Submission to the Nuffield Council on Bioethics call for evidence on Genome Editing

Dr Donald Bruce, Edinethics Ltd.

I have structured this submission around specific questions on which I feel I have some expertise to address, identified by the page number.

> P.7 Para 1 "... we want to explore whether it is helpful to think about genome editing as a single, 'general purpose' technology, or whether it is more helpful to examine it in relation to the many (albeit overlapping) fields in which it may be used. We are interested in the extent to which genome editing is seen as simply a more powerful tool, helping to achieve aims that are already pursued by other means, or as a transformative technology, capable of fundamentally reconfiguring our ambitions and expectations."

It is not a good idea to treat genome editing as a single 'general purpose' technology. This it would be to miss the vital significance of the context. There is an analogy with the term 'nanotechnology'. This was often used at first as though there was a clearly identifiable phenomenon called nanotechnology, but it soon became apparent that a much more appropriate term was 'nanotechnologies' applied with reference to particular areas of technology. When ethical, legal and social issues were considered, these were framed primarily by the context (medicine, food, solar energy materials, coatings, clothing, sports equipment, security, etc.) rather than by there being 'nano'. Even nanoparticle risk aspects, are a common thread to all, are different in how they affect, say, clinical trials, or food additives, or an advanced solar voltaic material. In this sense nanotechnology is seen primarily as an enabling technology, which transforms existing fields, sometimes quite radically and sometimes by more incremental changes.

There is a world of a difference ethically between editing a plant or animal embryo and a human embryo, even if the techniques may share things in common. Likewise in the aims being pursued, ethical considerations are rather different between producing a drought-resistant crop for use in sub-Saharan Africa and a novel colour of carnation for the UK, or between a heavily patent-protected drug for highly competitive first world medical markets and open access modifications that could revolutionise understandings of diseases. These technologies should primarily considered within their context, rather than treating genome editing as a generic.

1

Genome editing is a more easily identifiable phenomenon than 'nano', but looks to have something of the same role as tool and enabler. It might be transformative in several ways, (and here one can talk generically) :

- enabling one to do much better something that was only poorly done so far,
- enabling one to do something consistently that so far have been erratic in its outcomes,
- enabling a much wider set of applications for something which had only a limited range,
- enabling to do something economically that was so far too expensive to be marketed
- being radically transformative in making possible things that were never before imagined, or imagined but never thought feasible.

Presenting genome editing as a discrete thing also runs the risk that it will then be simplistically regarded in, for example, the popular media, and then get labelled as either 'good' or 'bad', as tended to happen with genetic modification.

P.7 The distinctive significance of genome interventions : Is there anything special about the genome that makes intervening in it different from other ways of manipulating nature (e.g. selective breeding of plants or animals)?

To what extent can the development of genome editing techniques be regarded as distinct from or continuous with existing techniques? In what way are the differences significant?

p.8 Science, morality and law What conventional moral principles, if any, do genome editing challenge?

Non-human species : I have grouped these three questions together for convenience. In so far as genome editing provides the potential tools to do more accurately and in a wider range of applications than 'conventional' genetic modification, most of the existing ethical issues of genetic modification are all raised again, but in a more focused manner, but there are also some important points of difference.

When GM crops began commercial use in 1996, the supporting rhetoric was its unprecedented precision and the unlimited scope, compared with the uncertainties and restricted range of selective breeding. When examined more closely, however, methods such as random ballistic insertion did not seem like precision, and many of the more appealing applications proved difficult like enhanced growth, nitrogen fixing, stress tolerance and nutritional enhancements. Such second and third generation crops are few. The vast majority of GM use remains two 20-year old traits, herbicide tolerance and insect resistance.

Public acceptability suffered greatly because such applications brought no tangible benefits to consumers or retailers, were perceived to carry long term environmental and health risks, and were imposed without choice. By altering individual nucleotides in the DNA sequence, genome editing seems to have the potential to deliver belatedly the claims for precision and perhaps at last enable the wide range applications, and does not normally involve transgenesis from other species. Some of these could have significant impact on ethical concerns raised

about some aspects of genetic modification, and may thereby also change its acceptability to some sections of the public.

In the case of animals and plants, most of the ethical issues which we originally identified in 1998 in our *Engineering Genesis* study (which was the first major UK work on the ethics of GM animals and crops) still hold true. See in particular our discussion of issues of principle, including

- the sense in which genetic modification is similar to or different from selective breeding (Chap 3) or other breeding methodologies

- the extent to which genetic modification raises issues of naturalness (Chaps 3 & 5)

- whether altering genes in an organism violates a concept of evolved ecological wisdom, or a sense of God's best design or more specific religious criteria (Chap 3)

- the extent to which the intrinsic value (as distinct from to the welfare) of animals should restrain what modifications of animals might be done (in our case the primary examples were all medical applications : xenotransplantation, pharmaceuticals in the milk of large animals and mouse models of human cancer (Chap 5)

- an ethical distinction drawn on the related issue of large animal cloning from the acceptability of use of sheep for special medical uses and the more controversial routine use of cloning elite breeding stock in food animal production (a distinction which prefigured the ongoing debate between the European Parliament and Commission). (Chaps 3 & 5). This distinction is likely to become relevant to genome editing as the techniques seem set to enable the modification of food livestock animals for production to be a serious prospect for the first time.

As a result of this study I have identified what I consider to be a set of main value criteria against which different stakeholders and publics assess genetically modified crops, as follows:

Scientific rationality - technological progress : the main technical and commercial drivers
Commercial values - economic growth, jobs, competition
Theological and philosophical values - is switching genes right or wrong?
Ideological values - industrial vs organic agriculture
Risk – uncertain outcomes; precaution; when do we know enough?
Trust – government, regulators, companies, NGO's
Food security - needing new technologies for food security
Development - whether or not GM helps or hinders global justice for the poor
Benefits – conflict of goals and interests among (e.g.) companies, consumers, the global poor.
Policy control & Democratic participation - who decides on GM issues and on what criteria?

Underlying these are social ethical issues such as equity, access, justice, power imbalances, the imposition of values and policies on the vulnerable by those holding commercial or intellectual power, human choice (especially to be able to choose foodstuffs and to avoid a potential risk).

There are also contextual issues such as undue power of transnational corporations to determine what happens, the predominance of applications of mainly commercial goals

which marginalise less profitable human benefits, the commercial and regulatory context within which it is often too expensive for local applications of genetic modification, the intellectual property context in which there is an imbalance towards large and rich organisations.

There are also contextual issues such as undue power of transnational corporations to determine what happens, the predominance of applications of mainly commercial goals which marginalise less profitable human benefits, the commercial and regulatory context within which it is often too expensive for local applications of genetic modification, the intellectual property context in which there is an imbalance towards large and rich organisations.

What changes with genome editing?

Before considering ethical impact it is important to note a significant difference which is in potential for genome editing to do things hitherto not considered possible or economic in livestock and farm animals, and also potentially in pets, sporting animals like racehorses. In 1998 the conventional wisdom was that no application had emerged in molecular genetic modification to improving the characteristics of farm animals for food production that was not more readily achieved by advanced selective breeding methods. Genome editing now has the opportunity to make changes to production and health characteristics, such as Whitelaw's work at the Roslin Institute in seeking to create genome edited UK pigs that would be resistant to African Swine Fever, and other work on the genetic dehorning of cattle.

But whether genome editing makes a major difference to ethical issues and public acceptability is a complex question depending first on what is deemed to be 'genetic modification' by experts and in the perception of different publics (which is not necessarily the same thing), and secondly on what is considered ethically acceptable or not by whom.

First what is genetic modification and what is not among the following?
1. Natural mutations : useful mutations *known* to exist in nature
2. Selected naturalness : selecting for a 'known' mutation over many generations
3. Random mutagenesis : artificially induced modification (e.g. radiation)
4. Induced naturalness : genome editing to create a known mutation of the plant species in plants that do not have it
5. Single novel modification : genome editing to create a 'foreign' mutation which exists in another species but not in host species (single base)
6. Multiple novel modification : the same as 5. but with many base changes
7. Transgenesis : adding a gene construct derived from other species
8. Synthetic biology : adding an entire metabolic pathway from combinations of modules derived from many diverse species
9. Induced Knockout : disabling a gene by 'conventional' genetic methods (e.g. in the original GM tomato paste and *FlavrSavr* tomato)
10. Internal Knockout : disabling a gene by genome editing

Putting it in terms of what people would accept, in increasing order of tolerance :

Someone might accept ...	Allowed	Disallowed
Only naturally alteration of a plant's natural genetic make-up	1,2	3-10

Artificially creating a natural mutation or breed-able mutation	1, 2, 4, 10	3, 5-9
Creating a mutation from another species	1, 2, 4, 5	3, 6-10
Creating a mutation not known to exist anywhere	1-5, 6, 10	7, 8
No mixing of genes across species, but OK within species	3, 4, 10	4-9
Mixing genes across fairly close species	1-6, some 7,10	some 7, 8, 9
Mixing genes across any species	All	None

Putting it in terms of the main objections, in decreasing order of impact :

Objection	Allowed	Disallowed
Artificially altering a plant's natural genetic make-up	1, 2	3-10
Principled objection typically from advocates of organic agriculture to the 'conventional' agricultural system	1, 2	3-10
Artificially creating a natural mutation or one that would have been possible by breeding	1, 2	3-10
Creating a mutation that has 'never' existed	1, 2, 4, 5, 6	7, 8
Mixing genes across *any* species	1-6, 10	7,8,9
Mixing genes from a remote species (e.g. fish gene in a strawberry)	1-6, some 7, 10	8, 9, some 7

avoiding transgenesis would be effective for those whose basic concern is about mixing genes across species or violating evolved or God-given 'barriers'. The notion that the edited sequence is capable of occurring naturally would be attractive if one's objection was to creating an 'unnatural' gene construct. On the other hand, it would not impress those for whom any genetic alteration beyond selective breeding is unacceptable, a philosophical objection, or people afraid of scientists 'tampering with our food', which has elements of risk and revulsion.

Genome editing in animals p.10 : What overall impact might genome editing have on animal lives? Can genome editing be expected to contribute to or inhibit the replacement, reduction or refinement (the '3Rs') of the use of animals in research?

Does genome editing give rise to special moral considerations about generating artificially modified animals for research (including disease models in large or highly sentient animals) or for trivial/ commercial reasons (*e.g.* 'toy' pigs)?

Similar issues arise as for genetically modified animals, and will vary from application to application. I include a speculative table of some applications and what might be the issues raised and acceptability. This is not based on any empirical data, but is my own prediction as one who has worked on this field since the early 1990's.

Postulates of Acceptability : Genome Edited Animal Applications

	Food Animal with Enhanced Growth / muscle	Food Animal Resistant to Serious Animal Disease	Food Animal preventing disease going into Humans	Large Animal 'Model' of Human Disease	Pig to provide Human heart transplant
Ethical	No?	Yes	Yes	Yes	?
Welfare	No	Yes	Yes	No	No
Risk/Harm	Animal & Human	(Human)	(Human)	Animal	Animal & Human
Benefit	Food	Animal	Human	Medicine	Medicine
Trust	No	Possibly	Yes?	Yes?	?
Vision	No	Possibly	Yes	Yes	?
Choice	Yes	No	No	Yes	Yes
Media Profile	No	Yes?	Yes	Yes	?
Overall	*No*	*?*	*Yes?*	*Yes?*	*No?*

Genome editing will act as the latest in the succession of new techniques which increase the demand for research animals, notwithstanding all the good work being done in 3Rs to reduce, refine and replace. The net effect is difficult to predict but my guess is that any positive effects of genome editing on the 3Rs will be overwhelmed by the increased applications requiring animal research.

The question of trivial use of animals was raised by such events as creating cloned cats to replace a dead pet. If the techniques are indeed as easy as supposed, there will need to be a regulatory change to outlaw trivial uses of animals arising out of genome editing.

> **pp.7-8 What obligations do scientists involved in developing and using genome editing technologies owe to society and what freedoms should society allow to these scientists? Do genome scientists have any special obligations to society that are distinct from those of other scientists?**

The sad history of genetic modified food is the case in point of the failure of the notion that, on sensitive technologies such as genetic manipulation, scientists know best and should be left to their own devices. Genome scientist have a special obligation by virtue of the public sensitivity of the technology, as would be the case in other fields, such as my former one of nuclear fuel research.

It is a matter of deep regret that HFEA has already agreed to license the first experiments on gene editing human embryos before there has been a substantial public debate on the whole trajectory of such research through to the potential of therapeutic and even non-therapeutic germ line editing. Such a debate was called for in September by Wellcome Trust and the Medical Research Council, but is now circumvented by what many will consider to be the premature granting of this licence on very speculative research. In this sense, HFEA's decision gives undue powers to scientists. It is of some concern that legal aspects have become now dominant over ethics in this area.

> **pp. 7-8 To what extent is the development of genome editing valuable as a pure research tool, and to what extent is its value dependent on envisaged practical applications?**

In the case of editing in human embryos, where the embryo is accorded a 'special' status, the ethical justification as a pure research tool is not sufficient. A human embryo is not just a laboratory reagent. The case for embryo research is predicated on the realistic expectation of a significant medical understanding, and I would argue that it needs to have a practical application that is not a vague hope but one seriously expected, for which a research and application trajectory can be mapped out to demonstrate that it is a reasonable expectation on the basis of current knowledge. I am very concerned that the Francis Crick application just today allowed by HFEA is problematic on those grounds, in the absence of seeing on what grounds it has been argued to be necessary. On the face of it, it seems unlikely that knocking each of four genes out will make anything like that sort of case.

> **p.8 What other issues do you feel need to be discussed in the context of genome editing? What do you consider to be the issues of greatest moral concern raised by genome editing?**

- Hype and raised expectations
- Pushing the techniques too fast, especially to premature human applications
- Researchers playing political power games to enable them to carry out the research they want with minimal public scrutiny or ethical control
- Pressure from scientists and Department of Health to allow germ line gene editing
- The claim for human enhancements using genome editing
- The illusion of 'designer babies' being promoted in the media.

p. 12-13 Biomedical Applications

What are the significant decisions that need to be taken before therapeutic use of genome editing may be contemplated (for non-heritable and heritable genetic changes) and who should have the responsibility for those decisions?

I am concerned that this question is phrased in such a way as to contemplate genome editing as though it might be a realistic prospect. In view of the serious an unpredictable risks involved in germ line modification, both to the individual concerned and to his/her subsequent generations, I can envisage no situation where a clinical procedure to perform heritable genetic changes could be tested and approved without creating what are in effect experimental babies, which would be monstrously unethical, and moreover such testing would be necessary on a large scale to determine effects through several generations. One would need a very large 'medical exception' to bypass what are the normal necessities of clinical testing. Nuffield should be very careful not to raise hopes or fears of germ line applications that will probably never happen or only under rare and exceptional cases. I think you question is ill-expressed.

I think there will be clinically preferable routes to germ line modification, such as PGD, which makes the question of research with germ line modification in mind highly dubious.

Research which involves the genome editing of embryos with other applications than germ line modification as its expressed aim might sometimes be justifiable along the lines I set out above, which I repeat here. The case for embryo research is predicated on the realistic expectation of a significant medical understanding, and I would argue that it needs to have a practical application that is not a vague hope but one seriously expected, for which a research and application trajectory can be mapped out to demonstrate that it is a reasonable expectation on the basis of current knowledge. However, bearing in mind the novelty of the techniques, it seems greatly premature to do such research until a great deal more is understood of off-target and other side effects.

Are the benefits and costs of treatments that involve genome editing likely to be distributed equitably (or any more or less equitably than existing or alternative treatments)? In what way might genome editing differentially affect the interests of people in vulnerable or marginalised groups?

Having in the past experienced two failed IVF procedures, the disparity between need and cost is a major issue. This is a present issue, which genome editing is likely to make worse, because of expanding the range of conditions for which IVF might be used. Steps must be therefore be taken to ensure that these are not available only to the rich and fortunate in our societies.

What other important questions should or might we have asked in this section?

Under what circumstances somatic or germ line changes might be made and whether this should be restricted to medical application. I refrain from comment, beyond what I have just said, except to say that modification for 'enhancement' purposes seems highly unlikely for the same reasons, but needs to be outlawed to prevent the modern equivalent of quack doctors from misleading the gullible.

A comment on the Call for Evidence

My final comment is that the call for evidence document was opaque and difficult to understand. It was written in a style that communicated to me : 'this is only for certain sorts of academic cognoscenti; others should keep away'. It presented the questions in what seemed to be unnecessarily complex social science framed conceptions and unnecessary jargon when ordinary English would have sufficed. On the first page, the paragraph beginning "We think it is impossible ..." was a masterpiece of poor style. You could have said the same thing much more clearly and in half the words. Even the English was strange at times; I have never heard of the expression 'forsworn' in relation to technology (p.4), and even referring a dictionary still made no sense, and I am a writer familiar with a wide variety of English usage. Why the continual use of 'direction of travel' for a technology, why not just say 'direction' or trajectory'. On p.5 'Insight: what are the relevant perspectives and the issues they foreground? ... How are different actions and outcomes value, and on what basis?' What does that mean, in plain English? It has not communicated to me what is being asked. One could repeat this sort of complaint elsewhere in the document. This is not up to Nuffield's usual standards.

On a practical point, it would also have helped if there was a .doc version to be able to put my responses to your actual questions instead of cutting and pasting out of a PDF file.

About myself

I am managing director of the independent consultancy Edinethics Ltd., working on the ethics and public engagement of emerging technologies. I hold doctorates in chemistry and in theology. After working 15 years as a chemist in nuclear energy research, risk regulation, and energy policy, I became Director of the Church of Scotland's Society, Religion and Technology Project (SRT) from 1992-2007. In this role I did pioneering ethical assessment of many emerging technologies including GM crops and animals, cloning and stem cells. I have worked extensively on nanomedicine and related technologies from 2003 to the present, in a series of EC projects and am a partner in the NanoAthero EC FP7 project on nanodevices to detect and treat atherosclerosis.

An integral part of my work has been in developing and writing public engagement tools with Perry Walker formerly of the New Economics Foundation, notably in Democs/Decide card games and Open-up argument map concepts. I have written games on nanomedicine, human enhancement, stem cells for therapy and for toxicity testing, GM crops, and synthetic biology. He has also worked on the implications of distributed healthcare for patients, carers, medical staff and the healthcare system, using the ethical matrix method.

I was a former member of the Scottish Science Advisory Committee, the Societal Issues Panel of Engineering and Physical Sciences Research Council, the Public Affairs advisory group of Biotechnology Research Council, the Nanotechnology Engagement Group, and the bioethics working group of the Conference of European Churches. I am a member of the Advisory Board of the Institute of Nanotechnology, of the Edinburgh University Research Ethics Committee, and the AWERB committee of the Roslin Institute.