ESRC genomics network

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Response to House of Lords Science and Technology Committee call for evidence on Genomic Medicine from the ESRC Centre for Genomics in Society (Egenis)

Egenis carries out a wide range of research on the interpretation and implications of contemporary biosciences. Specific areas of expertise relevant to the preparation of this evidence are the philosophy of biology, especially emerging areas of genomic and post-genomic science, regulation of biomedical technologies with a special focus on stem cells, and the use of family histories in the clinical management of common polygenic disease.

What is the state of the science? What new developments are there? What is the rate of change?

1. We must begin this response by expressing some doubts about what is meant by 'genomic medicine'. This would most naturally be taken to refer to systemic interventions in overall genomic function, but as yet no therapies of this kind exist. The term 'genomic' might be taken to contrast with more traditional genetic medicine, involving the diagnosis, prediction, and treatment of monogenic diseases, but these might also be thought of as encompassed by the broader term 'genomic'. It is common to understand the investigation of multifactorial, polygenic disease as genomic and we shall comment below on some research here in this area. Given that this includes the common killer diseases in the West (cardiovascular disease, cancer, diabetes) this is presumably an area that deserves serious attention. Anticipated developments such as the use of RNAis to block transcription of specific regions of the genome would probably be considered genomic.

2. The science in this area is developing at an extraordinary rate which, we suppose, provides a strong reason for interpreting the term 'genomic' in as broad a way as possible so as to encompass developments that are as yet difficult even to foresee. A general trend in those developments is a move away from a vision as the genome as a code or program intrinsically containing the future development of the organism, but rather to see the process of development as involving constant two-way interaction between the genome and other elements of the cell and even of the wider environment. The 'central dogma' that proposed one way causal processes running from DNA to RNA to proteins is in terminal decline if not quite yet dead. One area that is opened up by this recognition of constant two-way interaction is the possibility of epigenomic medicine, for example medical intervention directed at dysfunctional methylation patterns in the genome, increasingly implicated in cancer aetiology. A second possibility that can be anticipated partly as a result of this general reform of our understanding of the genome is the eventual application of systems biology based insights to medicine. And third, following on developments such as the human microbiome project (http://nihroadmap.nih.gov/hmp/), we anticipate medical implications for the increasing understanding of the symbiotic relations between humans and ectosymbiotic microbes. These include increasing awareness of the ways that humans and microbes mutually modulate gene expression, and therefore should surely be seen as a potential expansion of genomic medicine.

3. We assume that stem-cell based therapies would be included under the genomic rubric, since one interpretation of the central challenge in this area is the attempt to elicit specific patterns of genomic expression appropriate for specialised cell-types in unspecialised cells (or cells rendered effectively unspecialised). Moreover the spontaneous rearrangements of genomes observed in cultured cells are phenomena with wide implications not only for medical applications of stem cells but even for general understanding of life processes. Stem cell research has been constituted as an emergent scientific field of inquiry connected to hopes of biomedical innovations that will lead to the cure of major degenerative diseases. While the transplantation of haematopoietic stem cells has become a routine treatment in blood disorders such as leukaemia in the last 30 years, stem cell science is still in its early stages as regards the development of treatments for major diseases such as diabetes, cardiovascular diseases and neurodegenerative diseases. To date no clinical research has of yet been carried out with cells derived from human embryonic stem cells while tissue engineering uses of adult stem cells have only recently moved into the clinical trial stage, e.g. trials with autologous bone marrow stem cells for cardiac repair.

4. A very wide range of medical and other issues are raised by the growing storage of human genomic and genetic data. We cannot comment in detail on these here, but will mention some specific issues under the heading of regulation and translation.

5. Although all these are areas under active investigation at Egenis it is too early to predict in any detail the impact of such scientific developments on medical practice. None of the possibilities mentioned in paragraph 2 yet exist as part of medical practice, though in each case there are strong arguments for

anticipating that this will change over the next few years or decades. We mention them to emphasise the fast-moving and open-ended nature of the science and the need that any general account of the state of this science should be as broadly conceived as possible to make room for these as yet undeveloped, but potentially very powerful, medical technologies.

Policy Framework

6. Although there is no particular body dealing with genomic medicine, the existing regulatory and advisory bodies (especially within the DH) inevitably enter and regulate the field locally, through, e.g., cancer, heart disease, and epidemiology regulations. This leads to a complex and fragmented regulatory landscape. While it provides flexibility, it also enables a "pick and choose" policy, which can result in legal uncertainty and inconsistent patients' protection.

7. Direct-to-consumer genomic tests are inadequately regulated by existing legislation on quality and safety of diagnostic devices. The risk of adverse psychological effects on the individual and, very importantly, family members needs to be addressed. This has been confirmed by in the Draft Additional Protocol to the BioConvention on genetic testing for health purposes.

8. Legislation is desirable concerning biobanks (genetic data banks) setting up general rules regarding consent, privacy issues, benefit sharing, funding and management. Crucially, genomic studies are never restricted only to genetic/genomic data, but encompass medical and other data. Reconciliation between data protection legislation and provisions on biological material is required. This also raises very wide-ranging issues of potential genetic discrimination in health and life insurance and employment, especially due to the limited scope of the definition of genetic testing and the lack of clarity with regard to what is understood by genetic data.

Note: paragraphs 9-13 are specifically addressed to stem cell medicine.

9. Because of ethical problems connected to the sourcing and therapeutic use of stem cells – especially human embryonic stem cells - and the assurance of the quality and safety of stem cell technologies in human application, a complex and intersecting set of regulatory mechanisms and authorities apply to them in the UK. These include the Human Fertilisation and Embryology Authority (HFEA), the Medicines and Health Care Products Regulatory Agency (MHRA), the Human Tissue Authority (HTA) and the NHS research governance framework - and their regulatory responsibilities following the transposition of European regulation into UK law. As with other biotechnology-based medicinal products, advanced therapy medicinal products now fall under the centralised authorisation procedure of the European Medicines Agency (EMEA).

10. In broad terms, the three UK regulatory authorities have remits with regard to the regulation of tissues and cells and on the basis of the transposition of the EU tissue and cells framework into the UK regulatory system. In accounting for the special status that was accorded to the embryo in the HFE Act 1990, research on and use of embryos and gametes falls within the remit of the

HFEA as competent authority under EU law, which also regulates fertility treatment. The regulation of the procurement, donation, processing, storage and distribution of tissues and cells for human application of all other tissues and cells now falls within the remit of the HTA. If cells and tissues are classified as a medicinal product, they fall under the licensing conditions of the MHRA as competent authority. In this case the HTA will only be responsible for the procurement, donation and testing of cells, while the manufacture, storage and distribution will come within the remit of the MHRA. By contrast, if tissue or cell treatments are not classified as medicinal product, the manufacture, storage and distribution will remain within the remit of the HTA. Final market authorisation of medicinal products containing cells or tissues will be granted through the EMEA.

11. While this may be seen as a flexible system allowing for the tailoring of requirements to the specific stem cell treatments under consideration, it is equally in danger of inconsistencies and the creation of friction through the potential creation of overlaps as well as the integration of expertise when it comes to assessing particular treatments from the point of procurement through to application in patients. Currently, there exists some regulatory uncertainty as to the division of responsibilities between the HTA and the MHRA. The translation of regulatory boundaries in terms of institutional boundaries of the two regulatory authorities raises tensions insofar as the requirements of manufacturing, storage and distribution may have implications for the way in which material is procured and the testing requirements that might apply before further processing.

12. Given the complexity of tissue and cell-based treatments, it is highly desirable that expert oversight reaches across the entire process from ethical procurement to the manufacturing and distribution of particular treatments/product groups rather than being centred on one or particular steps in the authorisation chain. Overall, in light of the fact that multiple regulatory authorities have remits within this area and current regulatory uncertainties among the authorities in this area, it needs to be assured that a regulatory process is put in place which defines the responsibilities and points of contact between the HFEA, the HTA, and the MHRA as well as associated bodies such as research ethics committees and GTAC (as the national ethics committee which advises upon the carrying out of trials on gene therapy).

13. The development of stem cell therapies is dependent upon the collaboration of scientists working in the bio-sciences (molecular biology, biochemistry) and medical scientists. With regard to the translation of technologies from the laboratory to the clinic, preliminary findings suggest that this exchange is dependent upon social factors which facilitate this exchange, and suggest that the extent to which resources are available for clinicians in engaging in translational research within the NHS and the incentives present to do so across different levels of training need to be addressed in furthering translational research.

What opportunities are there for diagnostics, therapeutics and prognostics, now and in the future?

14. It is important to distinguish between the opportunities for diagnostics,

therapeutics and prognostics in monogenic conditions and more common, complex polygenic conditions (e.g. coronary heart disease, most cancers, diabetes). The possibilities for screening for monogenic conditions is high (indeed it already occurs); there is only one or a few genes to locate and their penetrance (i.e. the extent to which they will cause the given disease) is very high. This makes genetic screening, coupled with standard treatment, cost-effective but only applicable to the small number of people affected by monogenic diseases. The opportunities for genomic medicine as applied to common, complex diseases such as coronary heart disease and diabetes are different. Although advances in genetics have led to the discovery of some genes linked to diabetes and coronary heart disease, there are no clinically validated genetic tests currently available. This is because such diseases are the product of far more complex gene-gene and gene-environment interactions which at present are not well understood (over 250 genes may be associated with cardio-vascular disease [CVD], for example). In relation to CVD, tests have been developed for a handful of 'best-known' markers (mutations connected with LDL metabolism, blood pressure, homocysteine) but it is not clear they are the most significant or best predictors (except for monogenic familial hypercholesterolaemia). It is also arguable they offer no current benefit over and above existing tests (e.g. cholesterol, BP, HDL/LDL ratio) and interventions are generally the same (Mediterranean diet, statins and blood pressure modification). This has not stopped companies entering into the market offering tests such as Cardio for heart disease (e.g. GeneticHealth in the UK). However, the predictive value of such tests is likely to be very low and so are not justifiable either in terms of NHS cost or clinical utility.

15. In the absence of any clinically valid genetic tests for CHD and diabetes suitable for widespread use, there has been a resurgence of interest in using family history as a 'proxy' for genetic risk. Family history also encapsulates other factors which are transmitted from generation to generation, such as lifestyle behaviours and environment, is cheap and can be delivered by in primary care. Its use is advocated in the National Service Framework for diabetes and coronary heart disease in the UK.

16. If family history is to be used as an 'alert' or 'risk marker' for common and complex diseases, it needs to be planned and implemented at central level within the NHS if it is to deliver. Research conducted at Egenis (in conjunction with the University of Nottingham) on behalf of the Department of Health indicates several key features of current practice which could be improved:

(i) Health professionals need very clear guidelines on what constitutes a 'positive' family history of common and complex diseases (and therefore indicative of genetic/familial risk).

(ii) Having identified familial risk, health professionals need guidance/training on how best to communicate this information as the different understandings of GP/nurse and patient can lead to mis-communication.

(iii) The lack of standardization amongst recording systems used by GP practices makes recording and using family history/genomic information currently difficult (our ongoing study found as many as eight different systems being used, all with different family history criterion).

It is important to note that genomic medicine does not have to be operationalised using high tech and expensive processes to have considerable clinical utility.

Note: References in support of empirical claims made in this evidence are on file and available on request.

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