

# **The clinical application of new molecular diagnostic technologies – a review of the regulatory and policy issues**

## **A report for Health Canada**

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## Glossary and acronyms

**ACCE** – framework for evaluation of a test, this encompasses four criteria:

**Analytic validity** refers to the accuracy with which a particular genetic characteristic (for example, a DNA sequence variant) can be identified in a given laboratory test

**Clinical validity** describes the accuracy with which a test predicts a particular clinical outcome; when a test is used diagnostically, clinical validity measures the association of the test with the disorder; when used predictively it measures the probability that a positive test will result in the appearance of the disorder within a stated time period

**Clinical utility** is the likelihood that using the test result will lead to an improved health outcome; to evaluate this, the important information is about the effectiveness of the interventions available for people who test positive and the consequences for people with false positive or false negative results

**Ethical, legal, and social implications:** evaluation of these is essential in establishing the full impact of testing

**Biomarker** - a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

**CCD** - common complex disease

**CGH** - comparative genomic hybridization

**DTC** – direct to consumer

**EHR** – electronic healthcare record

**HTA** - health technology assessment

**IVDMIA** – In Vitro Diagnostic Multivariate Index Assay

**Laboratory-developed test** – test developed for in-house use by a clinical laboratory (i.e. the test is not then sold/distributed to other labs).

**SNP** – single nucleotide polymorphism

## Introduction

The first years of this century witnessed great enthusiasm for the promise of human genomics to create a revolution in healthcare. It was predicted that as early as 2010, pharmacogenetic tests would be guiding treatment decisions and susceptibility tests would be used for the early identification, monitoring and treatment of those identified as at risk of a range of common diseases.<sup>1</sup> Yet thus far, the most significant clinical development from the Human Genome Project has been the rapid growth in the number of new tests for monogenic rare diseases. These have brought valuable benefits to those who suffer from such conditions, but do not represent a fundamental revolution in medical practice.<sup>2</sup>

Broader genetic applications have not only been few and far between, but until recently where applications such as susceptibility testing have reached the market (often linked to nutritional and lifestyle advice) it has generally been dismissed as premature and of no real value.<sup>3</sup> This fringe sector in genetic testing was cause for much alarm and greater regulation was called for to ensure that the public were not misled by unreasonable claims for the utility of such tests.<sup>4</sup> These concerns were expressed as part of a broader debate about the rise of predictive genetic tests and our preparedness for a genomic revolution in health care. However, since the anticipated flood of products has yet to emerge, it is little surprise that there the sense of urgency which was present in the late 1990s and first years of this century began to dissipate.

Whilst we must still exercise some caution, particularly in predicting timelines, we seem to be at the beginning of a new phase of progress in genomics, in which the large public and private investment may finally start to pay off, a development we might term 'Genomics 2.0'. The term is used to draw a parallel with the world wide web: the hype of the dotcom bubble was followed by a spectacular crash, but in recent years a new phase of development has emerged with a host of popular and useful novel applications heralding the arrival of what has become termed 'Web 2.0'. There remains little imminent danger of healthcare being engulfed by a tsunami of genomic applications, but the trickle may soon turn into a stream.

We describe some of the main features which characterise Genomics 2.0 in detail below. They include: a new wave of scientific discoveries based on robust study models and high-throughput genotyping technologies; a new business model for the In Vitro Diagnostics (IVD) sector; an emergent market for CGH array in rare disease genetics; gene expression tests in oncology, and susceptibility tests for a range of common diseases; the beginnings of a move to plug some regulatory gaps, and a revitalisation of the policy debate. Whatever the scale and pace of change, the question remains: are we prepared for what lies ahead? Whilst the tests and business models may be new, the policy questions which they raise are not.

### ***Identifying the policy issues***

There has been much concern about both the ethical, legal and social consequences of genetic testing and also about the clinical dangers which arise from the premature commercialisation of tests which have not always been properly evaluated and which enter clinical practice when their predictive power and clinical utility are still unclear.

The dangers of inadequate evaluation can be seen in the early years of Phenylketonuria (PKU) testing in the US when numerous children were wrongly diagnosed as PKU sufferers and some received inappropriate treatment as a result.<sup>5</sup> There is concern that the premature use of poorly validated tests will increase as the number of gene-disease associations for common

complex diseases (CCD) increase, in part because there is still a tendency for many people to overestimate the predictive power of genetics. Recent reports on the discovery of a gene linked to obesity, heralded the finding as “the fat gene”, as if it was the most important determinant of obesity. Yet in fact the conclusions of the study were far more cautious, reporting that those who carry two copies of the gene risk variant weigh only about 3 kilograms more and have just a 1.67-fold increased odds of obesity when compared with those not inheriting a risk allele.<sup>6</sup> Concerns have also been expressed about the speed with which gene expression tests have entered clinical practice in oncology.<sup>7</sup>

These issues were first raised in the United States by the National Academies of Science as early as 1975<sup>8</sup> and have been the subject of heated discussion for the last ten years in the US, Europe, Canada, Australia and elsewhere. The key questions raised in this policy debate include:

- How do we decide when a test is ready to enter routine clinical practice?
- How do we protect the public from misleading claims and premature application of basic science, whilst at the same time encouraging and promoting innovation?<sup>9</sup>
- How do we foster public enthusiasm for progress in genetic science, whilst encouraging a healthy scepticism?

### **The potential harms of clinical genetic testing**

Clinical tests of low predictive value can lead to both false positive or false negative results. For patients the harm arising from a false positive result may include psychological anxiety and undergoing further diagnostic tests or even therapeutic interventions, either of which may carry unnecessary risks. Patients with false negative results may gain a false reassurance, and miss out on necessary treatment. Patients may also be harmed by tests which, whilst having strong predictive value, do not have any impact on the treatment or patient outcome.<sup>10</sup>

For physicians, poorly evaluated tests hamper their efforts to help patients, waste their time in unnecessary procedures and open them to the danger of accusations of malpractice and the threat of litigation. Such tests have economic consequences too wasting resources which could have been used to deliver genuine clinical benefits, or, in the case of false results, may trigger unnecessary and costly additional tests or treatments.<sup>11</sup>

These general points demonstrate that few, if any of the harms associated with genetic tests are unique to them, but they have raised particular concern for a number of reasons, not least the last century’s dark legacy of eugenics and fear of a ‘new eugenics’ based on genetic discrimination in insurance and employment. The clinical impact of genetic tests also gives cause for concern, particularly when they are used for reproductive decision-making; or where a test may have significant psychological impact because it predicts the later onset of an incurable disease. In the case of tests for common complex diseases there is a concern that overuse of susceptibility tests of limited predictive value will lead to the medicalisation of the worried well. Predictive tests raise other issues, for instance, doctors cannot learn from experience with predictive tests because they cannot compare test results with the patient’s signs and symptoms and by definition, such tests are ‘stand-alone’ i.e. there is no other testing method which can be used to confirm the test result.

### **The complexity of common diseases**

The new wave of genome-wide association studies are revealing that earlier research was often underpowered and poorly-designed. A recent study looked at 85 gene variants which had been linked to acute coronary syndrome (ACS) in earlier work. The new study failed to confirm any of the 85 markers,<sup>12</sup> indicating how easy it is to cherry pick statistically nominally ‘significant’ results from studies of thousands of markers and the dangers that result if researchers do not seek to replicate the results in independent populations. Of greatest concern is the fact that at least six of these unproven markers are being offered as clinical tests to assess risk of cardiovascular disease.

The science is difficult because common, complex diseases are multifactorial – environmental factors play a major role in disease risk and heritable risk will generally be determined by the small effects of a large number of different genes. Some of the markers emerging from recent GWA studies convey significant increased risk, for instance the gene for age-related macular degeneration, but in many other cases the risks involved are of a far lower order. Thus, most recently discovered variants merely convey degrees of risk, often moderate in size; in most recent cases odds ratios have been below 1.5 for allele phenotype associations in general population samples.<sup>13</sup>

Whilst such findings are of significance at a population level, attempts to apply them in the form of a test at an individual level will have limited clinical utility unless the relative risks are very high, say 50+.<sup>14</sup> In these cases it will only be possible to predict significant heritable risk effects, if tests combine large numbers of genes and use complex interpretative algorithms to provide a risk score. There is the further problem that most gene-disease association studies have been based on research predominately in Caucasian populations, and given genetic heterogeneity across populations, results and the predictive value of tests may not be reproducible across ethnic groups.

### **Genomics 2.0 – the changing landscape**

As indicated earlier the emergence of Genomics 2.0 is a multi-faceted development involving new developments in basic science, clinical practice, commerce, regulatory practice and public policy. These developments are moving on independent but interconnecting trajectories, it is a complex and rapidly evolving landscape.

### **Progress in science and technology**

For those wishing to understand the genetic basis of common, complex disease, the last year has been a promising one. Progress in both genotyping technology and our understanding of human genetic variation have facilitated a new wave of genome-wide association studies and genome-linkage studies. Scientific publications have described a series of robust, well-replicated gene-disease associations in areas such as cancer, diabetes, heart disease and arthritis.<sup>15</sup> Once again scientific leaders are promoting the vision of a genomic revolution in healthcare.<sup>16</sup> Biotechnology companies who share this vision are bringing the science into the clinic; predictive tests in areas such as diabetes, heart disease and cancer have been launched this year and more are in the pipeline (see table, page 15).

The technical and clinical intricacy of many of these tests is unparalleled. Microarray-based tests looking at large panels of genes and using complex interpretative algorithms to deliver a clinical

interpretation represent a quantum leap in diagnostic complexity. For instance, the OncoVue test developed by the US company InterGenetics is a polygenic test for risk of breast cancer which examines 117 common polymorphisms located in over 100 genes.

## Developments in business and regulation

It is not only the tests which represent a radical disruption with the past. The business model adopted by many of the biotech companies entering this space also challenges conventional practice. The traditional *in vitro* diagnostics (IVD) sector has been a high-volume, low margins business where companies hold intellectual property (IP) in testing platforms, and have not competed over biomarkers.<sup>17</sup> Companies such as InterGenetics, Celera and Genomic Health have emerged with a business model based on exploiting IP in biomarkers and selling their tests not as kits but as in-house tests delivered by the company's own reference laboratory (or through a licensing deal with a leading commercial reference laboratory). Such companies are beginning to gain higher reimbursement rates for their new tests: for instance Genomic Health's Oncotype Dx test which costs \$3,460 in the US and OncoVue's which costs £595 in the UK.<sup>18</sup> Such pricing present a significant challenge to publicly-funded healthcare systems suffering from severe financial constraints.

Regulation is also changing, although rather more slowly. One area where regulators have been active is pharmacogenetics, with the FDA and Health Canada producing a number of guidance documents about the development and validation of pharmacogenetic tests.<sup>19</sup> The FDA have also published new guidance documents indicating that it now intends to plug some of the gaps in its current regulatory framework.<sup>20</sup> Systems for the evidence-based evaluation of new tests have been introduced in the United States and the UK.<sup>21</sup> In Australia concern about genetic test regulation was a significant factor in the wholesale revision of the regime for regulating *in vitro* diagnostics.<sup>22</sup> International activities are also significant – not least the new OECD guidelines on quality assurance for molecular genetics labs.

## Policy movement

Just as the science now seems to be bearing clinical fruit, so too the policy world seems to be moving into a new phase of activity. In the United States the past year has seen an investigation of direct-to-consumer testing by the Government Accountability Office<sup>23</sup>, the introduction of two bills on oversight of genetic testing into the US Senate<sup>24</sup>; the Secretary's Advisory Committee on Genetics, Health and Society has begun work on a report which will analyse the regulatory framework and recommend changes, and a new Institute of Medicine Roundtable group is launching its own investigation of the issue. Regulatory questions left unresolved when the Secretary's Advisory Committee on Genetic Testing was disbanded in 2002 are now being revisited. Much of the momentum for these policy developments comes from support for pharmacogenomics and the concept of personalise medicine, particularly the US Health Secretary's Personalised Healthcare Initiative.<sup>25</sup>

Meanwhile in the United Kingdom the Human Genetics Commission (HGC) is revisiting the recommendations it made in 2003 about the regulation of direct-to-consumer (DTC) genetic tests, to see if it can galvanise the government to act.<sup>26</sup> These recommendations included preventing DTC provision of predictive tests; ensuring pre-market review of new tests; and establishing a code of practice to govern DTC testing services.<sup>27</sup> The HGC are not the only body to be concerned: the National Screening Committee is exploring how it might exercise its authority over private screening tests<sup>28</sup> and the Royal College of Pathologists are calling for a

new Health Technology Assessment (HTA) body for diagnostics.<sup>29</sup> These last two are not focused specifically on genetic tests but would impact on them. Similarly at European level, a revision of the IVD Directive is said to be imminent, with much expectation that it will become more prescriptive and plug some of the current regulatory gaps, in part to address concerns about genetic tests.<sup>30</sup>

The activities of regulators need to be understood in the context of changing policy priorities. A concern with limiting the inappropriate use of new technology and the political necessity for controlling healthcare expenditure continue to be major issues. However, in the last decade or so there has been a marked shift in emphasis, with a new imperative to support the healthcare innovation process emerging as a significant policy concern. Regulators, whether licensing agencies like FDA and European Medicines Evaluation Agency (EMA), or HTA bodies such as the UK's National Institute for Clinical Excellence (NICE), are beginning to reconceptualise their role in the innovation process. This involves a move from a strictly gate-keeping role based on evaluating the evidence for new technologies, to a more collaborative or facilitative role.<sup>31</sup>

This new policy orientation has taken concrete shape in programmes such as the FDA's Critical Path initiative<sup>32</sup>, the NIH's Roadmap<sup>33</sup> with its commitment to translational research, the CIHR's clinical research initiative and the work of its Knowledge Translation Branch, the Innovative Medicines Initiative in Europe<sup>34</sup>, the European Medicines Agency (EMA)'s Road Map strategy<sup>35</sup>, and the UK Clinical Research Collaboration<sup>36</sup>, and the new health research structures and processes to support translational research recommended in the UK government's recent Cooksey Report.<sup>37</sup> These initiatives may involve new models of evaluation, or new strategies to assist in the development of the evidence base for a new technology, by providing either the incentives or infrastructure for data collection, for instance through conditional reimbursement. They are often primarily focused on therapeutics but they have implications (and potential) for diagnostics innovation (not least because many are designed to support pharmacogenetic testing with new drugs).

So the scientific research is now bearing fruit, clinical applications are increasing, regulators are taking some action and the policy debate is entering a new phase with old concerns but some new priorities. There is no danger of a flood of applications in human genomics, but the trickle may soon turn into a stream. Because the change has been slower than anticipated, the nature of the policy concerns have changed somewhat. Tackling the bottlenecks in the research and development pipeline and the path to clinical uptake has become as significant as trying to prevent inappropriate or premature application. Nevertheless, the question remains: are we prepared for what lies ahead?

This report begins by describing the tests which are now in clinical use and those which are close to market, it then sets out the policy issues raised by this new wave of tests in three chapters which cover: building the evidence base, the regulatory framework for evaluating new tests, and the ethical issues they raise.

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## **I. Current clinical applications and tests close to the clinic**

DNA microarrays are now being used in clinical practice in a variety of fields, including rare disease genetics, oncology and pharmacogenetics. Common complex diseases such as cancer are highly heterogeneous, with significant phenotypic variation in severity of disease, prognosis and response to treatment. This phenotypic variability is matched by a corresponding complexity in aetiology; most common, complex diseases are the outcome of multiple genetic mutations, and gene-environment / gene-gene interactions. One of the main goals of new molecular diagnostic technologies is to improve understanding of the underlying molecular biology of disease through multivariate analysis of Single Nucleotide Polymorphisms (SNPs), copy number variation, gene expression, or proteins. The discovery of new biomarkers with these technologies offers the promise of improved disease staging, risk stratification, and treatment decisions.

Whilst some companies have chosen to use microarrays as a platform for clinical tests, others have preferred to use them for research purposes, and then, having identified a small panel of genes for use in a clinical test, moved on to a more robust platform such as Real Time Polymerase Chain Reaction (RT-PCR). Some companies developing gene-expression tests prefer RT-PCR for both research and clinical applications, in large part because of the greater dynamic range of gene expression captured by this technology.

### ***SNP-based tests for common complex diseases***

SNP-based predictive tests in areas such as diabetes, heart disease and cancer have been launched this year and more are in the pipeline. (see chapter 1). Most of these tests are for a single disease, however, a small number look at susceptibility to a range of diseases. Some of the companies offering these tests supplement the risk profile with nutritional advice and operate in a space between susceptibility testing and nutrigenetics (eg Sciona and Suracell).

Two new companies which have just emerged are the US companies Navigenics and 23andme. Although the full details of 23andme's services are not yet available, the companies would appear to be planning to offer similar direct-to-consumer services, whereby customers will supply a DNA sample and the company will provide them with information on a very broad range of disease risks, using the latest findings from the scientific literature. Each of these companies has the support of one of the leading microarray companies, Navigenics has Affymetrix as a partner and 23andme has Illumina. The huge scope of what these companies may offer is indicated by comments from the CEO of Illumina: "So if your target is to do consumer genotyping with SNPs that are medically relevant, you may want to trawl through the literature and discover every SNP that is known to have an association and make sure that is on your chip ... that is easy to do because we have the architecture in our product line so you could take a [HumanCNV370-Duo DNA Analysis BeadChip] and augment it with an additional 60,000 SNPs that you have gleaned from the literature, or you could do that on the HumanHap550 as well," he said. "That's very likely the kind of chip you will see used in consumer genotyping."<sup>1</sup>

The technical and clinical intricacy of some of these tests is unparalleled. Microarray-based tests looking at large panels of genes and using complex interpretative algorithms to deliver a clinical interpretation represent a quantum leap in diagnostic complexity. For instance, the OncoVue test developed by the US company InterGenetics is a polygenic test for risk of breast cancer which examines 117 common polymorphisms located in over 100 genes.

## **Rare disease genetics**

Microarrays have two clinical applications in rare disease genetics at present. The first is SNP analysis where the disease involves a large number of possible markers, either different alleles of the same gene or different alleles of more than one gene. Tm Bioscience's cystic fibrosis test and Progenika's LIPOchip for familial hypercholesterolemia are both examples of this type of application. The second type of application is array comparative genomic hybridization (CGH). CGH is a method for the identification of changes in copy-number of specific regions of DNA. With array CGH, it is possible both to identify and measure sequence copy number variation, but also map these sites within the genomic sequence. Current array CGH applications are primarily in the rare disease field, in particular developmental disorders and mental retardation. In this context CGH has the potential to replace traditional cytogenetic techniques such as chromosome banding and FISH (fluorescent in situ hybridization).

However, there are also array CGH applications in common, complex disease areas including autism and cancer. In cancer CGH is used for molecular profiling of tumours for prognostic, diagnostic or treatment outcome prediction (Combimatrix HemeScan test and Array Genomics UroChip). Clinical applications in oncology are expected to increase over the next five years. However, array CGH is currently the least popular technology for multivariate clinical testing in the common, complex disease area where SNP testing and gene expression tests are the most common technologies.

## **Gene expression tests**

Cellular gene expression refers to the production within a cell of active, functional proteins from selected genes. Clinical application of gene expression data, has been almost entirely limited to oncology. Gene expression patterns are observed in cancerous cells and certain genes or sets of genes can be identified as biomarkers for those cancers. Such biomarkers are beginning to be applied in the diagnosis and classification of cancers, whether for selection of the most appropriate treatment regimen, prognosis or predicting risk of metastasis. The traditional clinical / histological taxonomy of cancers is being superseded by this new molecular taxonomy which is able to differentiate tumours which appear indistinguishable at the morphological level.<sup>2</sup>

Other applications of gene expression include XDx's AlloMap test which is used to monitor heart transplant patients for possible transplant rejection and DiaGenic's test for Alzheimer's Disease.

## **Breast cancer – a poster child for gene expression?**

Breast cancer prognosis has become the paradigmatic application for gene expression tests. Companies who have developed tests which are now on or near the market include: Agendia, Almac, Applied Genomics, Avira Dx, Celera, Exagen, Genomic Health and Veridex. Tests may predict either breast cancer recurrence, response to chemotherapy or risk of metastasis. A variety of test platforms and techniques are used including microarrays, RT-PCR and FISH. The tests vary in complexity, interrogating anything from 70 genes to just five. Tests for small panels of genes can be sold as kits to multiple laboratories, but other companies, such as Agendia and Oncotype Dx, who test for a greater number of genes, have chosen to offer their tests through their own reference laboratories. Most companies which have developed breast cancer tests are now working on similar tests for other common cancers.

The primary purpose of testing for breast cancer gene expression is to identify those patients who are most likely to benefit from chemotherapy. In the US where there is aggressive

overtreatment of patients, it is estimated that as many as 80% of women receiving chemotherapy may not actually require it. A test which can predict risk of recurrence or metastasis may be used to identify those women for whom chemotherapy will provide no benefit. The clinical benefit of the test to the patient is not its only advantage; avoiding a significant proportion of unnecessary treatments may also produce cost-savings for reimbursers.

The current leaders of this emerging market would appear to be the Oncotype Dx test produced by US company Genomic Health and the MammaPrint test produced by Dutch company Agendia. Genomic Health have received a series of positive coverage decisions from reimbursers in the United States including Aetna, United Healthcare and Medicare. The company estimate that 120-130 million people have access to the test under insurance coverage. They have international partners in Israel, Japan and the UK, although all tests are performed in GH's lab in California. The company are in discussions with FDA about the regulatory status of the test, which would be considered an IVD MIA according to recent FDA guidance (see Chapter 3)

Agendia's MammaPrint test was approved this year by FDA. It is also gaining coverage in Europe but has been rejected by some US insurers.

### ***Point-of-care testing***

For a variety of commercial, clinical and regulatory reasons many of these tests are offered as LDTs in reference laboratories. In the traditional innovation process for IVDs, the next stage would generally be a kit which can be used by multiple labs. However, it may be that some tests will skip this stage and go straight to point-of-care applications. The point-of-care market is a fast-growing segment of the IVD industry and one recent industry report suggests that DNA POC tests will emerge in infectious diseases, foetal and newborn screening, cancer and heart disease. Whilst there is strong demand for point-of care (POC) tests and it is a fast-growing sector of the IVD business, many people involved in genetic testing are sceptical about POC applications in all but a small number of cases. There is a view that POC applications will only make financial and clinical sense where a very rapid result is required and that in most cases where genetic testing is carried out this is not the case. POC testing relies on being able to provide results which any doctor or nurse can understand, this is often not the case with genetic testing. Nevertheless were POC testing to emerge, then it may present serious capacity challenges to the healthcare system as regards education and support of the test users by clinical geneticists and genetic counselors.

## CGH Microarrays

Company	Test	Status	Kit/LDT
Perkin Elmer / Spectral	Constitutional Array Chip	RUO	Kit
Quest Diagnostics			LDT
LabCorp	Using Spectral kit (see above)		
Abbot / Vysis	mental retardation and learning disabilities	Research Use	Kit
Combimatrix	Constitutional Array (currently focused on rare diseases but new version will also diagnose/predict autism)		LDT
	HemeScan		LDT
Signature Genomics	Signature PreNatal Chip		LDT
Genome Dx	GenomeDx (applications of test include screening for autism <sup>3</sup> )		LDT
	CopyDx		LDT
Array Genomics (France)	UroChip (clinical urology test for for diagnosis/prognosis of bladder, kidney and prostate cancer)		LDT
Emory University	EmArray dystrophin test for muscular dystrophy		LDT

## Microarrays for monogenic disorders

Company	Test	Clinical use	Kit/LDT
Tm Bioscience / Luminex	Cystic Fibrosis	US / Europe	KIT
Progenika	LIPOchip (Familial Hypercholesterolemia)	Europe	KIT
Harvard-Partners Center for Genetics and Genomics	Hypertrophic cardiomyopathy / Hearing loss	In development	LDT

## SNP-based tests for common, complex diseases

Company	Test	Clinical use
deCODE (Iceland)	Diabetes and stroke	US
InterGenetics	OncoVue	Europe
IntegraGen (France)	Autism	Europe 2007?
Celera	Heart disease	US 2007?
GenoSense (Austria)	screening tests for risk of a range of common, complex diseases	Europe, Canada, US
Progenika (Spain)	Inflammatory Bowel Disease	Not known
Myriad	BRCA - breast cancer	US / Europe
	Melaris - skin cancer	US / Europe
Nanogen	Schizophrenia	In development
Interleukin (add others?)	Gensona – heart health tests	US
Navigenics	screening tests for risk of a range of common, complex diseases	US 2007?
23andme	screening tests for risk of a range of common, complex diseases	US 2007?

## Gene expression tests

Company	Test	Status
Genomic Health	Oncotype Dx	LDT
Agendia	MammaPrint	LDT but FDA approved and CE Marked
XDx	AlloMap – monitoring test for transplant rejection	LDT
Applied Genomics	MammoStrat	LDT
Aviara Dx	MCID – CUP test	LDT
	BCP test	LDT
Celera / LabCorp	Breast cancer metastasis risk	LDT
Exagen	Breast cancer prognostic – FISH-based 5-gene panel	submitted to FDA
ExonHit	Diagnosis of Alzheimer’s Disease	In development
Pathwork Diagnostics	Tissue of Origin test (submitted to FDA) – uses gene expression signatures to match Cancers of Unknown Primary (CUP) to tissues of known origin	Awaiting FDA approval
Roche Molecular	Gene expression test for differential diagnosis of leukaemia	In development
Veridex	RT-PCR test for breast cancer metastasis	FDA approved
DiagnoCure (Quebec)	PCA3 test for prostate cancer Test for colon cancer	Kit In development
Almac Diagnostics (UK)	Gene expression tests for colorectal and breast cancer. Pipeline includes similar tests for lung, ovarian and prostate cancer.	RUO
DiaGenic	Test for early diagnosis of Alzheimer’s	In development

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## 2. Developing the evidence base

As noted in the introduction, there has been concern that the investment in basic research in the field of genomics has not produced a greater number of practical applications. Given the relative paucity of clinical applications, there is much policy concern that this may be due to failures in the innovation process, exemplified by the Institute of Medicine's recent report on cancer biomarkers.<sup>1</sup> The issues raised in this discussion fall under two main headings – one is the need for standards/standardisation and the second is the issue of developing the incentives, infrastructure and investment needed for the development of the evidence base.

### *The need for standardisation*

#### 1) Quality control, data analysis and trial design

Some experts point to serious challenges with quality control for microarrays. Problems can arise in at least five places:

- array fabrication,
- target preparation,
- target hybridization,
- imaging,
- data analysis.<sup>2</sup>

Some experts point to the need for new statistical techniques and bioinformatics tools to deal with the huge quantities of data emerging from microarray studies as the key experimental issue. One recent paper re-analyzed data from seven major studies using microarray data to improve prognosis of cancer patients. The review found that "The list of genes identified as predictors of prognosis was highly unstable," with five studies publishing "overoptimistic results."<sup>3</sup>

Others suggest that the key problems are not in bioinformatics but are basic experimental design flaws which are common to other types of study: "overfitting of data, bias, and sample sizes that are disproportionately small compared to the number of variables measured," have all been cited by one expert as common problems. These have even affected studies whose findings have been translated into tests which are now in routine clinical use.<sup>4</sup>

These design flaws make it all the more important that researchers be able to review and compare each others data. However, such activity is hampered by lack of access to the necessary clinical and experimental data, or, where it is available, a lack of standardized data formats to facilitate comparison. One suggestion is that research funders should show leadership in this area by encouraging more standardized reporting of data. Standard-setting is currently being led by the Microarray Gene Expression Data Society (MGED) which seeks to establish standards for microarray data annotation and exchange, facilitate the creation of microarray databases and related software, and promote sharing of microarray data. Its most significant achievement to date has been guidelines for the Minimum Information About a Microarray Experiment (MIAME) which have been adopted by many leading scientific journals.

Attempts to deal with quality control issues, in particular the reproducibility of findings across platforms, have been led by the Microarray Quality Control project (MAQC). This initiative has been led by the FDA and has involved senior figures from industry, government, and academia.

Their findings have demonstrated that microarray data from a variety of platforms can be reproducible and comparable, if sufficient care is taken with experimental design and data handling.<sup>5</sup>

Notwithstanding these moves towards standardisation, many believe that large-scale DNA or protein microarrays are unlikely to become routine clinical tools. In part because they will generate far more data than could possibly be clinically useful, and in part because they will be too expensive. Issues of data handling and interpretation are also present when microarrays are used in rare disease testing. For instance, the use of the Tm Bioscience test has facilitated the moved to newborn screening for cystic fibrosis in Canada, yet given the limited panel of mutations used in the test (the ones approved by the American College of Obstetricians and Gynaecologists and the American College of Medical Genetics (ACOG/ACMG)) then in the context of a national screening programme a large number of clinically suspect cases arise which are not identified by the test. Such cases are referred for whole CFTR (cystic fibrosis transmembrane conductance regulator) screening which in turn generates significant amounts of new data the meaning of which is not clear, and so results must be returned classified as variant of unknown significance. Array CGH also throws up a large number of cases where the clinical interpretation of the result is challenging. Some leaders in the field have in the past publicly questioned whether array CGH is ready for routine clinical use suggesting that until more is known about normal CNV variation in different populations then the capacity to detect smaller CNVs across the genome could overwhelm pathologists with huge amounts of uninterpretable data.<sup>6</sup>

In such contexts the dividing line between clinical testing and clinical research is ambiguous. In both cases there is a pressing need for systematic data collection and data sharing on a national basis to build the evidence base but clinicians complain of a lack of resources. There is no obvious source of funding as provincial authorities will not fund initiatives which are national and national funding streams such as CIHR appear to focus on more basic research.

## **2) Improving standards in tissue banks – samples and phenotypic data**

The advances made in the Human Genome Project and subsequent genomic research have relied upon the sharing of sequence and other forms of data by national and international consortia. Recent initiatives such as the Genetic Association Information Network have reinforced the importance of this co-operative approach to research. Sharing data and samples facilitates the research process but brings with it a range of ethical concerns (see chapter four). However, there are also practical issues to address.

There are a huge range of biobanks or tissue repositories but their value is often limited because of variations in specimen collection, storage and use, collection and processing of data and informed consent procedures. The recent Institute of Medicine (IOM) report on cancer biomarkers highlights some of the most common problems: biomarker studies tend to use archived specimens which have been collected and stored for other purposes and include a heterogeneous mixture of specimens representing different disease stages and treatments.<sup>7</sup> The proposed solution is for NIH funding to create and maintain biorepositories which are developed in conjunction with large cohort studies and clinical trials. Similar initiatives have been developed in Canada and the UK. Long-term maintenance of such biorepositories will be a significant expense.

## Initiatives in oncology

As noted in the previous chapter, the field of oncology has seen the most rapid progress in the development of clinical tests based on the new high throughput technologies. It is perhaps not surprising then that cancer research is also showing leadership in standard-setting initiatives.

### 1) United States

**Cancer Biomedical Informatics Grid (caBIG)** - an integrated biomedical informatics infrastructure developed by NCI to share collated cancer research data between research groups to facilitate knowledge sharing, reduce unnecessary duplication of experiments and drive scientific discovery in the field.

**Early Detection Research Network (EDRN)** - a National Cancer Institute initiative which has led on a variety of standard-setting processes such as a joint workshop in 2005 with the National Institute of Standards and Technology on standards and metrology for cancer diagnostics.

### 2) Canada

**National Tumour Bank Network** – CIHR initiative which will develop and adopt standard operating procedures, as well as set up a network-wide database. Individual banks through the network will electronically publish a list of their holdings and will make tissue samples and their associated data-pathology reports, clinical outcomes, molecular profiles, etc.-available to cancer researchers across Canada and abroad.

**Ontario Tumour Bank** – co-ordinates collection and storage of tissue from six clinical centres, centralized data collection undertaken with patient privacy protections.

### 3) Europe

**Receptor and Biomarker Group (RBG)** – this is an initiative of the European Organization for Research and Treatment of Cancer (EORTC) which brings together researchers and clinicians from 18 countries to improve the analytic and clinical validity of biomarker tests through the use of quality assurance schemes which are mandatory for tumor assays used in EORTC research.

### 4) United Kingdom

**National Cancer Tissue Resource** – a novel UK tumour bank, established in 2003 by the National Cancer Research Institute (NCRI), to develop standardization of sample and data collection and storage, to establish a network of tissue acquisition centres and to link these collection centres with processing centres where microarray data can be generated and stored. A central information system will track samples and provide a bioinformatics hub to link histopathological data with clinical data and research results.

**NCRI Cancer Informatics Network** - international network established in 2003 to foster collaboration with bodies such as the US NCI Center for Bioinformatics (NCICB) and the European Bioinformatics Institute (EBI). Its aim is to encourage the use of standardised datasets and exchange mechanisms to allow the integration of data from different cancer research databases.

**NCRI Confederation of Cancer Biobanks** was created to harmonise and improve standards of collection, storage and distribution.

## **Investment, incentives and infrastructure**

Reform is needed to improve the incentives, infrastructure and investment which are required to run large-scale clinical trials and facilitate other forms of systematic data collection. Yet there is significant concern amongst many industry stakeholders that the prices they are paid for their products would not justify significant investment in trials to demonstrate the clinical validity and utility of new tests, and a concern amongst many other stakeholders that other parties do not have any strong incentives to participate in building the evidence base for new tests.

The example of the Roche Amplichip (see following chapter) clearly demonstrates structural problems which are leading to market failure. Since Roche do not control the IP in the CYP450 biomarkers, they would face immediate competition from me-too tests, were they to invest in major clinical studies. An enhanced evidence base will build the market not just for Roche but for every other company who wants to sell a CYP450 test. The example clearly illustrates the limitations of the traditional innovation process in the IVD sector: public sector research funds are focused on small-scale studies which do not meet the demands of reimbursers, private sector investment is focused on the development of testing platforms rather than enhancing the clinical utility evidence base.

The question for policymakers tackling this issue is: what can be left to the market and where must the public sector intervene? The first approach (holding testing labs and device makers responsible for clinical evaluation) involves market-driven restructuring of the traditional parts of the diagnostics industry, and would necessitate higher reimbursement levels to cover the costs of clinical evaluation. We have already indicated (see Introduction) that there are moves in this direction, with the emergence of a new business model based on IP in biomarkers and greater investment in clinical evaluation in return for higher reimbursement rates. Some stakeholders discussed this development as the rise of 'blockbuster diagnostics'. Whether this business model succeeds in the long-term remains to be seen, and the degree to which it will transform the entire IVD industry is also unclear.

Such a fundamental restructuring would take decades but it may already be underway and could bring significant benefits.<sup>8</sup> However, it necessitates an acceptance of some forms of IP in biomarkers and any forms of gene patenting remain highly controversial. The new business model also requires acceptance by healthcare reimbursers of higher prices for something they have traditionally paid little for. At a time when there is great pressure to control escalating healthcare costs, agreeing a 'reasonable price' will take much negotiation and possibly new methodologies for assessing the clinical and economic value of diagnostic tests. The example of Myriad's BRCA test suggests that it may be easier to gain higher prices for IVDs in the United States than in other countries, although whether they would have the option of creating homebrew alternatives is less likely in the case of tests with proprietary interpretative algorithms such as the MammaPrint and Oncotype Dx. The more likely alternative would be a cheaper rival kit but here the question would arise whether the cheaper version provided the same quality of clinical data.

For many tests with weak intellectual property protection, there is little alternative to public or health system funding of clinical evaluation. Thus far, investment in new clinical evaluation of genetic tests before introduction by health systems has been limited. Large-scale public sector research programmes such as the UK Biobank are one example of state-funded research.

However, it may be that it is not a question of choosing between market solutions or state intervention, but identifying the balance to be struck between the two approaches and ways of combining them. Public-private collaborations are being explored in the US through the development of consortia for biomarker validation, as part of the FDA's Critical Path initiative and through research programmes funded by NIH such as the Genetic Association Information Network. The SNP Consortium which brought together the Wellcome Trust and 13 private companies is another example of successful public-private partnerships.

Public-private partnerships can clearly be seen at two points in the commercial IVD development process. In basic research, companies need access to samples and this can be dealt with by partnerships with academic collaborators. Companies such as Genomic Health, Celera and deCODE have become the catalysts for international research collaborations which allow them to conduct large-scale studies and replicate their findings in multiple sites. However, some industry stakeholders expressed concern that discovery may now slow down because these resources have been mined and there are relatively few new large sample collections being developed. Pharmaceutical companies have large sample collections but they generally only give access for studies which suit their own R&D priorities. Public sector funding would be required to deal with this gap, and also to address the problem of ethnic diversity. Current sample collections are mostly made up of Caucasians; given the genetic diversity across ethnic groups, there is a pressing need for well-characterised samples from a broad range of populations. The ethical issues arising from this (consent and benefit sharing) are dealt with in chapter four.

As noted earlier, once an initial biomarker discovery has been robustly replicated, then further studies will be required to identify its possible application as a clinical test for a specific purpose in specific groups of patients: i.e. establish the clinical validity and clinical utility of each application. This may often happen after a test is on the market. Here too there is scope for public-private collaborations, as is demonstrated by examples from the gene expression market. Agendia and Genomic Health's tests prognostic tests for breast cancer recurrence are both now on the market (see previous chapter) but further studies are being run to learn more about their utility. These studies are collaborations between the public sector and the private sector. This is a promising model but public funding is limited, so it requires test developers to demonstrate that their products are likely to meet important, unmet clinical needs.

### ***The role of research funders***

Finally, there is the issue of translational research funding. As noted in the introduction, it is now commonly accepted that translational research is under funded and inadequately supported by the traditional academic infrastructure. Interdisciplinary team work is not fostered by academic career structures which reward individual achievement and there is a lack of relevant training for those wishing to conduct translational research. Publication of findings from studies designed to replicate someone else's discoveries are not prime candidates for high-impact journals. Individual initiatives to fund some translational research programmes may not be sufficient to build and maintain capacity in this area.

A guarantee of long-term career security will be needed to attract and retain high-quality staff in any numbers. Like the restructuring of the IVD industry this is an enterprise which will take time, in part because of the time needed to generate capacity through training and education, but in large part because in the absence of significant additional funding for biomedical research, it will be necessary to re-allocate monies currently spent on basic research, a move likely to meet with significant opposition from those who will be affected. The UK's Cooksey Report

comes down heavily in favour of maintaining existing basic research funding, with any new monies for research being channeled to translational activities. Such an approach requires new funding to be made available and recent experience in the US with the NIH budget illustrates how perilous that strategy may be.

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### 3. Evaluating the evidence – the regulatory framework

Successive policy reports in the US, Canada, Europe and Australia have highlighted the need for enhanced regulation of genetic tests, in particular the need for more rigorous and systematic evaluation of new tests. This chapter will map the regulatory space, outlining the role of statutory regulatory agencies, reimbursement/HTA and clinical practice guidelines developed by professional bodies. It will describe the gaps in regulation and the attempts to fill those gaps, identifying policy options and possible models of best practice emerging from current attempts at regulatory reform.

There are two broad regulatory challenges:

- 1) Ensuring that test developers/providers offer accurate and comprehensive information about the strengths and weaknesses of their tests to doctors and patients – truth-in-labelling / truth-in-promotion
- 2) Evaluating the clinical utility of new tests to make reimbursement decisions and to develop clinical practice guidelines

#### ***1. Statutory regulation – ensuring truth-in-labelling***

Canada and the United States share a similar regulatory gap. The medical device regulations have not been enforced against laboratory-developed tests (LDTs). The Canadian regulators have received a series of conflicting legal opinions on their authority to regulate LDTs but the most recent advice states that such tests do not fall under their regulations. Consideration is now being given to how to address this gap.

Much of the discussion of enhancing regulation in the United States has focused on the LDT issue, which is a larger problem in the US due to the large number of commercial clinical labs.<sup>1</sup> Last year we reported that after some years of vacillation over the nature of its authority and how to exercise it, FDA had begun to regulate LDTs on a piecemeal basis, focusing on complex tests with high-risk uses. We suggested that this trend would continue and would eventually require clarification through guidance.

FDA came under political pressure regarding its regulation of LDTs in July last year when a GAO report on nutrigenetic tests was presented to the Senate Committee on Aging at a special hearing where both testing companies and regulatory agencies were heavily criticized by the Committee Chair Sen. Gordon Smith. The most significant development in the hearing was that the Director of the Office of In Vitro Diagnostics at FDA, Dr Steve Gutman, under questioning from Sen Smith, stated that FDA both had the authority to regulate LDTs and should do so.<sup>2</sup> Shortly afterwards in September 2006 the FDA issued a draft guidance on what it termed In Vitro Diagnostic Multivariate Index Assays.

This guidance identified a subset of LDTs which FDA believe require regulatory scrutiny. These tests the agency has termed In Vitro Diagnostic Multivariate Index Assays (IVDMIA). First, IVDMIA “are developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratorians, and clinicians who order the tests.” Second, some IVDMIA have “high risk intended uses” and

patients rely on them to “make critical healthcare decisions.” These factors, taken together, led to the conclusion that “there is a need for FDA to regulate these devices to ensure that the IVDMIA is safe and effective for its intended use.” FDA also identifies two key hallmarks of IVDMIAs. First, such a test “combines the values of multiple variables using an interpretation function to yield a patient-specific result” that is used for diagnosis, prevention, treatment, or mitigation of disease. Additionally, the test result’s derivation must be “non-transparent and cannot be independently derived or verified by the end user.”<sup>3</sup>

The guidance proved controversial with many industry stakeholders raising concerns about the potentially harmful effects of FDA regulation and other stakeholders stating that FDA had not gone far enough. A revised version of the guidance document has just been issued which holds largely to FDA’s original intent but attempts to clarify which kinds of test will be considered IVDMIAs and which will not. The other major change is a period of grace during which FDA will exercise enforcement discretion.

Whilst it may be that FDA have correctly identified the category of tests where lack of regulatory oversight is of greatest concern, the broader issue of the unlevel playing field between test kits and LDTs has still to be addressed. A range of tests offered on a monopolistic basis by reference laboratories will not fall under this guidance as they do not fit the criteria of an algorithm-based test, for instance deCODE’s recently introduced tests for diabetes and stroke risk, and Myriad’s more well-established tests for breast and skin cancer. Other complex high-risk tests will also fall outside the new rule for the same reason, for instance array CGH tests used for prenatal screening. In clearly reasserting their authority to regulate LDTs but choosing to exercise enforcement discretion over the vast majority of these tests, FDA has merely highlighted the regulatory gap which is ever-widening as more and more US companies chose the reference laboratory business model to commercialise their tests.

Having asserted its authority over LDTs, the FDA may be called upon to exercise that authority. What will the Agency do if it receives complaints about a test which falls outside the IVDMIA guidance? It cannot state that the matter is outside its jurisdiction, and there is no other authority to whom the problem can be referred. Yet for the FDA to respond by investigating other tests on an ad-hoc basis would simply add to the confusion about its position. This is not a hypothetical situation – witness the current controversy surrounding DTC genetic tests, which are LDTs, but not all of which may fall under the new IVDMIA guidance.

The situation in Canada is somewhat different in so far as there is no equivalent growth of domestic companies offering new genetic tests through the reference laboratory route. The regulatory gap around LDTs thus chiefly concerns tests developed within public hospital or university research labs and those US or European companies who market their LDTs as testing services in Canada. Regarding the latter, it is not clear what the scale of this might be, but it is known for instance that whilst the company is not actively marketing their test in Canada, Genomic Health have received some requests for the Oncotype Dx test from Canadian physicians.

The primary policy considerations in dealing with this issue are: how to balance support for clinically useful innovation against protection of public from poor quality tests; and how to ensure that extension of regulatory responsibilities does not overwhelm the resources of the regulator. It may be appropriate to deal with the public health laboratory sector and the large commercial reference laboratory sector as two separate issues.



## **Approaches to the regulation of rare disease genetic testing**

Can rare disease testing be subject to an evidence-based approach to test evaluation? Recent experience in the United States and the United Kingdom would suggest that it is possible. In the UK evaluation has taken place for the purpose of reimbursement decisions through the UK Genetic Testing Network's Gene Dossier process. In the United States evaluation has taken place in a translational research context through the Collaboration, Education and Test Translation (CETT) programme funded by the NIH Office for Rare Diseases.

### **UK GTN**

For new tests to be offered through the NHS then the laboratories offering them must be members of the UK GTN which was established in 2002 and brings together labs from across England, Scotland, Wales and Northern Ireland. The purpose of the network is to ensure that NHS patients receive high quality genetic services on an equitable basis. Laboratory accreditation is a requirement of membership of the network. The network provides educational and information resources such as an online database of tests. Laboratories which wish to offer new tests must submit their test for formal evaluation by submitting a Gene Dossier.<sup>4</sup> The Dossier builds on the experience of test evaluation in Canada and the US and uses the ACCE framework of evidence criteria:

- A**lytic validity
- C**linical validity
- C**linical utility
- E**thical, legal and social issues

The review process begins with an initial assessment by the gene dossier subgroup which then summarises its findings in a report to the UK GTN Steering Group which makes a final decision before passing the matter on to GENCag. The initial round of submissions received 85 gene dossiers. Since then a further 61 have been received, of which 43 were accepted, 10 rejected, 7 are still under consideration and one was withdrawn. A significant enhancement of the Gene Dossier is the addition of what is termed 'test criteria'. These define the clinical circumstances in which a genetic test referral is appropriate. A test may be performed even if the criteria are not met, but only after the clinician and the laboratory specialist have discussed whether the analysis is justified. Plans are now underway for inclusion of cytogenetics and for the development of a post-implementation system of data-collection and monitoring.

The UK GTN gene dossier process represents a successful effort to bring evidence-based evaluation to rare disease tests but it also represents a model which could be used more broadly in the introduction of new tests into healthcare systems. However, a major limitation of the system is that whilst there has been strong government support for the introduction of evidence-based evaluation, there has been no corresponding support for systematic data collection in the form of enhanced research funding.

### **CETT**

The CETT programme in the US is funded by the Office of Rare Diseases and began its work in 2006. Its aim is to take new rare disease tests from the research setting to clinical use in an evidence-based manner by facilitating collaborations between researchers, clinicians and patient groups to facilitate data collection, the development of detailed educational materials which can inform clinicians and patients about the test. Test developers must also complete a more detailed Gene Review for inclusion on the Gene Tests website. Applications are considered by a Review Board. By March 2007 CETT had reviewed 21 tests and were now averaging 2 new

reviews per month. 19 had been approved, the remaining two had been encouraged to resubmit. 10 tests were now available. There are ten laboratories involved in CETT including one Canadian (Peter Ray's lab at the Hospital for Sick Kids in Toronto). They have also received applications from the US and Australia. They are currently reviewing Emory University's array CGH test for muscular dystrophy.

The CETT programme, although a translational research initiative performs some regulatory functions, in particular by:

- Developing some measure of when a test is “ready for prime time” based on the mutation detection rate and the relationship of proposed new tests to existing tests; currently this is strictly the decision of a laboratory director.
- Supporting the notion of “truth in advertising” by requiring quality test result reporting that clearly explains the detection rate and other limitations of the test and helps the affected individual and clinician understand the meaning of both “negative” and “positive” test results.<sup>5</sup>

### **Information disclosure as a minimal form of regulation**

Both these initiatives illustrate that evidence-based evaluation can occur through mechanisms other than a statutory licensing regime, an alternative to formal regulation which may be particularly useful for rare disease tests. As indicated earlier, premarket review of new tests can have a number of functions. At its most ambitious regulators will use premarket review to set out in detail the types of clinical studies they require a test developer to perform, as in the FDA's Pre-Market Approval process for Class III tests. At its most modest, premarket review will focus on ensuring truth-in-labeling, as in the FDA's 510k process for Class II devices.

One approach would be to focus on using premarket review to ensure truth-in-labeling (and truth-in-promotion) as a minimal approach to premarket review.<sup>6</sup> The advantage of this approach is that it can be met by all test developers. Even in the field of rare disease tests, small public sector laboratories can put together a technical file which provides the evidence for the use of a new test, as is evident from the UK GTN gene dossier process. Furthermore, this proposal chimes with one of the central recommendations of the Secretary's Advisory Committee on Genetic Testing (SACGT), whose initial report had recommended that where limited premarket approval was given for a test, it should be accompanied by transparency of information.<sup>7</sup> They therefore recommended that laboratories and test manufacturers should provide patients and healthcare providers with evaluative data on the validity and utility of tests. This approach was summed by one SACGT member in the maxim: “Tell us what you know, tell us what you don't know.”<sup>8</sup>

A focus on truth-in-labeling is consistent with the idea of regulation by information disclosure, which is now very popular in consumer protection fields where it is seen as a way to deal with “the asymmetries of information between trader and consumer.”<sup>9</sup> Regulation by information disclosure is seen as a way of balancing the need to protect the public with a desire to encourage freedom of choice. This minimal approach reduces the regulatory burden and passes on responsibility for risk management to doctors and patients, allowing them to make informed decisions about when and how to use a test.

## **Expanding the definition of a label and encouraging transparency**

Building a regulatory system which operates by transparency of information has some limitations which must be addressed. In the case of prescription drugs, the doctor and patient will see the information contained in the product label / instructions for use, but most tests are performed by laboratories and it is they who have this information, not doctors and patients.

It would be helpful for device regulators to broaden their concept of a label and ensure that all those offering tests make the necessary information available to clinicians and the general public. Test manufacturers could be obliged to keep their labels online, where they can be accessed by all. Samples of the results sheet for the test, which shows reference ranges etc. could also be provided online. Online labeling may be preferable for industry as it is cheaper and faster to update. Laboratories have a similar duty to ensure that those who order tests have access to the relevant information.

The provision of information is another area where there is a clear difference between device regulation and the regulation of in-house tests: even where there is pre-market evaluation of in-house tests, there is currently no regulatory equivalent of a label for an in-house assay offered as a clinical test. Although a significant move in this direction has been made in a recent FDA guidance, in general the concept of truth-in-labeling does not apply.<sup>10</sup> Of course many public and commercial labs work hard to ensure that those seeking testing are adequately informed, providing pre-test information sheets and/or information on their websites. Although laboratory regulation does cover the interpretation of test results and the communication of that to doctors/patients this is at the post-test stage, whereas the pre-test stage, where doctors and their patients are deciding whether to use a test, is not addressed. Furthermore there are no statutory regulations on what types of data should be in a test results report (although this is addressed in professional guidelines).

Regulators can also facilitate information disclosure by making public their device reviews and subsequent postmarketing data. However, whilst in the US OIVD publishes review summaries on its website, in Europe evaluative data is treated as confidential and so the regulatory agencies are under an obligation not to reveal it, unless they have the agreement of the manufacturer. This issue is currently under review and it is expected that in future some categories of information from assessment reports will be made public in summary format, probably on a centralised European website, and that a simplified administrative procedure will be established to review whether additional categories of information should also be made public.<sup>11</sup> However, this may only apply to high-risk devices and might thus exclude genetic tests. Transparency is particularly important in a system of regulation by information disclosure, as it pushes more responsibility for safety and effectiveness onto clinicians and lab directors, but they can only take greater control if they have the information on which to act.

## **Kite marking for quality**

However, there may be limitations to an approach which focuses solely on information disclosure because of limitations in how the information will be used by doctors and patients. Doctors generally do not have the time to make detailed studies of the clinical data to support new tests, and patients also need additional guidance, particularly in a context where a test is offered direct-to-consumer. Such views echo a general concern amongst regulatory theorists that an over-emphasis on information disclosure often provides inadequate protection for consumers.<sup>12</sup>

Nevertheless, whilst a focus on information disclosure must take into account the weaknesses of this mechanism, it has broad political support, and its importance and utility is likely to increase with time.<sup>13</sup> Furthermore, it clearly fits with an approach designed to minimise the regulatory burden, so it is worth looking at ways to enhance its utility. Pre-market regulatory mechanisms focused on information provision can go beyond verifying that performance claims are consistent with data held. For instance, labeling may also be used to communicate about standards. Our research showed strong support amongst many stakeholders for the view that tests should come with clear guidance about the *quality* of the data that supports their claims. Such a kite-marking scheme would both provide warnings about poorly-validated tests and highlight those tests which have been well-validated, acting as an incentive to increase the data available.

Such a system might take the form of a simplified schema which would indicate where a test lies on the development spectrum from research to well-established clinical use. This would require a clear consensus on the development pathway.<sup>14</sup> Alternatively, it might be based on evidence-based medicine standards as developed by the Cochrane Collaboration, which use a ranking system to indicate the quality of individual studies.

## **New gaps**

### **Risk classification and the GHTF**

Having discussed the current regulatory gaps it might also be worth highlighting possible future regulatory gaps. Canada is an active participant in the Global Harmonisation Task Force which is currently developing a new risk classification schema for IVDs. This is largely modelled on the Australian system (itself a modified version of Canada's model). It is a four-class system running from high to low risk. The risk of a test is assessed using a number of criteria, such as the intended use/indications for use, the skill of the user, the degree of reliance placed on the test result, and the potential impact on public health and the individual patient. Examples of existing tests have been assessed according to these criteria and placed in one of four categories and this guides manufacturers in how to classify their new tests.

The GHTF principle that some genetic tests pose greater risks than others seems sensible, however, it raises two problems:

- 1) subjectivity of risk assessment – this is particularly an issue when different types of test pose different kinds of risks. e.g. psychological impact of Huntington's test vs. clinical impact of PKU test? It is not clear from the guidance which genetic tests might fall into Class C and which into Class B, as no examples are given for Class B. This lack of clarity offers significant opportunity for divergence amongst different countries, militating against ideal of harmonised approach. It also offers opportunity for manufacturers, who will take initial responsibility for classifying their test, to opt for the least burdensome route.
- 2) Lack of pre-market review – the conformity assessment model states that tests in Class B will not be subject to independent pre-market review. This has particular problems when a test which might be considered Class B is novel and/or highly complex (see below).

Adoption of the GHTF model in Europe would be a significant advance on the EU's current incoherent and inconsistent approach to risk classification and would ensure that a far greater proportion of genetic tests will be subject to independent pre-market review. However, its adoption in Canada would mean that some genetic tests which currently are subject to pre-

market review would become exempt from this regulatory requirement, as Canada currently treats all genetic tests as Class C.

### **The rise of intermediaries**

Much of the policy discussion on regulation has focused on the regulatory gap around homebrew tests. The concern that lab-developed tests will not be regulated in the same way as test kits. This gap continues to exist and is a cause for concern. This assumes a model such as that adopted by Myriad where the test developer establishes its own reference laboratory and offers the test commercially as an LDT. However, there are other regulatory gaps which need to be addressed. Another business model has emerged involving a third-party. DNA Direct are neither a test manufacturer nor a reference laboratory, but they offer a range of genetic tests direct-to-consumer. They are in effect intermediaries between reference laboratories and doctors and patients. Similar arrangements can be seen in the UK, for instance the company Medi-Checks who offer a wide range of tests direct-to-consumer via the internet in collaboration with the private pathology laboratory TDL. Scienta Health Center are a Toronto-based company, who offer a range of tests developed and performed by the Austrian company Genosense. Genosense have partners across the globe, for instance their tests have recently been made available in the UK by a company called Genetic Health.

The regulatory gap which these companies operate within is that they are neither conventional device manufacturers nor pathology laboratories, thus in the United States they are regulated by neither the Food, Drug and Cosmetic Act nor the Clinical Laboratory Improvement Amendments. It is possible to regulate the laboratory which develops and provides the tests but not the intermediary. Thus a company who has developed a new test and wants to make strong clinical claims for their test directly to consumers without regulatory scrutiny of those claims could do so via such an intermediary.

## **2) Evaluating clinical utility**

Focusing premarket review on ensuring companies tell the truth about what they know about a test's analytic and clinical validity is no guarantee that a test is in fact worthwhile, and will not prevent tests entering clinical use at a time when the evidence base is still developing. As a consequence it is important to consider the role of postmarket controls, in particular a more systematic use of Health Technology Assessment by healthcare reimbursers to gain full understanding of a test's clinical validity and utility. Because of the regulatory gaps outlined above, reimbursement has been the *de facto* regulator of genetic tests, and reimbursers have made clear that they will generally set evidence standards far in excess of those established by licensing authorities. The point is well illustrated by the Roche Amplichip: in 2004 it became the first pharmacogenetic microarray to gain FDA approval, but since then the test has been rejected by a succession of negative HTA reports in the US, Canada and Europe.<sup>15</sup>

Clearly reimbursement decisions can have a profound effect on clinical uptake of new tests. Yet if reimbursers are regulators then they surely face the same challenges as licensing authorities: how to wield that power responsibly; how to balance thorough evaluation with the encouragement of innovation and equitable access? One option discussed by stakeholders was conditional reimbursement – paying for new tests but only on the basis that there is systematic data collection. This model has been adopted by CMS in its Coverage with Evidence Development programme, and is being used in the Netherlands, Germany and Australia.<sup>16</sup>

There was considerable concern from industry stakeholders that unreasonable evidence demands may be made by reimbursers more used to evaluating drugs than diagnostics. Many test developers suggested that they need greater clarity on the standards which reimbursers are going to apply - how much data, how many studies, how many patients - so that they understand what they need to do to gain coverage. Many stakeholders expressed concern that there was a general lack of agreement on evidence standards for diagnostic tests and that complex genetic tests may pose particularly severe evaluation challenges which need to be addressed by both licensing authorities and reimbursers.

Traditionally rare disease genetics has not been subject to HTA review. It has generally been considered too low an expenditure item to justify assessment. However the UK GTN gene dossier process is part of a growing trend towards more formal evidence-based review of new genetic tests by reimbursers. CETT in the US have also attracted the interest of reimbursers who are beginning to be concerned about the costs associated with some of the more expensive genetic tests. Canadian interviewees indicated that there also some moves towards more assessment of the case for new tests, although this is only beginning to emerge and there is no uniform trend.

More fundamentally there is the question of whether reimbursers should be doing more than just evaluating the evidence but should actually be helping to build the evidence base by providing either the incentives or infrastructure for data collection. Many stakeholders believe that healthcare payers have a role to play and a responsibility to act, primarily by leveraging the reimbursers' resources - access to patients and clinical data - to help facilitate systematic data collection.

Reimbursers can go further than offering conditional coverage in return for evidence development, they can actually conduct their own studies, for instance in the US Medco are funding a study into the benefits of pharmacogenetic testing for Warfarin treatment and Kaiser Permanente ran a study to examine the benefits of the Oncotype Dx test.<sup>17</sup> Data registries for the systematic collection of data on new tests, preferably facilitated by electronic healthcare records is one option (an idea now being promoted in the US by HHS Secretary Leavitt through his Personalised Healthcare Initiative).<sup>18</sup> One recent example is that of Kaiser Permanente who have launched their own biobank to study the genetics of common complex diseases.

## **Regulatory options for LDTs**

### **1) Do nothing**

#### Advantages

- No impact on regulatory resources
- No impact on innovation

#### Disadvantages

- Lack of public protection, danger of harms to patients and loss of confidence in sector.
- Scandals could lead to regulatory over-reaction.

### **2) Regulate high-risk LDTs across public and private sectors**

#### Advantages

- Ensure regulatory oversight where greatest potential for harm
- Improve public confidence in sector

#### Disadvantages

- Significant impact on regulatory resources as might encompass all genetic tests (currently Class III in TPD classification system).
- Impact on innovation not clear but potential for regulation to act as block
- Lack of resources in public sector labs to fulfil regulatory requirements
- Need to determine federal and provincial authorities and roles (e.g. public sector labs)

### **3) Regulate only private sector LDTs**

#### Advantages

- Limited impact on regulatory resources
- Addresses main concerns of some stakeholders

#### Disadvantages

- Creates unlevel playing field between private and public sector
- Less confusion of federal and provincial powers than option 2

### **4) Limit regulation to registration, QA and preparation of technical file, intervening only where concerns are raised.**

#### Advantages

- Limited impact on regulatory resources
- Limited impact on innovation

#### Disadvantages

- Maintains unlevel playing field between kits and LDTs
- Creates regulatory risk as labs do not know when regulator will intervene
- The reactive nature of this approach may result in lack of public trust/confidence (if the regulator only intervenes after harm has been caused)

### **5) Regulate commercial LDTs as devices, but limit regulation of public sector LDTs to registration, QA and preparation of technical file, intervening only where concerns are raised.**

#### Advantages

- Limited impact on regulatory resources
- Addresses main concerns of some stakeholders

#### Disadvantages

- Levels playing field between commercial LDTs and kits but leaves unlevel playing field between private and public sector
- Lack of resources in public sector labs to fulfil regulatory requirements
- Confusion of federal and provincial powers?

## 6) Reliance on reimbursement and professional practice guidelines as forms of control

### Advantages

- Limited impact on regulatory resources
- Addresses some concerns of some stakeholders

### Disadvantages

- Reimbursement could be as much of a barrier to innovation as other regulatory mechanisms if evidence bar is set too high.
- Lack of resources in public sector labs to fulfil reimbursement evidence requirements.
- Reliance on provincial powers and provincial HTA provision may create inconsistency.
- Lack of resources may make this an unrealistic option.

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## 4. Ethical issues

A range of ethical issues such as privacy, discrimination and equity of access will be explored. The chapter will also explore the ‘medicalisation thesis’ - the idea that susceptibility testing may exploit the worried well, creating a huge market for unnecessary treatments/monitoring, and the linked issue of DTC provision/advertising of genetic tests.

### **Privacy**

The traditional duty of confidentiality which clinicians owe to their patients is challenged by the forms of information revealed by genetic testing for heritable disorders (or heritable susceptibility to common disease), as they relate not only to the patient but to other individuals. For instance a patient who has a predictive test for Huntington’s Disease and tests positive, has information which may also identify the parent from whom the gene was inherited and who will also contract the condition. Similarly, a carrier test which identifies an individual is carrying a recessive gene for cystic fibrosis, has information which may also be of relevance to their siblings, who may also be carriers and thus run the risk of passing the gene on to their children.<sup>1</sup>

The ethical dilemma which arises is whether or not to reveal this information to the affected parties who have not been tested. The clinician’s obligation to maintain patient confidentiality is not absolute, particularly where the failure to release information may risk significant harm to another individual or the public.<sup>2</sup> The preferred approach - encouraging voluntary disclosure or permission to disclose by the patient – prioritises the rights of the tested patient and is particularly weak where relations between family members are strained or have broken down.

Similar dilemmas arise in the research process, as the established protocols governing confidentiality in biomedical research are challenged where the study involves inheritance, for instance by the use of family pedigrees in linkage studies. Broader privacy concerns arise in the research context where data sharing is promoted, necessitating anonymisation of samples and phenotypic data.

Concerns about privacy have been heightened by the moves towards electronic healthcare records (EHRs).<sup>3</sup> A pan-Canadian HER system is a priority for the Canadian Minister of Health and a privacy and confidentiality framework is being developed to review and revise existing legislation and enact new legislation in each jurisdiction. Issues to be addressed include:

- Definitions of personal information and personal health information
- Consent for collection, use and disclosure of personal information for health care
- Use and disclosure of personal information without consent for research
- Disclosure of personal information without consent for surveillance
- Disclosure of personal information without consent in the public interest
- Outsourcing and transborder flows of personal information

In the United States the promotion of EHRs has been made a priority by the current Health Secretary, and there is considerable concern that this is being taken forward without adequate attention to privacy and security concerns. For instance, the Government

Accountability Office issued a report which concluded that HHS has "not yet defined an overall approach for integrating its various privacy-related initiatives and addressing key privacy principles."<sup>4</sup>

## **Discrimination**

Concerns about privacy in part stem from the potential for misuse of confidential information and issues of stigmatisation and discrimination have been a central part of the debate concerning the ethical, legal and social implications of genetic research. This concern about the use of genetic test results is part of a broader concern about the rise of a surveillance society and the potential for biological tests of all kinds to be used "as a means to justify racial or gender bias, to legitimate arbitrary exclusionary practices, and to enhance institutional power with little regard for the rights or personal fate of individuals."<sup>5</sup>

In 1992 the US-based Genetic Screening Study Group conducted empirical research into genetic discrimination and found that it was affecting people in a range of ways. Some were refused insurance and employment and others were subject to discrimination by the army and by educational institutions. In the UK, a year after the US study, the Nuffield Council on Bioethics published an early and highly influential report which called for government, the NHS and industry to adopt measures to protect people "against the potentially adverse effects of screening, including the misuse of confidential information, the risk of social stigma and the possibilities of eugenic abuse in the future."<sup>6</sup>

Since this early discussion there has been considerable legislative activity. Legislation has been passed to prevent genetic discrimination in a number of states in the US, and whilst federal legislation has long been stalled, there is much hope that it will be passed this year. Meanwhile some commentators believe that there is still much distrust of genetic medicine amongst disadvantaged groups such as African Americans.<sup>7</sup> A number of public surveys have suggested that the public have significant concerns about genetic privacy.<sup>8</sup> In the EU limitations on the use of genetic information exist in a number of countries, including Norway and the Netherlands. However, Germany has recently announced it intends to legalise the use of genetic information by employers.

As the Nuffield Report suggested, the relationship between contemporary genetic science and the eugenics movement of the first half of the twentieth century underpins many fears concerning the use and misuse of genetic information. Eugenic beliefs led to forcible sterilization in Europe, the US and Japan and were the scientific justification for Nazi genocide.

Eugenics cannot be thought of as simply a distant historical phenomenon - as recently as the 1970s forcible sterilization continued to be practiced in Sweden and the US. However, postwar genetics has by and large rejected compulsion, favouring instead nondirective guidance, in the shape of what has become known as genetic counselling. Only occasionally does a more traditionally eugenicist approach surface, as when Margery Shaw, a former President of the American Society of Human Genetics argued that "parental rights to reproduce will diminish as parental responsibilities to unborn offspring increase" or when the IVF pioneer Robert Edwards stated "Soon it will be a sin of parents to have a child that carries the heavy burden of genetic disease."<sup>9</sup>

However, even the contemporary voluntarist approach, focused on parental choice has been criticised. Whilst many patients groups representing those with genetic disease and their families

are supportive of genetic testing, the disability movement has voiced considerable opposition based on its position that disability is a social rather than a medical problem. They fear that the growth of genetic testing and attendant rise in pregnancy terminations, represents a re-emergence of eugenics throwing into doubt the disabled person's right to life.

One recent analysis has countered such fears by suggesting that a eugenic concern with heritable traits has in fact been eclipsed as a trigger for pregnancy terminations by the development of new diagnostic technologies such as fetoscopy and ultrasound which allowed direct examination of the fetus for *non-hereditary* traits. This technological change both drove - and was reflected in statute by - the 1967 Abortion Act which allows handicap as a grounds for abortion but makes no mention of hereditary factors, an omission also reflected in the debate surrounding the Bill.<sup>10</sup>

However, the disabled are not the only disadvantaged group to fear a return of eugenic ideas and policies - as noted earlier, racial minorities are also suspicious of the new genetics. Genetic research is at the heart of what Marek Kohn has termed 'the return of racial science'.<sup>11</sup> The aborted Human Genome Diversity Project is only one expression of this, and its failure indicates the contentious nature of research on race and genetics. Clinical genetics has had to face head-on the issue of the genetic aspects of racial difference in areas such as cystic fibrosis screening. Meanwhile the behavioural sciences are increasingly working in a genetic paradigm - Kohn reports that in 1992 the US National Academy of Sciences and the National Research Council called for more research on biological factors related to violent crime as well as on whether 'male or black persons have a higher potential for violence than others, and if so, why?'"<sup>12</sup> The notorious *Bell Curve* applied such thinking to the area of intelligence. The Nuffield Council on Bioethics issued a report which expressed strong concerns about these trends:

... there remains a view that research on the genetics of human behaviour, particularly in the area of intelligence, is necessarily eugenic or will lead to the re-establishment of eugenic policies. It is possible that contemporary understanding of the heritability of IQ and other behavioural characteristics, and increasing knowledge of the processes of inheritance of other traits, could provide a scientific foundation for a programme of positive or negative eugenics, were there to be the political will or power to construct and implement such a policy.<sup>13</sup>

The medicalisation of behavioural traits is of serious concern to many and often involves the extension of more common complex conditions such as depression. In recent years anti-depressant drugs have been used to treat an increasing range of (often newly categorised) behavioural conditions such as social phobia. The Nuffield Council on Bioethics highlighted the dangers of applying genetics to human behaviour in a recent report. This concern was also raised by the SACGT: "the possibility of such tests raises profound concerns because their potential psychological, social and economic harms are so significant and the potential misuse of such information is so great."<sup>14</sup>

### ***Equity of access***

Concerns about equity of access have been an important issue in the socio-ethical implications of genetic testing. For instance the Council of Europe's 'Recommendation R(92)3 on genetic testing and screening for health care purposes' states that: "There should be equality of access to genetic testing, without financial considerations and without preconditions concerning eventual personal choices." Similarly the EU expert group on genetic testing recommended that:

“medically relevant genetic testing be considered an integral part of health service provision; [and] national healthcare systems ensure that genetic testing will be accessible equitably to all who need it.”

The possibility that inequities will grow with the emergence of a range of tests delivered outside the national healthcare system is a cause for concern in Canada and elsewhere. In the US such concerns run against the traditional model of private sector healthcare delivery and in the UK government policy is strongly in favour of increased role for private sector. In Canada however, it would seem that commercial provision of tests is more likely to be a matter of significant public controversy. Given that the emerging business model based on a combination of biomarker IP and monopolistic test provision in commercial reference labs is being presented as an engine for innovation, then the question arises how to balance support for innovation with the provision of equitable access.

Issues of equitable access will be exacerbated if new molecular diagnostics cost significantly more than traditional IVD tests.

### ***Informed consent***

The policy debate has highlighted the importance of providing accurate information to doctors and patients to facilitate informed decision-making, and it has articulated concerns about the quality of information provided both pre-test and post-test. Post-analytic issues such as result reporting have been highlighted by professional bodies in the US and Europe and recommendations on the format and content of the lab reports have been made by the Clinical Laboratory Improvement Amendments Committee (CLIA), the body charged with developing US laboratory regulation.<sup>15</sup>

Social and ethical concerns about genetic testing arise in large part from its historical link to the eugenics movement of the first half of the twentieth century, a dark legacy which underpins many fears concerning the use and misuse of genetic information. It was in an attempt to escape this historical legacy that the clinical practice of genetics has come to place an immense value on informed consent and on non-directional counselling and why it places a special kind of value on clinical data. In clinical genetics the act of diagnosis has a heightened status. On the one hand it is treated with fear because of its links to eugenics, so there is a considerable emphasis on confidentiality and consent; on the other hand it is greatly prized because dealing, as they do, with many very rare diseases for which there is no cure, geneticists place a special value on the diagnosis itself. In other areas of medicine the diagnosis is only the beginning of the story, in genetics it is often the climax of the narrative.

The policy debate’s focus on information has also been fuelled by wider developments, in particular a growing interest in the importance of shared decision-making. By the second half of the 1990s, the arguments in favour of shared decision-making between patients and professionals had largely carried the day. This was especially, but not exclusively, relevant where there were a variety of treatment options. Empirical evidence from such different areas of healthcare as hypertension, breast cancer, and diabetes all supported the claim that engaging patients might be preferred by patients, might reduce anxiety, and might empower self care with improved health outcomes<sup>16</sup>. The UK was not unusual in making a formal commitment to patient partnership.<sup>17</sup> {cite more literature here}

The debate about the policy implications of genetic testing therefore played into an existing set of values and assumptions. These existing concerns led to a focus on: information about

effectiveness; information about treatment options; information to help patients deal with uncertainty; and a more general concern that information should be up-to-date, reliable, and balanced. As experts began to predict that genetic testing would play a growing part in disease prevention, management and treatment, there were growing concerns about the quality of information that might be made available<sup>18</sup>. Not only were there fairly technical difficulties in understanding how best to communicate risk, how to understand how patients and physicians access and use health information, and how to deal with asymmetries of information and expertise, but also there were wider ethical, legal and social implications of genetic tests.

### **Medicalisation thesis**

Medicalisation, or more specifically the broadening of the spectrum of those considered to be, or at risk of being, sick and requiring treatment, or preventive action, is a long-established trend: “Over time, the tendency has been to expand diagnostic and treatment boundaries, and to include in the “disease” category people with milder manifestations of pathology and lower levels of risk.”<sup>19</sup> So whilst with monogenic disorders, a great deal of concern focuses on the problem of the therapeutic gap, with genetic testing for CCDs there is a fear that there may be too much therapy. If people who are identified as having genetic susceptibility to particular diseases are then targeted with therapeutic interventions, then there is a danger of large numbers of people taking medicines they do not necessarily require and running the risk of side-effects for little clinical benefit. Here the harm arises from the difficulty of establishing what constitutes a true or false positive, who is or is not considered either pathological or at risk.

As is suggested, this is not a harm unique to genetic tests but the concern in the case of susceptibility testing for common complex disorders is two-fold – firstly that when one is offering only a risk profile, and one that may show only a slightly elevated risk, then the balance between what constitutes a true positive result and a true negative result is more difficult to strike, and it is more likely to fall on the positive side in part because of widespread perceptions of the predictive power of genetics.<sup>20</sup> Even more dangerous is the scenario in which the genetic marker is taken not simply as a risk factor but as the presence of the disease.

The implications for the healthcare industry of such a paradigm shift and its application to common complex disorders would be the creation of large populations identified as requiring treatment. This is the second problem special to the application of genetic testing to common complex disorders - one of scale. Since what is envisaged by its proponents is a revolution in medical practice, the danger is that vast swathes of the population with perhaps only very slightly higher than normal risk profiles will be classified as sick and requiring treatment.<sup>21</sup>

Many are concerned that such medicalisation might lead not simply to a new flurry of dubious health fads but to unwarranted and costly health interventions and to an increase in the incidence of clinical iatrogenesis. A pharmaceutical approach to disease prevention may lead some people to neglect lifestyle changes, such as improved diet or regular exercise, which would be likely to bring greater all-round health benefits.<sup>22</sup> It may also increase the healthcare budget for little clinical effect. There is a further concern about the possible psychological impact of a genetic risk profile. Again in part because of the public perception of the highly predictive nature of genetic test results, some people may react very badly to being told they are at greater risk of diseases such as Alzheimer’s and cancer, experiencing fear of the disease and anxiety about, or actual, stigmatisation.

## Direct-to-consumer (DTC) genetic testing

The information imbalance between the test provider and the test user is most pronounced with direct-to-consumer testing. A number of questions are raised:

- Should the public only gain access to tests through the intervention of a ‘learned intermediary’ who can offer advice, guidance and interpretation?
- How do you control the quality of information which is provided in direct-to-consumer testing?
- Is direct-to-consumer advertising (even where a test can only be accessed via physician referral) inappropriate because of the dangers of misinformation?

Are some genetic tests acceptable to offer direct-to-consumer and others not? Currently in the UK the only test not legally available DTC is non-genetic - HIV. Some interviewees thought there might be a case for allowing some tests to be available DTC if their informational impact was relatively low.

There is a tension between control and individual freedom. I could foresee a situation where I might want to buy a genetic test without anybody telling me I can or cannot have it. I would be hesitant to go into an over controlled system that actually removes peoples’ individual choice ... I think there may be sub-categories where you may need tighter controls, but how you define those sub-categories is enormously difficult.

**Genetic counsellor**

... the consumers will drive the decision-making process more for their own health. And this includes I think that they should have the free choice of insurance. I think this part of individualised healthcare if you want. If you don’t do this you will never be individualised or personalised because you are depending on decisions that some people in a centralised body are taking for you.

**European IVD industry executive**

There were a range of views with some interviewees leaning towards DTC access for at least some tests and others arguing that DTC usurps the role of the clinician; that test results cannot be understood by lay people, they need expert interpretation and so DTC tests should be discouraged through public education initiatives. However, despite considerable hostility to DTC tests, most of those who expressed opposition to them did not favour an outright ban. Furthermore, some participants were broadly supportive of DTC tests, providing appropriate regulatory safeguards were in place. It was suggested that it is important to distinguish between concern about the type of tests being offered - some of which people think are of dubious value - and the question of whether consumers should have direct access to them; the implication being that the policy solution to the problem of ensuring test quality is not necessarily restricting consumer access.

I would like to make it a requirement that people have access to genetic counselling – to make this step necessary legally speaking. And then in my opinion you can ... the rest can lead direct-to-consumer marketing or whatever, as long as the tests you provide are high quality, they have got through the clinical validation step and the one providing the service must offer genetic counselling in conjunction with the test result. All the rest can be left free.

**European IVD industry executive**

Another issue was whether, regardless of the issue of physician referral or the provision of genetic counselling, DTC marketing should be permitted for tests. There was some concern that this would lead to scaremongering about genetic risks. But other interviewees felt that as long as the test had been independently validated and was being offered with genetic counselling then DTC marketing was acceptable.

Whilst there was some support for the idea that complex genetic tests should only be available with detailed pre- and post-test counselling, it was suggested that this view was out of kilter with prevailing trends in the US, where there is strong public support for direct access to medical tests in general and where an increasing number of states are permitting this.<sup>23</sup>

One perspective was that people should be free to spend their money on worthless goods or services. In the US the claims made by those selling tests DTC can fall under the regulatory authority of the Federal Trade Commission but the trade Commission tend to want evidence of substantial harm before taking action.

Another perspective on the information needs of patients was that they were not simply passive consumers of information. The role of patient groups as advocates and users of direct-to-consumer testing was discussed in our focus groups. The idea of consumer empowerment, of people taking their health into their own hands is a significant one, affecting many areas of healthcare.

<sup>1</sup> Pilnick, A. (2002) *Genetics and society: an introduction*. (Buckingham : Open University Press) p207

<sup>2</sup> Melzer, D and Zimmern, R (2002) Genetics and medicalisation. *BMJ*, 324, 863-864

<sup>3</sup> Hodgkins R Overview of health policy as it pertains to electronic health information. Presented at Electronic Health Information & Privacy Conference, November 13, 2006

<sup>4</sup> US General Accounting Office (2007) *Health Information Technology: early efforts initiated but comprehensive privacy approach needed for national strategy*, Available at <http://www.gao.gov/new.items/d07238.pdf>.

<sup>5</sup> Nelkin, D and Tancredi, L *Dangerous diagnostics: the social power of biological information* (Basic Books: New York, 1989)

<sup>6</sup> Nuffield Council on Bioethics. (1993) *Genetic screening – ethical issues*. (London: Nuffield Trust) p3

<sup>7</sup> Alper, J et al 'Perspectives on perspectives' in Alper, J et al (eds) *The double-edged helix- the social implications of genetics in a diverse society* (John Hopkins University Press, 2002)

<sup>8</sup> See for instance Rothstein, M . and Hornung, C Public attitudes. In (Rothsten, ed.) *Genetics and life insurance: medical underwriting and social policy* (2004)

<sup>9</sup> Quoted in Beckwith, J 'Geneticists in society, society in genetics' in Alper, J et al (eds) *The double-edged helix- the social implications of genetics in a diverse society* (John Hopkins University Press, 2002) p 49

<sup>10</sup> McNally, R 'Post-eugenics, 'eubionics' and the 'handicap ground' for abortion' in Wellcome Trust Genome website, Genetics and Society section – <http://www.wellcome.ac.uk/en/genome/geneticsandsociety/hg14f009.html>

<sup>11</sup> Kohn, M *The race gallery – the return of racial science* (London, Jonathan Cape, 1995)

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- <sup>12</sup> Kohn, M *The race gallery – the return of racial science* (London, Jonathan Cape, 1995) p 276
- <sup>13</sup> Nuffield Council on Bioethics *Genetics and human behaviour – the ethical context Summary* (London: 2002) p 3
- <sup>14</sup> SACGT *Enhancing the oversight of genetic tests: recommendations of the SACGT( Secretary’s Advisory Committee on Genetic Testing)* (NIH, 2000)
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- <sup>16</sup> Coulter, C, Entwistle, V and Gilbert, D (1999) ‘Sharing decisions with patients: is the information good enough?’ *BMJ* 1999, 318-322 (30 January)
- <sup>17</sup> NHS Executive (1996) *Patient Partnership: building a collaborative strategy* London: Department of Health.
- <sup>18</sup> Burke, W. et al (2002) ‘Genetic test evaluation: information needs of clinicians, policy makers, and the public’ *American Journal of Epidemiology* 156, 4 311-318.
- <sup>19</sup> Zimmern, R. and Melzer, D. Genetics and medicalisation. *BMJ* 2002; 234: 863-864 (13 April)
- <sup>20</sup> Bates, BR et al. What does “a gene for heart disease” mean? A focus group study of public understandings of genetic risk factors. *American Journal of Medical Genetics* 2003; 119A:156-161
- <sup>21</sup> Zimmern, R. and Melzer, D. Genetics and medicalisation. *BMJ* 2002; 234: 863-864 (13 April)
- <sup>22</sup> Wallace, H. ‘Genetics and preventive medicine: selling pills, ignoring causes?’ in *Genetic testing: help, hope of hype?* Bair, P. and Williams-Jones, B. (Eds) (British Columbia, 2004)
- <sup>23</sup> Cite GPPC survey



## Conclusion

We are seeing the emergence of a clearer understanding of the genetic basis of common, complex disease. Whilst the signs are now more promising, we should anticipate that the integration of genomic science into healthcare will be gradual, in large part because it will still take time to unravel the complex molecular biology which underlies diseases such as cancer, diabetes and osteoarthritis. However, the recent development of a range of gene expression tests in oncology, and the discovery of high-risk genes such as those associated with age-related macular degeneration suggests that we should expect some of the near future.

The transition from Genomics 1.0 to Genomics 2.0 has been marked by rapid technological progress, a major improvement in the scale and rigour of basic research and innovations in business practices. Policymakers must demonstrate an equal willingness to innovate and experiment, if there are to meet the challenges laid down by the new science as it makes its way into the clinic. They will have to address both long-term structural issues and more immediate challenges. There are important problems to be addressed. Improving regulation to protect patients and improving incentives and infrastructure to promote innovation are equally pressing priorities, both of which may result in the swifter integration of high-quality tests into routine clinical practice.

## **Annex 1 Methodology**

This report draws on four years of research in the area of clinical genetic testing and our previous work for Health Canada on pharmacogenomics. In the course of this research we have surveyed both the academic and grey literature and engaged with over 150 individuals through one-to-one interview and small focus groups – talking to opinion leaders in key stakeholder groups – regulators, industry, clinicians, patients groups and health policy-makers. For this report we supplemented our existing knowledge base with a further literature review and with a series of one-to-one interviews with key opinion leaders in Canada and abroad, and participated as observers in five meetings in Europe, the US and Canada at which stakeholders discussed issues relevant to the report. Participation in these meetings facilitated formal interviews, informal discussions and allowed us to observe at first-hand interactions between regulators, industry, clinicians, healthcare policymakers and academic researchers.