Title of case study: The regulation of commercial genetic testing

1.Summary of the impact (indicative maximum 100 words)

Hogarth and external collaborators at Cambridge have developed a regulatory model for the governance of commercial genetic testing in the EU that requires pre-market review of all new commercial genetic tests and greater public disclosure of clinical data about test performance. Drawing on this model they recommended a number of changes to the current European regulations. In 2012 the European Commission published a proposal for a new regulation on In Vitro Diagnostic (IVD) medical devices that *incorporated most of the changes which they recommended be addressed in the revision of this regulation.* Hogarth also helped the Human Genetics Commission to draft the first transnational guidance for the regulation of direct-to-consumer genetic testing services.

2.Underpinning research (indicative maximum 500 words)

Scientific advances arising from completion of the Human Genome Project in 2003 have expanded understandings of the genetic contribution to health and disease. They have also resulted in the development of *in vitro* diagnostic tests that can help identify genetic predisposition to disease and tailor medical treatment to individual genetic profiles. The promise of personalised medicine will not be realised, however, if tests are not adequately regulated, as failure to validate the accuracy, reliability, and clinical implications of a test may result in patient harm from misdiagnosis, failure to treat, delay in treatment, inappropriate treatment, or avoidable adverse events. Direct To Consumer (DTC) genetic testing or consumer genetics presents particular challenges in terms of its ability to circumvent existing regulatory protocols. Hogarth has been leading global research into the analysis and reformation of regulatory regimes for genetic testing since 2004 when he began a 3.5 year project to perform a comparative mapping of existing regulatory frameworks for genetic testing in Europe and North America that identified key regulatory concerns and options for reform (with Prof. Melzer ,University of Cambridge). Two allied consultancies were carried out for the Canadian government and a commissioned briefing was provided for the Genetic Services subgroup of the UK Human Genetics Commission (HGC).

Since joining KCL in 2009, Hogarth has further extended this programme of research on the regulation of genetic testing through development of a multivariate methodology that has involved comprehensive reviews of literature, regulatory guidance documents, scientific papers, policy reports, commercial industry surveys and news publications; qualitative interviews with senior regulatory and policy advisors; and five policy workshops with stakeholders (clinicians, scientists, industry executives, policymakers and regulatory officials) in Europe and North America. This has produced a number of highly cited, state of the art publications (see below). In addition, Hogarth has hosted key international workshops in 2011 involving industry, regulators, clinicians, NGOs and scientists that have directly informed policy development in Europe, North America and Japan. Since 2011 this work has been funded through two research projects: EuroGentest, an FP7 network (£40K, 2011-2014, KU Leuven and UC Dublin key collaborators); and an ESRC-funded project on the governance of biomedical innovation (£600K, 2012-2015).

Cumulatively this research programme has produced the first detailed analysis of the international landscape of genetic testing governance, comprised of a mosaic of statutory regulation, health technology assessment policy and clinical practice guidelines implemented with varying degrees of commensurability in the USA, EU, Canada, and Australia. Drawing on this analysis, this research has produced a set of policy proposals for reformation of governance of genetic testing and a regulatory model to meet that end, since implemented, as set out below.

3. References to the research (indicative maximum of six references)

Where DOIs or URLs are not given, hard copies are available on request.

S Hogarth, K Liddell, T Ling, D Melzer and R Zimmern (2007) 'Closing the gaps: enhancing the regulation of genetic tests using responsive regulation' *Food and Drug Law Journal* 62(4) 831-848.
D Melzer, S Hogarth, K Liddell, T Ling and R Zimmern 'The new common disease genetic tests: new insights, old concerns' *British Medical Journal* 2008; 336: 590-593 (15 March). Doi: 10.1136/bmj.39506.601053.BE
S Hogarth, G Javitt and D Melzer (2008) 'The current landscape for direct-to-consumer genetic testing: legal, ethical and policy issues' *Annual Review of Genomics and Human Genetics* 2008; 9: 161-182. Doi: 10.1146/annurev.genom.9.081307.164319
S Hogarth (2010) 'Myths, misconceptions and myopia: searching for clarity in the debate about The regulation of consumer genetics.' *Public Health Genomics* 2010; 13(5): 322-326. Doi: 10.1159/000313330
S Hogarth (2012) 'Regulatory experiments and transnational networks: the governance of pharmacogenomics in Europe and the United States.' *Innovation: the European Journal of Social Science Research* 2012; 25(4): 441-460. Doi: 10.1080/13511610.2012.726423

Policy reports / briefings/consultation responses

S Hogarth, D Melzer and R Zimmern *The regulation of commercial genetic testing services – a briefing for the Human Genetics Commission* (Cambridge University, 2005)
S Hogarth and D Melzer *The regulatory framework for genomic tests. Evidence to the House of Lords Science and Technology Sub-Committee on Genomic Medicine* (Loughborough University/Exeter University, 2008)
S Hogarth and D Barton, *IVD device regulation and genetic testing: EuroGentest Network response to European Commission proposal for a regulation on IVD medical devices* (2008, 2010 and 2013)

Grants: **2012-2015 Co-investigator on ESRC-funded project:** 'State strategies of governance in global biomedical innovation: the impact of China and India'. Total value: £600,000.
2011-2014 FP7 project: EuroGentest. Policy co-ordination work package focused on impending changes to EU regulatory framework for genetic testing. £40,000
Spring 2007 Client: Health Canada PI on research on the policy/regulatory issues arising from the clinical application of microarrays. CAD $15,000.
Spring 2006 Client: Health Canada PI on survey of international developments in regulation of pharmacogenomics. CAD $25,000

4.Details of the impact (indicative maximum 750 words)

The underpinning research produced a set of proposals for regulatory reform of genetic testing and a regulatory model for achieving this. The model demands a minimum common requirement of pre-market review of all new commercial genetic tests in order to ensure truth-in-labelling and truth-in-promotion and greater disclosure of clinical data on test performance. Hogarth and colleagues describe this approach as "regulation by information disclosure". It requires that:
1. Test manufacturers should provide patients and healthcare providers with evaluative data on the analytic and clinical validity of tests; and
2. That independent pre-market review should be used to evaluate whether this information is an accurate account of a test's strengths and weaknesses.
The team identified broad support for the view that data on analytic and clinical validity of tests should be a minimal requirement for market approval, but that data on clinical utility could be gathered post-market and assessed through health technology assessment mechanisms. They have promoted this regulatory model in Europe and North America since 2007 through invited presentations to policymakers, regulatory agencies, industry and clinicians; public consultations; informal interactions with policymakers and regulators, and through membership of (and consultancy for) government advisory groups. The research was fed into regulatory and policymaking bodies in specific ways in each jurisdiction as outlined below:

European Union: At EU level efforts have focused on reform of the IVD Directive, which constitutes the basis for statutory regulation of in vitro diagnostic tests as medical devices within

the EU (and EFTA). In 2007 Hogarth was invited by European Commission (EC) officials responsible for the Directive to present his team's ideas for regulatory reform to the annual meeting of representative member states' Competent Authorities. A written briefing was prepared that summarised the research, outlined the main weaknesses of the existing IVD Directive and made a series of proposals for reform. The briefing was welcomed by leading member states for providing a cogent and comprehensive analysis. In a press release issued after the meeting the Competent Authorities highlighted this 'identified need' to monitor whether device regulations were keeping pace with technological developments, using it to justify a "critical review" of legislation on genetic testing. The issues Hogarth and colleagues highlighted were also raised in the European Commission's 2010 public consultation on reform of the IVD Directive. The Commission published a summary of responses to the consultation which demonstrated broad support for the changes they had specifically advocated, thus providing independent confirmation that their in-depth engagement with stakeholders had successfully identified a pragmatic remedy to a very contentious issue that was acceptable to many different interest groups.

Subsequent to the consultation Hogarth's EuroGentest team organised an international workshop in 2011 which brought together regulatory officials, policymakers, industry and other stakeholders from Europe, USA and Australia to discuss regulatory reform in the regulation of IVDs and its likely impact on genetic testing. This meeting was attended by EC officials with primary responsibility for the drafting of the proposed new EU regulation on IVD devices. This dialogue had direct impact on various aspects of the new draft EU regulation on IVD devices published by the Commission in September 2012. In 2013 EuroGentest were invited to present at a workshop convened by the MEP who is the Rapporteur for the IVD Regulation. A written response to the draft Regulation which welcomed the proposed changes but also made specific suggestions on how the proposal might be strengthened was prepared for that meeting. Dialogue with EC officials, MEPs, representatives of member states and other stakeholders continues and the team expect to be directly involved in providing detailed advice on textual changes to the final Bill.

UK: The main impact of this research on UK governance is evidenced through engagements with the Human Genetics Commission supporting their work on the regulation of consumer genetics. Hogarth was first invited to provide a briefing for the Genetic Services subgroup of the HGC which summarised developments in the regulation of commercial genetic testing services in the UK. He then provided an overview of regulatory developments in the USA to a plenary meeting of the HGC and later helped the HGC to organise an international stakeholder workshop to review developments since their 2003 report Genes Direct. His input included development of the agenda and list of participants, giving presentations at the meeting and work in drafting the influential meeting report More Genes Direct. He played the same role in a further international meeting convened in 2008 to explore whether there was support for development for an industry code of practice. Having identified widespread support for this in 2009 the HGC formed a small working group to develop guiding principles for such a code, of which Hogarth was a key member. Additionally he provided oral and written evidence to the House of Lords enquiry on genomic medicine in 2008 (below).The ensuing report included a recommendation for revision of the IVD Directive to ensure premarket evaluation of genomic diagnostics – his key proposal to the enquiry. The adoption of his regulatory model is clear evidence of impact in influencing the direction of regulatory and policy reform. Hogarth continues this work as a member of the Emerging Science and Bioethics Advisory Committee, the successor to the Human Genetics Commission, which is the main UK advisory body on emerging healthcare scientific developments and their ethical, legal, social and economic implications. He is also a member of the external strategy group advising the UK's MHRA on its negotiating position on the European Commission's proposal for a new regulation on IVDs (see above).

North America USA: Since the commencement of his research Hogarth and his team have enjoyed excellent access to senior FDA officials responsible for IVD regulation. They ran two policy workshops in Washington DC which enjoyed strong FDA support (both were attended by the Director of the Office of In Vitro Diagnostics) and led to their being given a "Leveraging and Collaboration" award by the agency. They have remained in regular dialogue with senior FDA officials and have sought to involve them in a more international dialogue about policy in this area.

At their suggestion an FDA official attended the HGC workshop and the Director of the Office of In Vitro Diagnostics (OIVD) and OIVD's Director for Personalised Medicine both attended the team's 2011 workshop in Leuven. In 2011 Hogarth was invited to give a presentation at the FDA's advisory committee meeting on the regulation of direct-to-consumer genetics, providing an overview of global developments in regulation in this area. Canada: Hogarth and his collaborators produced two reports for Health Canada one on the emerging regulatory frameworks for pharmacogenomics and one on the policy implications of high-throughput genomic platforms.

Dissemination of the impact: public engagement. Hogarth is now considered a leading expert in the national and international regulation of genetic testing and is regularly asked to appear in the national and trade media to discuss issues relating to regulation and reform. Broadcast media appearances include BBC Newsnight, Channel 4 news, the BBC Politics Show, and Sky News. He has also written commentaries on this topic for The Guardian's Science blog and in 2009 appeared on Radio 4's Analysis programme on consumer genetics. To coincide with this broadcast he organised a public event at the Dana Centre on the politics of genetic testing.

5. Sources to corroborate the impact (indicative maximum of 10 references): all available on request.

USA: Letter from Director; and Director of Personalised Medicine, Office of In Vitro Diagnostics, Food and Drug Administration, confirms Hogarth's contributions to US genetic testing regulatory arena. Letter from Deputy Director for Science, Outreach and Policy, National Institutes of Health, confirms international impact of research, and impact on developing US policy.
EU: Letter from Former President of European Society of Human Genetics, confirms Hogarth's study, analysis and drafting of suggestions for improvement of European policies pertaining to genetic testing.
UK: Letter from Head of Medical Devices (EU Policy), Medicines and Healthcare Products Regulatory Agency, confirms Hogarth's membership of MHRA's external strategy group supporting the UK Government in revisions to existing EU legislation governing in vitro diagnostic medical devices.

Evidence of impact, UK: *Consumer genetics: A common framework of principles for direct to consumer genetic testing services* – published by Human Genetics Commission **1)** Paragraph 3.41 of House of Lords report on Genomic Medicine – reclassification "We recommend that the Government support the re-classification of genetic tests to "medium risk" in the current review of the EU InVitro Diagnostic Medical Devices Directive so as to ensure that all genomic tests on the market have been subject to pre-market review before their use either by the consumer directly or by the NHS and private healthcare services."

EU commission proposed regulation on IVD devices

1) Risk classification of genetic tests: Annex VII - all human genetic tests class C
2) Direct-to-consumer genetic services: brought within scope of regulation – see Article 5
3) Enhanced use of technical standards for greater range of tests – Article 7
4) Predictive testing: brought within scope of regulation – Article 2
5) Transparency and data sharing: Performance data made public - Article 24
6) Pharmacogenomics: role for European Medicines Agency in pre-market review of companion diagnostics – see Article 40
7) Clinical evidence: greater emphasis on need for data demonstrating clinical performance of IVD devices – Chapter VI