

House of Lords Science and Technology Committee, Sub-committee on Genomic Medicine

Memorandum of Evidence prepared by Dr Steve Sturdy on behalf of the ESRC Genomics Policy and Research Forum, 15 April 2008

The ESRC Genomics Policy and Research Forum is part of the ESRC Genomics Network (EGN), a major investment by the Economic and Social Research Council (ESRC) dedicated to examining the development and use of the science and technologies of genomics. Established in August 2004, the Forum acts to integrate the diverse strands of social science research within and beyond the EGN; to develop links between social scientists and scientists working across the entire range of genomic science and technology; and to connect research in this area to policy makers, business, the media and civil society in the UK and abroad.

The Forum welcomes this opportunity to address evidence to the House of Lords Science and Technology Committee, Sub-committee on Genomic Medicine. Social science research on genomics illuminates a number of questions posed by the Sub-committee on Genomic Medicine, as follows:

1. Use of genomic information in a healthcare setting

1.1 What impact will genomic information have on the classification of disease? How will it affect disease aetiology and diagnostic labels?

1.1.1 Genetic information has had a significant impact on the diagnostic classification of a number of single-gene disorders. Even in single-gene diseases such as cystic fibrosis, however, genetic techniques have generally been assimilated in dialogue with existing clinical methods of diagnosis and treatment, resulting in modification rather than straightforward replacement of established disease categories (Kerr 2000; Hedgecoe 2003; Latimer et al. 2006). Simple reductionist models of “geneticization” consequently do not hold. Rather, the incorporation of genetic and genomic information and techniques into clinical practice, and the reformulation in practice of disease categories, depend as much on how that information comes to be used in the clinic as on basic scientific ideas of aetiology.

1.1.2 The impact of genomic information is even harder to predict when dealing with the much larger and epidemiologically more important class of common complex diseases. It is in relation to such diseases that new genomic techniques are likely to be most fruitful in identifying genes that confer an increased risk of disease. In most such cases, however, susceptibility genes confer only a relatively small increase in the risk of developing symptomatic disease, while a wide range of environmental, social and

lifestyle factors may contribute to the development of disease in the presence or absence of any genetic predisposition. Consequently, the impact of such information on the clinical classification and diagnosis of disease will depend upon a wide range of variables, including the size of the genetic contribution to risk and the availability of effective preventive or therapeutic interventions. The context of use, and the meaning and utility of genetic and genomic information in that context, will be a key factor in determining how such information will be incorporated into clinical practice and health care delivery.

1.2 How useful will genomic information be as part of individualised medical advice? What provisions are there for ensuring that the individual will be able to understand and manage genomic information, uncertainty and risk?

1.2.1 Utility for patients must be the starting point for considering how genomic information should be incorporated into medical advice and health care delivery. From the patient's point of view, genomic information may be read in a number of ways. In some cases, knowledge of a genetic predisposition may relieve feelings of guilt or responsibility for an illness. In other cases, however, identification of a genetic risk may entail an additional burden of responsibility on the patient. Indeed, the language in which medical and policy discussions are couched commonly tends to suppose that patients have a duty to take appropriate preventive or prophylactic action. But such action is not always in the patient's best interest: patients identified with BRCA1/2, for instance, often feel compelled to undergo prophylactic surgery out of a sense of duty towards dependent children or out of consideration for the presumed wishes of their family -- submitting themselves to operations which they would not have chosen solely on their own account (Hallowell 1999, 2006). Health care professionals and others also commonly use identification of a genetic susceptibility as an opportunity to offer advice on other forms of prevention including changes in behaviour or lifestyle. However, there is evidence that patients are less inclined to follow such advice than to seek specific medical interventions (Saukko et al. 2006). Increased testing for susceptibility genes may consequently lead to a corresponding increase in the numbers of "worried well" demanding medical monitoring and support (Bharadwaj et al. 2006; Lock et al. 2007). Any such increase will obviously have resource implications for the health services.

1.2.2 The language in which preventive advice is offered may play an important role in the failure to effect behavioural change among those deemed to be at increased genetic risk. Patients often have a complex multi-causal understanding of inherited risk and prevention that draws on knowledge of their own family history and the health of relatives (Lock et al. 2006). While lay ideas of kinship commonly differ significantly from genetic accounts of relatedness, knowledge of family history nonetheless provides a useful medium of communication between health care advisors and patients. In this respect, overly rigorous insistence on a strictly genetic understanding of relatedness may inadvertently lead to a failure of communication and foreclose on a valuable channel for offering meaningful advice on risk and prevention (Hall et al. 2007).

1.3 What are the implications of developments in genomic technologies for the training of medical specialists and other health professionals? Are there any gaps that need addressing? What is the assessment and planning for future needs in capacity?

1.3.1 Until recently, responsibility for providing genetic health care and advice has largely devolved onto genetic medicine specialists and genetic counselors. With increased knowledge of the genetic dimensions of common complex diseases, however, a much wider spread of practitioners are likely to find themselves called on to offer advice on genetic matters. There will therefore be a need not only to increase provision of specialist training, but also to integrate appropriate training in providing genetic health care into the core medical curriculum.

1.3.2 In view of the necessity, discussed above, of engaging with lay understandings of disease inheritance and causation, such training should not be confined to a scientific appreciation of disease genetics. It should also emphasise the value of family history as an effective means of structuring communication with patients, and should stress the importance of understanding that history from the patient's perspective as well as from a strictly genetic point of view.

1.3.3 Awareness of genetic risk necessarily has implications not just for individuals but also for their relatives. Patients' decisions about whether or not to disclose information about genetic risk to other family members are commonly guided by lay ideas about who counts as a relative, as well as by judgments about whether relatives will be able to cope with the knowledge that they are at risk (Clarke et al. 2005). Here too, sensitivity to lay understandings of kinship, and an appreciation of the dynamics of family life and the judgments that inform disclosure within the family, will be invaluable to the practitioner. This will involve far more than an understanding of the kinds of general ethical principles that are commonly taken to guide disclosure of medical information, but which often prove difficult to apply to complex concrete situations, particularly where family relationships are concerned. Experience suggests that training in such issues is often more effectively achieved by working through actual cases than by consideration of abstract principles.

1.4 Use of genomic information in a healthcare setting: conclusion

1.4.1 Genetic and genomic information represent a significant addition to the medical information available to health care practitioners and their patients. But the meaning and utility of that information in a healthcare setting is not determined solely by the possibility of estimating the extent of the genetic risk that patients face. It also depends upon the practitioner's ability to relate that risk to the patient's life and circumstances, including the social and moral complexities of family life. As more and more genomic information becomes available in an increasingly wide range of healthcare settings, it is important that practitioners learn to help their patients make sense of that information on their own terms and in their own interests.

2. Translation

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

2.1.1 As discussed above, practical returns on the identification of specific genetic risk in common complex diseases are diminishing, in view of the relatively low penetrance of most susceptibility genes, the confounding aspects of environment and lifestyle, and the resulting difficulties in drawing useful lessons or identifying useful interventions. It is possible that improved genomic understanding of disease aetiology may in time lead to novel forms of therapy, but such gains are likely to be piecemeal and unpredictable.

2.1.2 Developments in the field of pharmacogenetics, including the identification of genes for positive or adverse drug responses, are likely to follow a similar pattern to the identification of disease susceptibility genes. A number of single-gene pharmacogenetic effects have already been identified that may prove useful in practice, and it is likely that further such effects will be found. However, genetic explanation of remaining variations in drug response, and the development of effective tests, will be complicated in practice by factors including low penetrance and other sources of personal variation. There is thus a likelihood of significant but relatively localised pharmacogenetic gains in the efficiency and efficacy of drug use, but a revolutionary shift towards so-called “personalised medicine” is unlikely.

2.2 How meaningful are genetic tests which use genome variation data? What progress has been made in the regulation of such tests?

2.2.1 The question of the meaning of genomics-based genetic testing in medical practice and in patients’ lives has been considered above. These considerations also have implications for how the utility of new genetic and genomic techniques should be evaluated (Wilfond and Thomson 2000). Any assessment of utility should take account of the complex meanings that attach to genetic testing, and the ethical and social consequences that follow from the application of such tests. This would be best achieved by adopting recent developments in health technology assessment which pay explicit attention to the context of use, and which draw on new methods of engaging with users -- including both practitioners and patients -- to ensure that new technologies meet genuine needs (Lehoux and Blume 2000; Lehoux et al. 2004).

3. Policy Framework

3.1 Does the existing regulatory and advisory framework provide for optimal development and translation of new technologies? Are there any regulatory gaps?

3.1.1 Within the limits discussed above, significant public benefits are likely to accrue from pharmacogenetic targeting of medicines on those genetic sub-populations that are most likely to benefit. However, there are a number of ways in which the existing regulatory and policy environments are less favourable for such developments than they might be.

3.1.2 First, commercial incentives alone may prove insufficient to encourage commercial development, validation and marketing of pharmacogenetic interventions. Pharmaceutical companies continue to favour “blockbuster” models of commercialisation, and are generally reluctant to pursue

strategies that potentially segment their markets. Consequently, development of new genetically targeted drugs has been slow, despite high-profile exceptions such as Herceptin. Where already-licensed medicines are concerned, pharmaceutical companies are particularly disinclined to encourage the development of genetic tests that may lead to segmentation of existing markets. Development of such tests therefore tends to fall to small and medium-sized companies, which do not have the resources to pursue the large-scale clinical trials needed to demonstrate efficacy and stimulate demand. There is thus a serious risk of market failure in such areas. Policy measures to combat these problems might include extension of orphan drugs legislation to cover “orphan genotypes”, and increased funding from public sources for clinical studies to develop the evidence base in support of pharmacogenetic testing and prescribing (Melzer et al. 2005; Hedgecoe et al. 2006; Martin et al. 2006).

3.1.3 Secondly, while regulatory control over the licensing and marketing of medicines is chiefly exercised at EU level, regulation of genetic and other diagnostic tests remains a national responsibility, with considerable variation between member states. Also, licensing procedures for diagnostic tests generally require little information about clinical utility, so fail to generate the kind of information that would encourage uptake by clinicians and patients. Harmonisation of regulatory procedures, stronger requirements to demonstrate utility, and incorporation of test procedures into the licensing requirements for pharmacogenetic medicines might all serve to address these deficiencies (Melzer et al. 2005; Hedgecoe et al. 2006; Hopkins et al. 2006).

3.1.4 Thirdly, while pharmaceutical companies have been reluctant to adopt pharmacogenetic methods as a means of targeting prescribing practices, they have incorporated pharmacogenetic methods into drug development and evaluation processes. To this end they have collected considerable amounts of genetic data from trials participants. Regulations governing these biobanks also vary widely between European states, inhibiting research initiatives that might cross national boundaries. Harmonisation of the relevant EU regulations might do much to address this problem (Hedgecoe et al. 2006).

3.2 Policy Framework: Conclusion

3.2.1 The development of pharmacogenetics is one of several factors conducing to a radical reorganisation of innovation pathways in the pharmaceutical and diagnostic technology sectors. To date, pharmaceutical companies have resisted such changes, but they appear increasingly inevitable. An appropriately structured regulatory and policy environment, including effective engagement with relevant stakeholders, will be crucial in managing such changes to minimise disruption and maximise public benefit (Tait and Mittra 2004; Tait 2007).

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