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POLICY

The perspective from EASAC and FEAM on direct-to-consumer genetic testing for health-related purposes

Robin Fears*, Volker ter Meulen and the EASAC–FEAM Working Group

Participants in the Working Group were: Stefania Boccia, Martina Cornel, Marc Delpech, Anne De Paepe, Xavier Estivill, Mats Hansson, Katia Karalis, Andres Metspalu, Markus Nöthen, Peter Propping, Jorge Sequeiros, Ron Zimmern, Volker ter Meulen (Chair), Robin Fears (secretariat)

Direct-to-consumer (DTC) genetic testing services raise scientific, regulatory and ethical questions. A report was prepared by consultation with an expert Working Group and published by the academies of science (European Academies of Science Advisory Council, EASAC) and medicine (Federation of European Academies of Medicine, FEAM). This report reviews current scientific evidence, ascertains the principles that should underpin the options for action by policy-makers, and discusses the potential for devising proportionate and flexible regulation that enables future innovation, taking account of the work of other expert groups, most notably the European Society of Human Genetics. EASAC–FEAM concluded that DTC genetic testing has little clinical value at present, and expresses especial caution in several specific respects, for example relating to testing for high penetrance, serious disorders, prenatal screening, nutrigenomic and pharmacogenetic testing. It was emphasised that regulation must be on the basis that claims about the link between genetic marker and disease are scientifically valid. Other key issues to address include quality assurance (that includes the professional interpretation of results), transparent supply of accurate information, consideration of the implications for established health services, and clarification of consent procedures for any use of data for research purposes. There are important implications: for the European Commission, in revising the Directive on *In Vitro* Diagnostic Medical Devices; for professional bodies, in supporting training and guideline development; for the broader research community, in generating the evidence base; and for the public health community, in improving the routine translation of research advances into clinical practice.
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Advances in genomics are leading to the discovery of new genes that cause disease or increase its risk. Until recently, human genetic testing was usually confined to specialist medical genetic services, focused on relatively rare, inherited diseases. However, in a changing landscape, there has been increasing interest in the development of genetic tests for determining susceptibility to the more common, complex disorders.[1] Since 2007, such tests are increasingly offered through the internet, but action by regulatory authorities to scrutinise this provision has been relatively slow.[2]

Consumer genetic services raise scientific and ethical as well as regulatory questions. There are concerns that overstated claims create unrealistic consumer expectations, may harm privacy and induce confusion and anxiety. For example, one recent study[3] finds little concordance in results for cancer risk from personal genome screening and the family history-based risk assessment commonly used in genetic counselling services. There have been several initiatives by professional or advisory bodies to identify the issues for managing such tests, most notably by the European Society of Human Genetics (ESHG)[4] but also, for example, in the UK by the Human Genetics Commission[5] and in the United States by the American Medical Association.[6]

THE ACADEMIES INITIATIVE

In 2010, academies in Germany published a report on predictive genetic diagnostics,[7] taking a critical view of direct-to-consumer (DTC) genetic testing, which is prohibited in Germany according to the national Genetic Diagnostics Act. The current legislative situation on DTC genetic testing across Europe varies[8] and it would seem to be highly desirable to harmonise the principles governing such services, to ensure consistent use of the clinical evidence base and support a standard regulatory framework to protect patient safety and support innovation, even if some EU Member States wished to retain flexibility to implement these principles within their current national health strategies.

Following the academy work in Germany, other European academies recognised that the issues appertaining to DTC genetic testing services for health-related purposes are sufficiently important to warrant their collective attention. The Academy networks, the European Academies Science Advisory Council (EASAC, http://www.easac.eu) and the Federation of European Academies of Medicine (FEAM, http://www.feam.eu.com), were formed, respectively in 2001 and 1993 by the national academies of science and of medicine of the EU Member States and they provide a means for the

EASAC, German National Academy of Sciences Leopoldina, Saale, Germany
*Correspondence: Dr R Fears, EASAC, Biosciences Programme, German National Academy of Sciences Leopoldina, Postfach 110543, Saale 06019 Halle, Germany. E-mail: robin.fears@easac.eu

collective voice of European science to be heard. Because of their mutual interests in this important area, EASAC and FEAM initiated their first joint project to draw upon broad expertise in the relevant scientific disciplines and experience across the EU. The EU academy networks have an important role, free of vested interests, to review the state of the science, to provide an independent perspective on fundamental principles, and to explore how the available evidence can be used to inform policy options for regulation and the associated priorities for innovation, professional governance and clinical service, and public engagement. Such advice complements the other, intersectoral, initiatives involving public regulators, specialist professional bodies and industry, aiming to develop and implement a practical framework to govern and implement this rapidly developing technology.[9]

Both the academy networks have significant experience in biomedical policy issues. For example, in previous work EASAC has addressed EU regulatory and innovation policy priorities in infectious disease,[10,11] synthetic biology[12] and nanotechnology.[13] FEAM has recently presented recommendations on EU policy relating to the regulation of clinical trials,[14] the EU Physical Agents Directive and biomedical imaging[15] and mental health strategy.[16] The latest, joint, report on DTC genetic testing[17] was prepared by consultation with a Working Group of academy-nominated experts, acting in an independent capacity: the work commenced in May 2011 and finished in May 2012.

In the present article, we summarise conclusions from the report in support of the goal to achieve a good balance between increased use of responsible testing and protection against unsound testing.

THE SCOPE OF DTC GENETIC TESTING

While the focus is on genetic testing, the report recognises that controversy continues on whether using a nucleic acid-based test is different in principle from using other types of biomarker as the risk predictor and, hence, whether concerns expressed about DTC services are specific to the use of nucleic acids as the analyte or can be generalised to the use of other predictive risk information. In the view of EASAC–FEAM, efforts to devise guidelines relating to genetic testing should be regarded as part of longer-term efforts to encompass all medical testing.

The report emphasises that all kinds of genetic testing require an appropriate level of professional advice. Based on the evidence reviewed, it was concluded that on the whole, DTC genetic testing has little clinical value at present and, on occasion, has potential to be harmful. EASAC–FEAM would not wish to encourage EU citizens to use such services at the present time—but in considering regulatory options for testing, it is important to ensure the flexibility to respond to and enable future innovation, taking account of advancing science and experience.

The report recommends caution about DTC genetic testing in several specific respects:

- Individuals should not seek such services if they have symptoms or are at known risk of disease. Equivalent advice is implicit in the ESHG statement; EASAC–FEAM advise that it is important to stimulate better public engagement on these issues.
- In particular, testing for monogenic, high penetrance, serious disorders should be presently excluded from the range of DTC services. The reason for advising this exclusion is not for lack of clinical validation but rather the greater need for individualised medical supervision and genetic counselling. In practice, because of the difficulty in defining the boundary between high and low penetrance genotypes, it is recommended that DTC services are discouraged from including those tests that the public health services currently deploy for investigating serious (including monogenic) disorders.
- Prenatal screening should also be excluded. This application was not considered specifically in the ESHG statement but, although research advances are now opening up new opportunities for diagnosis based on free fetal DNA and RNA in maternal blood samples, there are significant ethical implications[18] and serious potential consequences for mother and foetus that mandate the highest quality information, appropriate genetic counselling and close medical supervision.
- EASAC–FEAM agree with the ESHG statement that nutrigenomic testing should be discouraged perhaps primarily because of its linkage with the sale of dietary supplements of little or no proven value.
- Pharmacogenetic testing, to measure individual variability in drug metabolism, that may influence drug efficacy or safety, is becoming part of clinical practice, but should not be offered within DTC genetic testing unless necessary safeguards are in place. Although pharmacogenetics was not discussed in the ESHG statement, there are potential problems for inclusion in DTC services[19] if, for example, the consumer is then tempted to adjust their dose of prescribed medicine without seeking medical advice.
- Testing of samples from minors (including carrier testing) and third parties (who have not consented) should not be permitted but there is evidence that some DTC services are including genetic testing in minors,[20] contradicting established professional guidelines, including those of the ESHG.

GOVERNANCE PRINCIPLES FOR INFORMING POLICY DEVELOPMENT

In addition to highlighting these cautions, EASAC–FEAM recommended developing general principles for the governance of DTC services. Such procedures need to address issues for ensuring quality and completeness of that information supplied in seeking informed consent and for managing test data and providing access to counselling, as recommended in the ESHG statement. In appraising these general principles, EASAC–FEAM emphasised the following:

Establishing scientific validity

Susceptibility testing for complex disorders should be regulated on the basis that claims about the link between genetic marker and disease are scientifically valid. However, it is still a matter of debate what sort of evidence is required along the continuum of analytical validity-scientific validity-clinical validity-clinical utility. While the ESHG has made the case that clinical utility is an essential criterion in offering a genetic test, it should be noted that clinical validity and utility are more difficult to regulate than analytical validity.[21] Furthermore, clinical utility has a subjective dimension in that, for example, the consumer may find a result useful whereas a physician may not.[22,23]

In the view of EASAC–FEAM, it is essential that whatever information exists on the validity and usefulness of a test it is placed in the public domain so that physician and consumer can judge whether or not to avail of a particular service. There is a concomitant need to educate the public to understand what is offered in DTC services, for example to explain the distinction made between testing for monogenic and complex disorders. The US National Institutes of Health has recently created a genetic testing registry[24] but this is based on voluntary submission of data by companies and it is questionable

if this can be adequate. A corresponding EU initiative should be considered, but to share validated data, perhaps involving the European Medicines Agency and other relevant bodies including the ESHG and the European Network for Health Technology Assessment. The European Commission, with its international partners must also ascertain what is required to assemble high-quality research evidence on gene–disease associations—establishing the relative roles of research funder, academia and industry—particularly in generating data on lower penetrance genes by analogy with the Clinical Utility Gene Cards of EuroGentest[25] and as discussed in the ESHG statement. Alongside this research on disease-gene associations, it is also vital to design research studies to collect evidence on the impact of testing on health outcomes[26] and on alternative models for communicating genetic risk.[27]

Extending quality control

Test quality assurance must cover not only analytical quality but also the professional interpretation of results and the provision of counselling that is appropriate to the disease risk and burden, as discussed in the ESHG statement. The objective is agreed, accredited quality standards to support international acceptance of tests. In addition, EASAC–FEAM recommend that, while awaiting public policy development, it would be prudent for DTC companies to work together to develop and implement industry-wide standards and code of conduct.

Supervising disclosure of information

Accuracy and transparency in information provision prior to consumer consent is of fundamental importance, as discussed in the ESHG statement, because it enables easier distinction between claims that are justified and those that are not. There must be consistent enforcement of advertising standards for evidence-based claims according to the norms of consumer protection—truth in labelling—currently governed by the EU Directive 2005/29/EC (Unfair Commercial Practices). In addition, in the view of EASAC–FEAM, such information must also specify who is advised not to use DTC services.

Consent and privacy issues are discussed in detail in the ESHG statement and it will be important to take into account recent thinking that it may not always be possible to guarantee protection of privacy when data sharing and re-identification of anonymised data become increasingly likely—and this must be made clear during the consent process. Furthermore, as noted in the EASAC–FEAM report, it is important for DTC genetic testing companies to specify their procedures for data storage and use, including discussion of the consequences if a company changes ownership.

The conclusions from the EASAC–FEAM report regarding the necessary steps to embody in consumer protection in DTC genetic testing are summarised in Table 1.

Understanding and addressing consequences for health systems

The effects on the established public health services and others (eg, health insurers) warrant further assessment. One concern, expressed in the ESHG statement, is the potential waste of scarce public resources, if DTC tests stimulate unnecessary follow-up. In addition, there are issues for equity of access to health information, when private provision is determined by ability to pay, and for the potential for public confidence in genetic testing more generally to be undermined by controversy about DTC services.[28] While one recent study[29] found that DTC genetic testing is not yet a major reason for referral for follow-up with clinical genetic services in Australia and New Zealand, analysis from the United States[30] indicates that a relatively high proportion of subjects using DTC genetic testing services discussed the results with their own physician—and this has resource implications.

Whatever the additional, knock-on, effects of DTC provision, there is already need to do better in educating medical and other health professionals about genetics,[31] for example to improve the confidence of primary care physicians to interpret and explain risks and benefits based on genetic information.

Clarifying research use

While there is some evidence for a possible useful contribution by DTC testing in identifying novel gene–disease associations (eg, in Parkinson's disease[32]), the provider–consumer relationship risks circumventing the normal regulatory controls for research and might undermine public confidence in clinical research more generally. It is imperative that a framework for good practice is developed by companies for the conduct of research in this setting. When desiring to use data for research, companies must seek proper, additional, consent, specifying the handling of samples and information derived, as discussed in the ESHG recommendations. In addition, companies also need to ensure that their research data are available to other researchers seeking to replicate conclusions, according to the customary scientific conventions.

ISSUES FOR THE EUROPEAN COMMISSION

The principles described above have implications, determining the responsibilities for professional bodies (eg, in training health professionals in genetics and managing the mechanisms for professional and clinical good governance), for the broader research community (in developing an accessible evidence base), for public health services (for improving the routine translation of research advances into clinical

Table 1 Key issues for consumer protection in DTC services

Criterion	*Necessary translational step*
Information provision	Agreed guidelines on appropriate information available before, during and after the test, with proportionate consent, interpretation and follow-up
Analytical validity	Implementation of proper quality assurance and quality control programmes to ensure that the testing laboratory meets required standards
Scientific and clinical validity	Establishing that the tests offered have genuine association with the claims made
Access to advice	Involvement of appropriately qualified, competent, responsible professional, subject to normal clinical governance procedures, including follow-up measures, management and treatment
Control of claims	Prevention of misleading assertions in publicity and promotional material about meaning and usefulness of results

practice), and for regulatory authorities. For the latter in the EU at this time of reform of the Directive 98/79/EC on *In Vitro* Diagnostic Medical Devices, the priority is to clarify the scope of the Directive to cover all genetic information that is used to make medical claims and to introduce a responsive and proportionate assessment during pre-market approval of claims, followed by post-market surveillance. In revising this Directive, the European Commission will need to determine how best to support independent review of the quality and validity of claims made for a test, based on some form of risk stratification but independent of the nature of the analyte. The evidence base for approved tests, whether genetic or other, whether DTC or other, must be accessible and verifiable.

There are three other major, related issues for the European Commission, discussed in the EASAC–FEAM report. First, there must be evaluation of the implications for the other Directives on Medical Devices (93/42/EC and 90/385/EC) if there is to be a consistent requirement for demonstration of clinical efficacy as part of the policy harmonisation. Second, there is much to be done to prepare for the transposition of whole genome sequencing from the research phase to the routine clinical setting. Currently, such sequencing and analysis occupies only a small proportion of the DTC genomics market but it can be expected to grow rapidly.[33] Challenges for consenting, communicating and acting on data will be magnified by whole genome and exome sequencing with its greater propensity to reveal incidental information that was not anticipated or requested by the consumer. Third, the EU regulatory bodies will need to continue to work with their partners worldwide to deliver appropriate harmonisation of diagnostic regulatory systems. There has been, for example, significant discussion by US regulatory and policy-making bodies on the principles and practicalities for managing DTC genetic testing, led by the Food and Drug Administration, the Centre for Disease Control and Prevention, the US Secretary's Advisory Committee on Genetics Health and Society and the Government Accountability Office. However, within the global context, difficulties in interpreting the gene–disease association evidence base are accentuated by differences in the relevance of genetic information for disease susceptibility and drug responsiveness in different populations.[34] There are major implications for a global DTC industry, necessitating global databases on DNA variants and their phenotypes. EASAC–FEAM recommended that these issues be addressed in the WHO global public health initiative[35] to identify genomic research priorities.

CONCLUSION

There are opportunities to improve the regulatory and innovation framework for DTC genetic testing services, and for genetic testing and other testing more generally. However, in this area, market development is often faster than the ability of the legislator to regulate.[36] Revision of legislation will only be effective if accompanied by efforts to understand and implement the additional mechanisms whereby quality and relevance of testing can be secured. Among these necessary collective actions for the public sector, also requiring international harmonisation, are: improvement of clinical governance and professional and public education; support for research to collect and validate new evidence, subject to agreed standards; and creation and curation of databases for sharing of accurate test information.

The academies of science and of medicine are ready to continue playing their part, engaging with professional societies and other advisory bodies, the research community more broadly, policy-makers and society-at-large, to inform debate and the necessary strategy development.

1 Janssens ACJW, Ioannidis JPA, van Duijn CM, Little J, Khoury MJ: For the GRIPS Group: strengthening the reporting of genetic risk prediction: the GRIPS statement. *Eur J Hum Genet* 2011; **19**: 833–836.
2 Patch C, Sequeiros J, Cornel MC: Genetic horoscopes: is it all in the genes? Points for regulatory control of direct-to-consumer genetic testing. *Eur J Hum Genet* 2009; **17**: 857–859.
3 Heald B, Edelman E, Eng C: Prospective comparison of family medical history with personal genome screening for risk assessment of common cancers. *Eur J Hum Genet* 2012; **20**: 547–551.
4 European Society of Human Genetics. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. *Eur J Hum Genet* 2010; **18**: 1–3.
5 Human Genetics Commission. A common framework of principles for direct-to-consumer genetic testing. Report, 2010. Available from http://www.hgc.gov.uk.
6 American Medical Association. Genetic testing should be conducted by qualified health professionals. Letter to FDA, 2011. Available from http://www.ama-assn.org/resources.doc.washington/consumer-genetic-testing-letter.pdf.
7 Leopoldina academy, acatech and Berlin-Brandenburg academy of Arts and Sciences. Predictive genetic diagnosis as an instrument of disease prevention. Report, 2010. Available from http://www.leopoldina.org.
8 Borry P, van Hellemondt RE, Sprumont D *et al*: Legislation on direct-to-consumer genetic testing in seven European countries. *Eur J Hum Genet* 2012; **20**: 715–721.
9 Caulfield T, Ries NM, Shuman C, Wilson B: Direct-to-consumer genetic testing: good, bad or benign? *Clin Genet* 2010; **77**: 101–105.
10 EASAC. European public health and innovation policy for infectious disease: the view from EASAC. Report, 2011. Available from http://www.easac.eu.
11 Fears R, van der Meer JWM, ter Meulen V: The changing burden of infectious disease in Europe. *Sci Transl Med* 2011; **3,** 103cm30 1–4.
12 EASAC. Realising European potential in synthetic biology: scientific opportunities and good governance. Report, 2010. Available from http://www.easac.eu.
13 EASAC-European Commission Joint Research Centre. Impact of engineered nanomaterials on health: considerations for benefit-risk assessment. Report, 2011. Available from http://www.easac.eu.
14 FEAM. Opportunities and challenges for reforming the EU Clinical Trials directive: an academic perspective. Statement, 2010. Available from. http://www.feam.eu.com.
15 FEAM. Statement on the EU Physical Agents Directive. Statement, 2011. Available from http://www.feam.eu.com.
16 Fears R, Hoschl C: European mental health policy: opportunities for science and innovation, challenges for implementation. *Eur J Publ Health* 2011; **21**: 550–551.
17 EASAC-FEAM. Direct-to-consumer genetic testing for health-related purposes in the EU: the view from the academies of science and medicine. Report, 2012. Available from http://www.easac.euand. http://www.feam.eu.com.
18 De Jong A, Dondorp WJ, Frints SGM, de Die-Smulders CEM, de Wert GMWR: Advances in prenatal screening: the ethical dimension. *Nature Rev Genet* 2011; **12**: 657–663.
19 Vijverberg SJH, Pieters T, Cornel MC: Ethical and social issues in pharmacogenomics testing. *Curr Pharm Design* 2010; **16**: 99–106.
20 Howard HC, Avard A, Borry P: Are the kids really allright? Direct-to-consumer genetic testing in children: are company policies clashing with professional norms? *Eur J Hum Genet* 2011; **19**: 1122–1126.
21 Wright CF, Hall A, Zimmern RL: Regulating direct-to-consumer genetic tests: what is all the fuss about? *Genet Med* 2011; **13**: 295–300.
22 Nuffield Council on Bioethics. Medical profiling and online medicine: the ethics of 'personalised healthcare' in a consumer age. Report, 2010. Available from http://www.nuffield.co.uk.
23 Kopits IM, Chen C, Roberts JS, Uhlmann W, Green RC: Willingness to pay for genetic testing for Alzheimer's disease: a measure of personal utility. *Genet Test Molec Biomarkers* 2011; **15**: 871–875.
24 NIH. Genetic Testing Registry. Announcement, 2012. Available from http://oba.od.nih.gov/GTR/gtr_intro.html.
25 Mattocks CJ, Morris MA, Matthijs G *et al*: A standardized framework for the validation and verification of clinical molecular genetic tests. *Eur J Hum Genet* 2010; **18**: 1276–1288.
26 Botkin JR, Teutsch SM, Kaye CI *et al*: Outcomes of interest in evidence-based evaluations of genetic tests. *Genet Med* 2010; **12**: 228–235.
27 Roberts J, Christensen K, Green R: Using Alzheimer's disease as a model for genetic risk disclosure: implications for personal genomics. *Clin Genet* 2011; **80**: 407–414.
28 Van El CG, Cornel MC: on behalf of the ESHG Public and Professional Policy Committee: genetic testing and common disorders in a public health framework. *Eur J Hum Genet* 2011; **19**: 377–381.
29 Brett GR, Metcalfe SA, Amor DJ, Halliday JL: An exploration of genetic health professionals' experience with direct-to-consumer genetic testing in their clinical practice. *Eur J Hum Genet* 2012; **20**: 825–830.
30 American Society of Human Genetics. Researchers shed light on implications and assessment of using direct-to-consumer and clinical genetic testing in disease risk assessment. Statement, 2010. Available from http://www.ashg.org/pdf/PR_DTC_Clinical_110510.pdf.
31 Skirton H, Lewis C, Kent A, Coviello DA: The members of Eurogentest Unit 6 and ESHG Education Committee: genetic education and the challenge of genomic medicine: development of core competences to support preparation of health professionals in Europe. *Eur J Hum Genet* 2010; **18**: 972–977.
32 Do CB, Tung JY, Dorfman E *et al*: Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. *PLoS Genet* 2011; **7**: e1002141.

33 Foundation for Genomics and Population Health. Next steps in the sequence. The implications of whole genome sequencing for health in the UK. Report, 2011. Available from http://www.phgfoundation.org.
34 Li R, Li Y, Zheng H *et al*: Building the sequence map of the human pan-genome. *Nature Biotech* 2010; **28**: 57–63.
35 World Health Organization. Grand challenges in genomics for public health in developing countries. Statement, 2011. Available from http://www.who.int/rpc/grand_challenges.pdf.
36 Grimaldi KA, Look MP, Scioli GA, Clavero JC, Marinos S, Tagaris T: Personal genetics: regulatory framework in Europe from a service provider's perspective. *Eur J Hum Genet* 2011; **19**: 382–388.