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Nuffield Council on Bioethics: Emerging Biotechnologies

Response from the PHG Foundation

Introduction

The Foundation for Genomics and Population Health (PHG Foundation) is a non profit making charitable company and the successor body to the UK Public Health Genetics Unit. Its overarching purpose is to foster and enable the application of biomedical science, particularly genome-based technologies, for the benefit of human health. Among its specific objectives is the promotion of a social and regulatory environment that is receptive to innovation, without imposing an undue or inequitable public burden. The Foundation has a particular interest in the way that new technologies are translated within health services, in genetic research and its impact upon clinical and public health services.

General Comments

A core element of the work of the PHG Foundation has been to assess the scope and possible impact of emerging genome-based technologies, as well as identifying potential barriers to their implementation. In most cases, this has included an assessment of the ethical, legal and social implications associated with these biotechnologies. This consultation response is therefore based upon this body of work, together with a number of reflections and comments that build upon our knowledge of the field generally. We have therefore been intentionally selective in our responses to the consultation questions.

Consultation questions

1. **How would you define an 'emerging technology' and an 'emerging biotechnology'? How have these terms been used by others?**

No comment.

2. **Do you think that there are there features that are essential or common to emerging biotechnologies? (If so, please indicate what you think these are.)**

No comment.

3. **What currently emerging biotechnologies do you consider have the most important implications ethically, socially and legally?**

A number of emerging technologies in the genomics field have profound ethical, legal and social implications. Cell-free fetal nucleic acid technologies allow fragments of fetal DNA to be detected in maternal blood. This technique was first described in ground-breaking work by Dennis Lo and colleagues in 1997[1], and further work has built upon this discovery such that it is now possible to reliably detect genomic changes that are inherited from the father, (such as rhesus status, or susceptibility to x-linked disease), the sex of the baby and both dominantly and recessively inherited genetic conditions. The PHG Foundation reviewed the use of this technology for non-invasive prenatal diagnosis in 2009 and published a report[2], supported by an appendix

[1] Lo YMD *et al* (1997) Presence of fetal DNA in maternal plasma and serum. *Lancet* **350**: 485-487
[2] Caroline Wright (2009) Cell-free fetal nucleic acids for non-invasive prenatal diagnosis: Report of the UK expert working group. PHG Foundation.

reviewing many of the associated ethical, legal and social issues[3]. Many commercial companies are now exploring these technologies, particularly for targeted use in Down's syndrome screening, and the biggest players (such as Sequenom) are predicting a launch date of late 2011- early 2012. The transformative nature of the cell-free fetal blood test lies in its potential to change a series of discrete tests into a single probabilistic intervention. Existing tests for conditions such as Down's syndrome involve a risk based assessment based upon maternal blood test, followed by a confirmatory invasive test (through chorionic villus sampling or amniocentesis). The current rates of uptake for these invasive tests in the UK are around 2% (bearing in mind that between 0.25% - 1% of these invasive interventions result in miscarriage). The prospect of an easier, earlier, and safer test could result in much higher demand for cell-free fetal testing: some commentators such as Ainsley Newson (University of Bristol) have suggested that the levels of uptake for this novel test could be closer to 100%[4].

Another emerging technology is the ability to sequence the entire human genome using 'next generation sequencing'. This term describes a variety of different methods, combining novel technologies and increased automation, which allow quicker and more reliable sequencing of the individual DNA bases that form the human genome. Although these technologies remain in the research phase, as processes are honed and streamlined, there is a real prospect of more widespread adoption within clinical settings in the short term, as the costs of these technologies become more competitive. The PHG Foundation has recently undertaken a review of these technologies, the economic factors linked with their adoption, and the ethical, legal and social issues that might arise from their implementation in clinical settings within the NHS. This has suggested that whilst there are no fundamentally new ethical associated with these technologies, that they are likely to be unprecedented in their scale, particularly if whole genome sequencing technologies come into widespread use. For this reason, a number of pressing issues should be urgently addressed by a wide constituency, such as the role of informed consent, the testing of children and the generation and use of information derived from whole genome sequencing that is additional to the immediate clinical question. The PHG Foundation is in the process of finalising a report on the impact of whole genome sequencing upon the NHS, with a particular focus on its implementation within clinical settings. This report will be available in Autumn 2011.

These two technologies, used in combination, could be very powerful and have important consequences especially in the context of decisions about reproductive choice. Together these technologies might allow for the selection (or termination) of embryos or fetuses on an unprecedented scale, which could influence how disability is viewed and tolerated within society in the future.

4. Are there examples where social, cultural and geographical factors have influenced the development of emerging biotechnologies (either in the past or currently)?

The UK has had a liberal approach to technologies which utilise human embryos both in research (such as research into chimeras or hybrid embryos) and within clinical settings (such as their use in preimplantation genetic diagnosis). Nevertheless, social

[3] Hall A *et al* (2009) Ethical, legal and social issues arising from cell-free fetal DNA technologies: Appendix III to the report: Cell-free fetal nucleic acids for non-invasive prenatal diagnosis. PHG Foundation.

[4] Van den Heuvel A *et al* (2009) Will the introduction of non-invasive prenatal diagnostic testing erode informed choices? An experimental study of health care professionals. *Patient Education and Counseling* **78** (2010) 24-28; Vence T 13 June 2011 Prep for prenatal dx. Genome Technology News.

and cultural issues were highly pertinent to the debate concerning the granting of research licences for work on hybrid embryos by the Human Fertilisation and Embryology Authority. An informative report setting out some relevant issues was prepared by the Academy of Medical Sciences[5].

The Academy followed up this work with a programme of public engagement activities exploring how the public regard animals containing human material. This work contained both qualitative and quantitative elements, and used mixed methodologies including focus groups and qualitative interviews. Some differences emerged between focus groups that were selected on the basis of certain characteristics (including those with experience of serious medical problems or for whom religious faith or animal welfare was important)[6]. This suggests that identifying public responses to biotechnologies may be a complex matter, and that there may be heterogeneity of views.

The prohibition of the use of stem cell lines derived from embryos in the USA is another high profile example of how religious convictions have influenced research agendas.

5. Are there examples where social, cultural and geographical factors have influenced public acceptance or rejection of emerging biotechnologies?

See comments above.

6. Are there examples where internationalisation or globalisation of research, markets and regulation have influenced the development of emerging biotechnologies?

In the emerging area of whole genome sequencing technologies, pockets of expertise have developed both in higher income and emerging economies. Indeed China represents one of the world leaders in whole genome sequencing capacity (if this is defined in terms of generating the assay or sequence of bases from the raw DNA). However, other countries might have increased capacity to interpret that sequence data (in order to determine which variations from the reference genome are likely to be associated with pathological changes or disease).

7. How have political traditions (such as liberal democracy) and political conditions (e.g. war) influenced the emergence of biotechnologies?

We have already commented on the liberal democratic tradition within the UK, in relation to hybrid embryos.

8. Are there ethical or policy issues that are common to most or many emerging biotechnologies? Are there ethical or policy issues that are specific to emerging biotechnologies? Which of these, if any, are the most important?

In the context of genomics, a number of themes are important in the policy debate. Our understanding of the relative contributions of genomics and environmental influences to the development of diseases (particularly common complex diseases) is in its infancy. We do not yet understand properly how combinations of genetic variants and environmental factors such as lifestyle and diet combine to cause disease in some people and not in others. Lack of knowledge about the pathogenicity of particular variants, and how this knowledge might be used more widely in health care, but also within society more generally (by employers or insurers) suggests that it is sometimes difficult to meaningfully

[5] Academy of Medical Sciences (2007) Inter-species embryos: a report for the Academy of Medical Sciences.
[6] Ipsos Mori et al (2010) Exploring the Boundaries: public dialogue on animals containing human material.

discuss the risks associated with genomic research. There are therefore limitations in using the existing model of informed consent (used to legitimise individual participation in research).

Another important issue is that there is a tension between an individualistic approach to research processes and outcomes, and a population based approach that has customarily been used in public health interventions. Thus the ethical basis for obtaining consent to research is often directed at gaining consent from the individual: the outcomes of research might also be focused at the individual (in terms of informing an appropriate therapeutic response via pharmacogenomics or stratified medicine). Yet in the future, many of the most pressing ethical and policy issues, arise because these might be implemented on a population basis (by state funded institutions and services).

The emerging market for direct-to-consumer testing suggests a need for an integrated and creative regulatory response[7]. Direct-to-consumer testing allows the public to access genetic or genomic testing without intervention or support from a knowledgeable health care professional. This raises a number of concerns about the clinical validity and utility of the tests being offered, and that individuals might be harmed if they do not understand the potential benefits and risks associated with testing. The adequacy of consumer protection and advertising legislation and regulation is particularly relevant in this context.

9. Do you think that some social and ethical themes are commonly overlooked in discussions about emerging biotechnologies? If so, what are they?

An area that seems to be consistently overlooked is the need for robust empirical work (both qualitative and quantitative) on public opinions relating to these biotechnologies. Our work also suggests that there is often a need for robust systems to collect relevant evidence that can inform policy development. Typically evidence is generated in a fragmented fashion and may be anecdotal or lack statistical rigour. Many measures of cost-effectiveness are insufficiently developed to take proper account of how predictive genetic information can be used preventatively to stop future ill-health: these measures are also likely to be inadequate to take account of complex bio-technologies.

10. What evidence is there that ethical, social and policy issues have affected decisions in (i) setting research priorities, (ii) setting priorities for technological development, and (iii) deploying emerging biotechnologies, in either the public or private sector?

In the field of genomics and genetics, the vast majority of the research funding is targeted at primary research, rather than at translational research. This is a consistent finding across many countries. Given that the full potential of a technology may only be realised through implementation (rather than research), this finding suggests that research in this area could be organised more effectively[8].

11. What ethical principles should be taken into account when considering emerging biotechnologies? Are any of these specific to emerging biotechnologies? Which are the most important?

There are a number of themes which have consistently arisen in relation to emerging technologies. For example, in the public engagement work carried out into the use of animals containing human genetic material, participants seemed to make an

[7] Wright CF *et al* (2010) Regulating direct-to-consumer genetic tests: what is all the fuss about? *Genetics IN Medicine* (in press)

[8] Khoury MJ *et al* (2007) The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med* **9**:665-674.

assessment of the proposed utility of the technologies (in which there was a trade-off between the purpose of the research and concerns about the process, which included consideration of the severity of the condition that it was intended to ameliorate, and the identity of those who were likely to benefit from the research)[6]. Thus participants in the research tended to take a view of the legitimacy of the novel technology after weighing up its perceived risks and benefits.

Other ethical reasoning identified as possible barriers in the 2007 Academy of Medical Sciences report[7] included the 'yuk' factor and 'slippery slope' judgements. The public engagement work also identified factors such as 'what it means to be human'. In our view, some of the most problematic issues concern the impact of these potential risks upon future generations.

12. Who should bear responsibility for decision making at each stage of the development of an emerging biotechnology? Is there a clear chain of accountability if a risk of adverse effects is realised?

Policy making should be as inclusive as possible, taking into account the views of multiple stakeholders. At the same time, the very nature of these emerging biotechnologies means that uncertainties are inevitable. There should be transparency about areas of ignorance as well as the balance of likely risks and benefits.

13. What roles have 'risk' and 'precaution' played in policy decisions concerning emerging biotechnologies?

One problem in the field of genomics is that there is a tendency towards researchers overstating the likely benefits of the research and understating the risks involved. Others have commented that this is an inevitable outcome of the struggle to gain research funding, because researchers tend to 'talk up' their applications, with the result that 'there is a tendency to oversell'[9] .

14. To what extent is it possible or desirable to regulate emerging biotechnologies via a single framework as opposed to individually or in small clusters?

The debate surrounding inter-species hybrids might be helpful here: in their 2007 report, the Academy of Medical Sciences noted the requirement for a conceptual and regulatory framework in order to inform the approach towards transgenic and chimeric animals containing a significant amount of human genetic material. They also suggested that decisions about the legitimacy of research should take place on a case-by-case basis in order to allow a body of judgement to be built up (rather than the matter be determined by primary legislation). We believe that this is sensible model that builds on existing knowledge, but is responsive to emerging research (as well as wider social factors such as shifts in public and professional opinion)[5].

15. What role should public opinion play in the development of policy around emerging biotechnologies?

In many instances, identifying and taking account of public opinion is a vital part of developing policy around emerging biotechnologies. However, depending upon the context, public opinion should not necessarily be determinative. We favour an approach that takes account of multiple stakeholders and the pluralistic nature of public opinion: a deliberative democratic approach.

[9] Evans J et al (2011) Deflating the Genomic Bubble. *Science* **331**:861-862.

16. What public engagement activities are, or are not, particularly valuable with respect to emerging biotechnologies? How should we evaluate public engagement activities?

Our experience of public engagement in the context of genomic technologies (based upon knowledge of the literature rather than primary qualitative research) is that in general, the general population demonstrates a low level of genetic literacy. This is the case regardless of the medium (oral or written) or route (online or paper hard copy) of that communication. This suggests that one difficulty might be in ensuring that publics are sufficiently educated to understand the risks and benefits that are being proposed. But merely to regard these educational needs in terms of a 'deficit' that needs to be filled should be regarded as paternalistic and outdated.

17. Is there something unique about emerging biotechnologies, relative to other complex areas of government policy making, that requires special kinds of public engagement outside the normal democratic channels?

In our view, genomic and genetic technologies do not justify a unique or singular approach: we do not subscribe to genetic exceptionalism. We would speculate that each type of emerging technology might have a particular package of issues associated with it, and as such, proposing a single mechanism for public engagement outside the normal democratic channels might not be justified. However a number of different strategies have either been proposed or implemented in the past. When the revised Human Embryology and Fertilisation Act (2009) was debated, there were wide-ranging discussions about the scope of acceptable research on embryos, and one proposal was that a permanent parliamentary ethics committee should be established (which would include representation from lay members). Other strategies have included setting up a panel of representative individuals who have particular knowledge of or interest in a subject area, such as the consultative panel convened by the Human Genetics Commission.

One novel aspect of emerging genomic technologies is the extent to which technologies such as whole genome sequencing may be accessed via the internet on a direct-to-consumer basis in advance of other publicly funded routes. This suggests that different sectors of the public might have access to these technologies in unprecedented ways (such as social networkers) and that novel strategies might need to be employed to canvas their views accurately. Alternatively creative use of proxies could be used as a measure of public opinion[10]. The use of novel direct-to-consumer testing is arguably in itself an emerging biotechnology that might require an integrated and creative regulatory response[11].

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[10] Wright CF *et al* (2010) Size of the direct-to-consumer genomic testing market. *Genetics IN Medicine* **12(9):**594.

[11] Wright CF *et al* (2010) Regulating direct-to-consumer genetic tests: what is all the fuss about? *Genetics IN Medicine* (in press)