The regulation of genetic tests: a global overview

Presentation at DNA Testing Policy conference Prague, October 2011

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Outline

Why regulate?

What are the regulatory instruments?

Where are the regulatory gaps?

How are policymakers addressing these gaps?

Why regulate?

Policy analysis

USA

- **1975 – *Genetics screening programmes, principles and research* (National Academy of Sciences)**
- **1994 - *Assessing genetic risks* (IOM)**
- **1999 - *Promoting safe and effective genetic testing in the United States* (Task Force on Genetic Testing)**
- **2000 - *Enhancing the oversight of genetic tests: recommendations of the Secretary's Advisory Committee on Genetic Testing* (SACGT)**
- **2008 - *Recommendations on the U.S. System of the oversight of genetic testing* (SACGHS)**

Policy analysis

European Union

- **2000 -** ***Report of European Parliament's Temporary Committee on Human Genetics and New technologies in modern medicine***
- **2003 -** ***Towards quality assurance and harmonisation of genetic testing services in the EU*** **(Institute for Prospective Technological Studies)**
- **2004 -** ***Ethical, legal and social aspects of genetic testing: research, development and clinical applications*** **(EC Expert Group)**

Policy analysis

Transnational

- **2001 - *Genetic testing: policy issues for the new millennium* (OECD)**
- **2005 - *Quality assurance and proficiency testing for molecular genetic testing: summary report of a survey of 18 OECD member countries* (OECD)**

Regulatory concerns

Key issues

- **Is the laboratory performing the test correctly?**
- **Has the clinical validity of the test been clearly established?**
- **Can the test provide useful information to guide clinical management?**
- **Has the patient sufficient information to make an informed decision about use of the test and to understand the test result?**

Regulatory concerns

Moving targets

- Are we offering monogenic disease testing with appropriate standard of care (e.g. counselling)?
- Is it useful to offer susceptibility testing for common diseases when the risks we can report on are minimal?
- Do we need randomised control trials before using pharmacogenetic testing for well-established drugs like warfarin?
- Should genetic tests be offered direct to consumer?

Policy drivers

- Sensitivities about genetic data
- Market growth
- Technological developments
- New business models
- Growing importance of pharmacogenetics
- International harmonisation

What are the regulatory instruments?

Mapping the regulatory space

Three dimensions

- **Statutory**
  - regulation of *in vitro* diagnostic tests as medical devices
  - regulation of clinical laboratories
  - consumer law
- **Reimbursement**
  - Health technology assessment
- **Clinical governance**
  - practice guidelines
  - Laboratory quality assurance

Where are the regulatory gaps?

Where are the gaps?

1. **Failures in our medical device regulations**

- **Europe – nearly all tests are classed as low-risk so are not subject to independent pre-market review**
- **USA – until very recently Laboratory Developed Tests (LDTs) have not been subject to FDA authority (NB same gap exists in Canada).**

Where are the gaps?

2. Failures in our clinical lab regulations

- **Many countries lack comprehensive statutory framework for regulation of clinical labs.**
- **In the US the CLIA regulations are widely viewed as insufficient (esp. lack of proficiency testing)**
- **The OECD guidelines have set very clear standards but so far there has been limited implementation by member states.**

How are policymakers addressing the regulatory gaps?

Regulatory developments

1. International treaties/standards (e.g. OECD)
2. National legislation on genetic testing (e.g. Germany)
3. Reform of IVD device regulations (e.g. Australia)
4. Expansion in role of HTA / reimbursement as gatekeeper

International treaties/standards

OECD Best Practice Guidelines for Quality Assurance in Molecular Genetic Testing (2007)

Council of Europe Convention on Human Rights and Biomedicine (1997) / Additional Protocol on Genetic Testing for Health Purposes (2008)

OECD Guidelines

Context

- Organisation for Economic Cooperation and Development
- 30 member states
- Collects and analyses data and provides forum for exchange of ideas and policy development including international guidelines
- Active in health, biotechnology, biomedical innovation
- 2003 survey on genetic testing
  - International trade in samples
  - Lack of uniformity in laboratory quality assurance
- Work on quality assurance guidelines
  - Initiated 2003, completed 2007

OECD Guidelines

Molecular genetic testing should be:

- Delivered within healthcare framework
- Practised under a quality assurance framework
- Comply with applicable legal, ethical and professional standards

OECD Guidelines

Informing the patient

- counselling should be available (proportionate + appropriate)
- test results should be reported to referring healthcare professional
- Advertising, promotional and technical claims … should accurately describe the characteristics and limitations of the test offered.
- Laboratories should make available to service users current evidence concerning the clinical validity and utility of tests they offer.

OECD Guidelines

Implementation by member states

- Survey in 2008
  - 13 member states responded
  - Most responding countries indicated they had either implemented the guidelines or were preparing to do so

- OECD will be carrying out a survey to assess what is happening, evaluate the utility of the guidelines and to review whether any changes needed

Council of Europe

- Established 1949
- Intergovernmental organisation fostering cooperation amongst its 47 members to protect democracy and human rights
- Active in bioethics since 1980s
- Convention on Human Rights and Biomedicine (1997)
- Additional Protocol concerning genetic testing for health purposes adopted by Committee of Ministers in 2008
  - First internationally legally binding instrument concerning health-related genetic testing

Council of Europe

Additional Protocol on Genetic Testing (2008)

- Clinical utility should be an essential criterion for a test to be offered
- Parties shall take the necessary measures to ensure that genetic services are of appropriate quality. In particular, they shall see to it that:

  a) genetic tests meet generally accepted criteria of scientific validity and clinical validity

  b) a quality assurance programme for laboratories including regular monitoring

  c) persons providing genetic services have appropriate qualifications

Council of Europe

Additional Protocol on Genetic Testing (2008)

Art. 7 Individualised supervision

1) A genetic test for health purposes may only be performed under individualised medical supervision.

2) Exceptions to the general rule referred to in paragraph 1 may be allowed by a Party, subject to appropriate measures being provided ...

However, such an exception may not be made with regard to genetic tests with important implications for the health of the persons concerned or members of their family or with important implications concerning procreation choices.

Council of Europe

Additional Protocol on Genetic Testing (2008)

Art. 8 Information, genetic counselling and consent

2) For predictive genetic tests as referred to in Art. 12 of the Convention on Human Rights and Biomedicine, appropriate genetic counselling shall also be available for the person concerned. The tests concerned are:

- **tests predictive of a monogenic disease**
- **tests serving to detect a genetic predisposition or genetic susceptibility to a disease**
- **tests serving to identify the subject as a healthy carrier of a gene responsible for a disease.**

Council of Europe

Current status of Additional Protocol

- Entry into force requires ratification by five states including four member states
- So far only five members states have signed the protocol but only one member state has ratified it
- (NB some key member states have not signed or ratified the main Convention on Human Rights and Biomedicine,
- However, some member states are implementing or have implemented legislation based on additional protocol e.g. Germany

National legislation on genetic testing

Austria

Gene Technology Act 1995

- Regulates GMOs, genetic testing and gene therapy
- Predictive genetic testing – special lab requirements, pre-and post-test counselling, written informed consent
- Part IV, Section 65
  - Genetic testing may only be carried out where it is at the request of a doctor specializing in medical genetics

Belgium

Royal Decree1987

- Restricts genetic services to small number of centres
- Sets various standards including need for pre- and post-test counselling (offered on a non-profit basis)
- All genetics centres must produce annual reports detailing their activities

France

Decree no. 2000-570: Articles R1131-4 of the Public Health Code

- Standards for laboratories
- Restrictions on labs which can perform testing
- Need for informed consent and medical supervision

French Bioethics Law 2004

- Gave regulatory powers to Agence de la Biomédicine
  - Authorises institutions permitted to carry out PGD
- Current debate on renewal of 2004 Bioethics Law

Germany

Genetic Diagnosis Act, 2009

- Prohibits genetic discrimination
- Requires laboratory accreditation
- Informed consent and counselling
- Diagnostic genetic examinations may only be conducted by medical doctors and predictive genetic examinations may only be conducted by medical doctors with specialist genetics training
- Establishes independent Genetic Diagnostic Commission
  - Develop guidelines
  - Review new developments in science/technology

Norway

Law No.56 1994 : Act relating to the Application of Biotechnology in Medicine

- General guidelines for research on embryos, gene therapy and genetic testing
- Institutions undertaking these activities must report regularly to the government
- No restrictions on diagnostic genetic testing
- Presymptomatic/predictive/carrier testing
  - cannot be carried out on minors
  - must be accompanied by pre- and post-test counselling
  - Confidentiality restrictions

Portugal

Law No.12/2005 Personal Genetic Information and Health Information Law

- Restricts use of genetic data, forbids discrimination
- Carrier, presymptomatic and susceptibility testing must be preceded by genetic counselling and written informed consent, and requested by a medical geneticist (does not apply to diagnostic/PGx tests)
- Counselling should be proportionate to the severity of the disease, usual age at onset and existing treatment
- Full implementation of law awaiting final decree

Sweden

Law 114, 1991 - on gene technologies within the context of general medical examinations

- Focuses on genetic screening
- Organisations wishing to carry out testing must have authorisation from the national government
- Additional guidelines on PGD published in 1995
  - Restricted to diagnosis of progressive, hereditary diseases which may lead to death and for which there is no cure/therapy

Switzerland

Federal Act on Human Genetic Testing 2004

- Informed consent, privacy etc.
- Organisations wishing to carry out testing must have federal authorisation
- Genetic tests may only be prescribed by medical doctors (or under their supervision)
- Presymptomatic and prenatal genetic tests and tests for the purpose of family planning may only be prescribed by doctors who have received appropriate postgraduate training ... and must be provided with pre- and post-test non-directive counselling

South Korea

- Advisory committee convened by Korean Society of Medical Genetics review common DTC tests with funding from Ministry of Health and Welfare
- Since 2007 14 genetic tests banned and six restricted
  - Banned include tests for obesity, diabetes, alcoholism
  - Restricted include BRCA, APOE
- DTC genetic tests are prohibited
- 2005 – Korea Institute of Genetic Testing Evaluation established with support of government
  - Quality assurance and evaluation of clinical validity

Common themes

- Restrictions on
  - who can perform testing
  - who can order testing
  - how test data can be used
- Standards for how genetic testing is performed
  - quality assurance
  - protection of privacy
  - informed consent
- Genetic information is special, but some is more sensitive
  - predictive testing
  - prenatal testing

Reform of IVD regulations

- **Australia**
- **European Union**
- **USA**

FDA and LDTs

Past and present

- 2000 SACGT recommendations
- Data template piloted in nine labs, plans for lab registry
- Election of Bush, SACGT disbanded, FDA retreat
- FDA intervene on ad-hoc basis
  - 2004 Correlogic – Ovacheck
  - 2006 LabCorp – PreGenPlus
  - 2006 Genomic Health – Oncotype Dx
  - 2006 InterGenetics – OncoVue

FDA and LDTs

Past and present

- 2006 Congressional hearing on DTC genetics
- 2006 FDA write warning letters to DTC companies
- 2007 FDA issue IVDMIA draft guidance
- 2008 SAGHS report
- 2010 FDA issue warning letters to DTC companies
- 2010 Congressional hearing on DTC genetics

- 2010 FDA hold public meeting on LDT regulation
- 2011 FDA LDT guidance imminent?

Review of IVD Directive

Issues raised in European Commission consultations (2008/9) include:

- **Adoption of new risk classification system**
  - **GHTF model – pre-market review for genetic tests**
- **Revision of essential requirements**
  - **Clinical validity, clinical utility**
- **Clarification of status of LDTs**
- **Special measures for DTC genetics**

Commission reform proposal due later this year

Australia's new IVD regulations

- All LDTs are medical devices
- High-risk tests reviewed by TGA
- Low and moderate-risk tests
  - labs must register with TGA
  - labs must notify TGA when tests introduced
  - test validation carried out by bodies responsible for lab accreditaton - NATA and NPAAC

BUT

- TGA participate in standard setting
- TGA can intervene where there is a concern

Australia's new IVD regulations

Restrictions on IVDs for self-testing (home use)

IVDs intended for self-testing are tests that are used in the home or a similar environment and are not carried out under the supervision of a health care provider. Certain types of self-testing IVDs will be prohibited from supply. These include:

- **IVDs used to test for pathogens or diagnose notifiable infectious diseases**
- **tests to determine genetic traits**
- **IVDs used to test for serious disorders, for example cancer or myocardial infarction.**

Reimbursement as regulation

"[reimbursement] is the only place where genetics has ever been regulated. It's the *de facto* regulatory system in the United States – if somebody isn't going to pay for the test, the test isn't going to be out there for long. ."

Clinical geneticist, United States

"I think Europe has a hidden system of control – it's called reimbursement."

FDA official

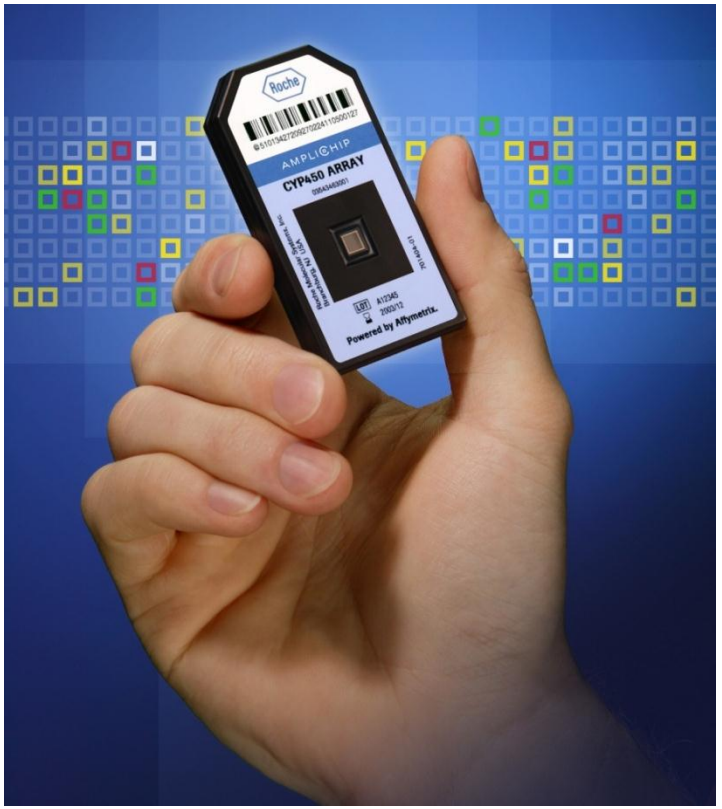
HTA for genomic diagnostics

New initiatives

- UK Genetic Testing Network
- USA - EGAPP

Roche Amplichip

FDA approval December 2004



A necessary failure?

"Genotyping for cytochrome P450 polymorphisms to determine drug-metabolizer status is considered **investigational/not medically necessary**... A literature search did not indentify any published controlled studies that demonstrated that therapy directed by the results of genotyping resulted in improved patient management."

Blue Cross / Blue Shield TEC

Conclusions

- Regulation is developing through both transnational harmonisation of standards and divergent national legislative instruments
- Number of countries imposing legal restrictions on genetic testing has increased at same time as number of companies, and range of tests offered has grown
- Rule-making activity is not matched by enforcement activity
- The applicability of standards derived from clinical genetics (esp. pre- and post-test counselling) are unclear in areas like susceptibility testing
- Clinical genetics has driven policy agenda in the past, in future the main driver may be pharmacogenetics

Conclusions

- **Our ability to generate genomic data has vastly outstripped our ability to make clinical sense of it**
- **The need for a robust but flexible regulatory framework to ensure is more pressing than ever**

Acknowledgements

For information on national legislation in Europe:

Pascal Borry

Rachèl van Hellemondt

Camilla and Bruno Jales

Jorge Sequeiros

Further useful information:

https://www.eshg.org/270.0.html

See also (not fully up-to-date but still very useful):

http://www.nature.com/ejhg/journal/v11/n2s/full/5201111a.html

Thanks for listening

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