions the issue of whether human embryonic stem cell (hESC) research is likely to lead to the medical benefits being promised by its proponents. One of its key questions was:

> *"what are the limits of the use of in vitro fertilisation (IVF) and related methods (collectively known as assisted reproductive technology, or ART) and human embryo research?"* [2: v]

It was recognised explicitly that there are "several challenges" to stem cell researchers in the development of cellular therapies, including difficulty maintaining stem cell lines in culture and difficulty controlling differentiation to derive populations of the required cells. The Committee also recognised that there is ongoing controversy among researchers as to whether adult or embryonic stem cell research is likely to be more successful, and that there is even debate about the nature of the biological entity known as an "embryo." [2: pp40-1]

In keeping with recognition of this scientific uncertainty, two sections of the Lockhart Report were devoted to debate surrounding "developments in medical and scientific

research." Controversy over the scientific merit of stem cell science was evident in the submissions which ranged from being highly supportive to being strongly sceptical. On the one hand, it was argued that:

> *"there is still a strong case for ongoing efforts to derive new stem cell lines, particularly since this is a rapidly developing field in which technical innovation will result in steady improvement in the means for producing and maintaining hESC."* [2: p46]

In contrast, another submission claimed that:

> *"Nothing in the experiments on human cloning in Britain or Korea have improved the likelihood that this will ever lead to successful therapies. There is still not a single therapy utilising human stem cells, whether from a cloned embryo or an embryo created by IVF."* [2: p47]

This difference between the ALRC Inquiry and the Lockhart Review is clearly related to the fact that the Lockhart Review was performed at a time when stem cell science is relatively new, whereas the ALRC Inquiry focused on a type of science (genetic research) that has been in development for decades. One could speculate that this is because embryo research raises what, to some, are fundamental ethical issues relating to killing—such that even small-scale scientific developments are seen as being ethically and legally charged. But the maturity or otherwise of the science does not seem to explain completely the difference between the two reviews in managing scientific uncertainty. While genetic research is more established than is stem cell research, it still raises numerous scientific issues (eg. relating to the capacity to attach meaning to microarray results and the problems of ignoring what used to be considered "junk DNA") and will continue to do so as technology evolves. This suggests that the exclusion of these concerns from the ALRC Inquiry may reflect not so much a difference between genetic science and stem cell science, but rather the fact that legislative reviews are driven by complex political, moral, social and economic concerns and limited by terms of reference, time-frames and resources.

The challenge of scientific uncertainty in legislative review

Whatever the reason for this difference between the two reviews, the fact remains that legislative review may occur at a time of significant and explicit scientific uncertainly and that this kind of uncertainty needs to be managed. Drafting legislation in the face of scientific uncertainty raises substantial ethical and epistemic challenges.

First, it means that ethicists involved in legislative review need to consider not just questions of risk to research subjects and the moral status of people, animals or embryos, but also the possibility that the medical benefits being promised by some will never actually materialise. These issues are not "just" scientific, as it is highly unethical to put research subjects at *any* risk or engage in *any* morally controversial techniques if there is not likely to be medical benefit. This challenge was recognised by the Lockhart Committee which noted that:

> *"…the higher the potential benefits of an activity, the greater the need for ethical objections to be of a high level and widely accepted in order to prevent that activity. Conversely, where benefits are not yet established, or where*

> *there is widespread and deeply held community objection, then total prohibition through the legal system may be justified."* [2: xiv]

A second problem is the potential for asymmetry in arguments, such as the pitching of questions of scientific merit against deontological questions about the moral status of the embryo. Sensitivity to the existence of such asymmetry was evident in the Lockhart Review process, which characterised the debate as follows:

> *Proponents of embryo research argued that the potential benefits of these activities meant that it would be unethical not to pursue the research and development made possible by such technologies. They also argued that current ART arrangements already sanction the possibility of the destruction of embryos, in the process of helping people to have a family, and hence not to allow embryo destruction to help people with other medical problems would be unfair. Opponents of embryo research argued that a human embryo, from the earliest stages of development, is an entity that deserves full protection and it is wrong to create such an entity for any purpose apart from ART treatment of a woman."* [2: xiv]

Third, there is also the problem of the integrity of arguments. There is a tendency to frame arguments as "scientific" when, in fact, the concerns are moral (or vice versa). The Review Committee recognised this problem, noting that:

> *"much of the debate regarding the relative merits of …(stem cell)research was underpinned by differing attitudes towards the moral status of human embryos, and at times it was difficult to distinguish moral arguments from scientific or biological ones."* [2: p53]

Managing scientific uncertainty in health legislation

While there is no simple solution to these challenges, steps can be taken to ensure that the problem of scientific uncertainty is dealt with as effectively as possible.

Three related strategies might assist with the management of scientific uncertainty in legislative processes: 1) maximising philosophical symmetry and transparency, 2) managing "peer review" processes and 3) recognising that legislative review is a "discourse."

First, efforts could be made to ensure that arguments are as symmetrical and honest as possible. Three types of argument can be distinguished: 1) arguments that pitch scientific claims against conflicting scientific claims, 2) arguments that pitch moral concerns against conflicting moral concerns and 3) arguments that pitch scientific claims against moral concerns. It is worth reiterating that the last of these is not philosophically incoherent—there is nothing wrong, for example, with the argument that scientific benefits are less important than respect for embryos or vice versa. What matters, however, is that these various types of arguments are clearly distinguished and navigated in a consistent manner. The importance of philosophical symmetry and honesty was highlighted recently in the Australian debate about RU486 (the "abortion pill") where there was perilous conflation of scientific arguments (whether the drug is safe and effective), moral arguments (whether abortion of this kind is morally permissible and whether women should have the

right to access such technologies) and political arguments (whether the government should have control over such decisions).

A second strategy for managing scientific uncertainty is to recognise explicitly that some legislative review processes rely significantly on "peer review of scientific merit." Peer review of scientific merit refers here to the process by which scientists review the "scientific merit" of other scientists' work, where "scientific merit" refers to the quality of the research question and of the choice of methodology with which to answer this question. This places the legislative review process in a broader context since peer review of scientific merit occurs at several other stages of the research endeavour, including peer review of the scientific quality of funding proposals and of manuscripts submitted to journals.

Placing legislative review in this broader context might assist by enabling guidelines used in these other peer review contexts to be adapted for use in the policymaking process, thus ensuring that the policy-level review of scientific merit is carried out, at the very least, to the standards set out for reviewers of funding proposals and potential journal publications. Placing legislative review in this context would also ensure that the problems that plague peer review in other settings (such as perceived bias, inconsistency, misunderstanding and destructive criticism) [13-18] are recognised and managed, as well as possible, in the legislative review setting.

An understanding of peer review should not be limited to those "experts" involved directly in the legislative review process. Patients and the general public, too, need to understand how it is that assessments of scientific validity are reached, be they assessments of potentially promising but morally controversial clinical technologies (as in the case of stem cell science with its promise of widespread cures) or assessments of the latest controversy involving mobile phone radiation, red meat or vaccination side-effects. A recent UK working committee convened to address public understanding of peer review found that the public has little understanding of peer review and that scientists are defensive about the peer review process and about explaining its importance to others. It is arguable that scientists, clinicians and ethicists involved in legislative review should take the opportunity presented in processes like the Lockhart Review to educate (other) health professionals, patients and the general public about both science and peer review, and to "put pressure on the people who bring research claims to the public to explain exactly what the status of the work is " [19: p10]

A third strategy for managing scientific uncertainty, and one that was embraced to some extent by the Lockhart Committee, is to recognise that review processes, although legislative, cannot be viewed in a static, "legalistic" manner. Rather, they need to be viewed as ongoing social and communicative *processes*—i.e. "discourses"—which take place in the face of ongoing disagreement and uncertainty, both moral and scientific.

In the case of the Lockhart Review, the inevitability of unresolvable dissent was recognised explicitly with the acknowledgment that:

> *"Australian society is made up of diverse 'communities' with different perspectives, interests and values. Furthermore, an individual may be the member of multiple communities, each with divergent perspectives or'standards', and these standards vary between and within communities and over time. Because of these divergent values and interests represented within*

Australian society, the Committee has accepted that some disagreement will remain, whether or not any changes are made to the two acts." [2: xiii]

Whilst this might represent an insurmountable problem from a philosophical perspective, the Review Committee, charged with a *practical* agenda, did not see it this way. For one thing, it was noted that "certain moral values are held in common by all communities, such as commitment to social justice and equity and to care of vulnerable people." The Committee recognised, in other words, that dissent was inevitable, but that this dissent could be managed.

The Lockhart Committee was explicit about the need for a discursive response to the "difficulties associated with drafting legislation in areas of rapid technological and scientific advance." [2: p16] Their response involved the (implicitly) discursive endorsement of flexible "regulatory" rather than rigid "prescriptive" legislation on the basis that "a more flexible approach than that ordinarily provided by legislation can be achieved by the use of regulations, guidelines and rulings from a regulatory agency." [2: p154] Another implicitly discursive recommendation was that the act be subject to a further review after several years in view of the fast-moving developments in the field. The Lockhart Committee's discursive recommendations make particular sense in that the two Acts under review (which were passed in 2002), each included a requirement for an independent review of its operation to be carried out in 2005. The Lockhart Review was, therefore, part of a larger discursive process.

Viewing legislative review as a discourse allows such procedural strategies to be implemented on sound theoretical and practical grounds. Whilst discourses cannot be broken down into a series of mechanical "steps," there are strategies for ensuring that discourses are as productive as possible. These include: allowing everyone to participate, ensuring that nobody is coerced into participating, allowing introduction and questioning of any assertion, and allowing expression of attitudes, desires and needs[20, 21] In a sense, discursive processes create procedural symmetry even where there is philosophical asymmetry (as in the debate between moral status of the embryo and the need to cure disease).

In theoretical terms, proponents of "discourse ethics" assume that there are *always* shared, fundamental moral norms and that our arguments can be designed in such a way that we can agree at least in terms of these norms. This can occur even in the face of significant dissent and uncertainty. Indeed, one of the key characteristics of "discourse communities" is their capacity to tolerate dissent and uncertainly [22] provided they share a basic "agenda" and a desire to balance interests, and provided they have the opportunity to engage in ongoing discussion that meets certain communicative criteria.[23]

There are, therefore, several strategies that might assist with legislative reviews, such as the Lockhart Review, which need to take place in the face of scientific uncertainty. Recognising the potential for asymmetrical and disingenuous argument could be the first step towards clearer debate. Recognising that peer review of scientific merit is occurring in the legislative review setting could be the first step towards ensuring that the policy-level review of scientific merit is carried out, at the very least, to the standards set out for reviewers of funding proposals, ethics applications and potential journal publications. And recognising that these processes are "discourses" could be the first step towards a deeper understanding of the

foundational (discursive) nature of the process—an understanding that may have normative (diagnostic and therapeutic), as well as explanatory, power.[24]

References

1. Australian Law Reform Commission. Essentially yours: the protection of human genetic information in Australia (ALRC96). Canberra: Commonwealth of Australia; 2003.
2. Legislation Review Committee. Legislation Review: *Prohibition o*f *Human Cloning Act* 2002 and *Research Involving Human Embryos Act 2002*. Canberra: Commonwealth of Australia; 2005.
3. Davey Smith G, Ebrahim S, Lewis S, Hansell AL, Palmer LJ, Burton PR. Genetic epidemiology and public health: hope, hype, and future prospects. Lancet 2005;366(9495):1484-98.
4. Vastag B. Cystic fibrosis gene testing a challenge: experts say widespread use is creating unnecessary risks. JAMA 2003;289(22):2923-4.
5. Davey Smith G, Harbord R, Ebrahim S. Fibrinogen, C-reactive protein and coronary heart disease: does Mendelian randomization suggest the associations are non-causal? QJM 2004;97(3):163-6.
6. Humphries SE, Ridker PM, Talmud PJ. Genetic testing for cardiovascular disease susceptibility: a useful clinical management tool or possible misinformation? Arterioscler Thromb Vasc Biol 2004;24(4):628-36.
7. Vineis P, Schulte PA. Scientific and ethical aspects of genetic screening of workers for cancer risk: the case of the N-acetyltransferase phenotype. J Clin Epidemiol 1995;48(2):189-97.
8. Haga SB, Khoury MJ, Burke W. Genomic profiling to promote a healthy lifestyle: not ready for prime time. Nat Genet 2003;34(4):347-50.
9. Khoury MJ, Yang Q, Gwinn M, Little J, Dana Flanders W. An epidemiologic assessment of genomic profiling for measuring susceptibility to common diseases and targeting interventions. Genet Med 2004;6(1):38-47.
10. Haga SB, Burke W. Using pharmacogenetics to improve drug safety and efficacy. JAMA 2004;291(23):2869-71.
11. Taubes G. Epidemiology faces its limits. Science 1995;269(5221):164-9.
12. Marcum JA. From the molecular genetics revolution to gene therapy: translating basic research into medicine. J Lab Clin Med 2005;146(6):312-6.
13. Atkinson M. Regulation of Science by Peer-Review. Stud Hist Philos Sci 1994;25(2):147-158.
14. Williamson A. What will happen to peer review? Learn Publ 2003;16(1):15-20.
15. Hojat M, Gonnella JS, Caelleigh AS. Impartial judgment by the "gatekeepers" of science: Fallibility and accountability in the peer review process. Adv Health Sci Educ 2003;8(1):75-96.

16. Goldbeck-Wood S. Evidence on peer review-scientific quality control or smokescreen? BMJ 1999;318(7175):44-5.

17. van Rooyen S, Godlee F, Evans S, Black N, Smith R. Effect of open peer review on quality of reviews and on reviewers' recommendations: a randomised trial. BMJ1999;318(7175):23-7.

18. Mulligan A. Is peer review in crisis? Oral Oncol 2005;41(2):135-41.

19. Brown T. Stop whispering about peer review. Scientist 2004;18(17):8-8.

20. Benhabib S, Dallmayr FR. The Communicative ethics controversy. Cambridge, Mass.: MIT Press; 1990.

21. Habermas J. Moral consciousness and communicative action. Cambridge, Mass.: MIT Press; 1990.

22. Fuller S. Social epistemology. Bloomington [Ind.]: Indiana University Press; 1988.

23. Habermas J, Derrida J, Borradori G. Philosophy in a time of terror : dialogues with Jürgen Habermas and Jacques Derrida. Chicago ; London: University of Chicago Press; 2003.

24. Little M, Jordens C, Paul K, Sayers E, Cruickshank J, Stegeman J, et al. Discourse in different voices: reconciling N=1 and N=many. Soc Sci Med 2002;55(7):1079-1087.