

# GeneWatch UK evidence to the House of Lords Science and Technology Committee inquiry 'Genomic medicine'

April 2008

## Summary

1. GeneWatch's work in the area of genomic medicine has focused on concerns about the marketing of misleading genetic tests, and the limitations of an approach to health based on the genetic 'prediction and prevention' of common diseases in the general population.
2. We are concerned that a 'genetic revolution' in healthcare has been widely promoted in the absence of any analysis of the cost-effectiveness, impact on health, or impact on the NHS, of genetic screening in the general population.
3. We recommend that Government should:
  - commission an independent assessment of the costs and benefits of implementing genetic 'prediction and prevention' in the NHS;
  - end gene patenting, which distorts the 'knowledge-based' economy, and stop commercial interests from dominating the research agenda;
  - require medical oversight and statutory regulation of genetic tests – including an independent pre-market assessment of whether they are valid and useful for health;
  - adopt new legislation to prevent genetic discrimination and protect privacy.

## Introduction

4. GeneWatch UK is a not-for-profit policy research group concerned with the science, ethics, policy and regulation of genetic technologies. Our aim is to ensure that genetics is used in the public interest. We welcome the opportunity to input to the Committee's inquiry on genomic medicine.
5. Our evidence focuses on four of the questions in the Committee's Call for Evidence:
  - How meaningful are genetic tests which use genome variation data? What progress has been made in the regulation of such tests?
  - What impact will genomic data have on data emerging from projects such as UK Biobank, Generation Scotland and other biobanks?
  - How useful will genomic information be as part of individualised medical advice? What provisions are there for ensuring that the individual will be able to understand and manage genomic information, uncertainty and risk?
  - What are the implications of the generation and storage of genome data on personal data security and privacy, and on its potential use or abuse in employment and insurance? How should these be addressed?
6. In addition, we make some comments on research priorities.

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

7. *“There is insufficient scientific evidence to conclude that genomic profiles are useful in measuring genetic risk for common diseases or in developing personalized diet and lifestyle recommendations for disease prevention.”* Janssens et al. (2008).<sup>1</sup>

8. *“There is a growing business selling new genetic tests based on very preliminary research - the evidence is far too flimsy to be accepted by evidence-based medical practice.”* Sense about Science (2008).<sup>2</sup>

9. No common genetic variants that meet medical screening criteria for the general population have been identified to date, however many tests for common genetic variants are already being marketed. This has the potential to harm health by:

- targeting the wrong health advice at the wrong people;
- confusing healthy-eating messages or advice to quit smoking;
- leading to the over-treatment of healthy people who may take unnecessary medication or supplements;
- undermining public health approaches and diverting resources from the social, environmental and economic changes that are needed to prevent ill-health.

10. The ACCE process, which takes its name from the four components of evaluation—analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications—is a widely supported model process for evaluating data on emerging genetic tests.<sup>3,4</sup> However, no pre-market assessment is currently made of the clinical validity or utility of genetic tests. This means that ‘genetic information’ – combined with medicines, supplements, foods, skin creams, lifestyle advice and additional tests – can be marketed when it is not valid (for example, even when the gene plays no role in the claimed disease) or when it serves no useful purpose (for example, when the proposed intervention is no more effective or necessary in people with one genetic variant than with another).

11. The issue of clinical utility is different for genetic tests than for most other types of test, because genetic risk factors cannot be removed or reduced; unlike smoking, or LDL cholesterol levels, or blood pressure. For risk factors that are amenable to intervention, it is generally reasonable to assume that individuals at highest risk are also those who have most to gain from an intervention: however, this is not the case for genetic risk factors. Those who are at highest genetic risk may or may not be those who have the most to gain from a particular medicine, supplement or change in lifestyle. Harm to population health will result if a genetic test is used to target lifestyle advice or medication at a high risk group which has less to gain from the intervention than the low risk one: assessing the clinical utility of the test, not just its clinical validity, is therefore essential. For this reason, any assessment of the likely impact on health of genetic tests combined with environmental or lifestyle advice requires knowledge of the magnitude (and sign) of any gene-environment interaction. No interaction means that the test performs no better than randomly selecting the same number of people from the population.<sup>5</sup>

12. Scientists from the Netherlands and from the US National Institutes of Health – including the Director of the National Office of Public Health Genomics – recently published a critical appraisal of the scientific basis of commercial genomic

profiles.<sup>1</sup> Their review found significant associations with disease risk for fewer than half of the 56 genes included in commercially available genomic profiles used to assess health risks and personalise health interventions. The authors also questioned how the companies studied could provide meaningful genetic risk assessments for complex diseases in the absence of information about multiple genes and gene-gene interactions, and how personalised advice on supplements and diets could be given in the absence of any reliable data on gene-diet interactions.

13. Health regulators in New York State and California are now investigating claims made by online gene testing companies such as 23andMe and Navigenics, but the US Food and Drug Administration has so far left it up to individual states to decide what to do about these so-called 'home brew' tests (tests marketed using individual laboratories, rather than sold as test kits).<sup>6</sup>
14. These problems are not limited to genetic risk profiles marketed by US companies on the internet. For example, GeneWatch UK has supplied evidence to the MHRA regarding the tests offered by the UK company Genetic Health via its Harley Street clinic.<sup>7</sup> Genetic Health acts as the UK partner for the Austrian company Genosense Diagnostics, and our assessment was based on the description of the tests provided on Genosense's website in May 2007. Overall we found that:
  - For most genes included in the tests, no large-scale evidence is available to conclusively establish a relationship between the common genetic variant identified (the polymorphism) and the claimed disease. Even where this relationship is clearly established, the clinical validity of the test is unclear and for most tests the predictive value is unknown.
  - For several genes included in the tests, large-scale evidence suggests that the association between the genetic variant and increased risk of a particular condition is invalid.
  - Large-scale evidence of clinical utility in the general population is not available for any of the genes included in the tests.
15. An ITV programme which featured Genetic Health providing four celebrities with tests, broadcast on 8<sup>th</sup> November 2007, was the subject of a complaint by the British Society of Human Genetics.<sup>8</sup> Geneticists and health professionals subsequently warned the public that genetic tests that claim to predict the risk of developing life-threatening diseases are a waste of money and can frighten healthy people.<sup>9</sup>
16. Genetic Health has since introduced some additional tests, including tests for common variations in the so-called 'fat gene', FTO<sup>10</sup>, the first common genetic obesity susceptibility gene to have been confirmed in multiple data sets.<sup>11</sup> However, the FTO gene accounts for only about 1% of the variance (differences across the population) in body mass index (BMI) in the UK population. Testing for the gene is not useful to decide who should take action to reduce their weight, because it does not make any difference to advice on eating healthily and getting enough exercise, or any other medical intervention (i.e. there is no evidence of clinical utility).
17. Other genetic tests that have been marketed in the UK are described in GeneWatch UK's 2007 evidence to the MHRA.<sup>12</sup> They include tests marketed by UK companies via the internet (the so-called 'Nicotest'); by US companies via alternative healthcare providers (the 'Genovations' tests); and by the then UK-based company Sciona, which sold genetic tests with dietary advice in the Body

Shop in 2001/02. Following criticism of its claims by GeneWatch, Sciona relocated to the USA and has been the subject of a critical investigation by the US Government Accountability Office (GAO),<sup>13</sup> as well as being one of the companies investigated in the critical appraisal of the scientific basis of commercial genomic profiles cited above.<sup>1</sup>

18. The gene testing market is expanding rapidly and leading UK psychiatrists have recently denounced plans by other US companies to market genetic tests claiming to identify susceptibility to bipolar depression or schizophrenia on the internet.<sup>14</sup>
19. GeneWatch UK has long argued that a statutory regulator should make a pre-market assessment of the clinical validity and utility of all genetic susceptibility and pharmacogenetic tests, and that, in addition, health-related tests require interpretation by medical professionals. Unless tests are adequately regulated, large numbers of people are likely to be either falsely worried (and over-treated) or falsely reassured that they do not need changes to be made in their lifestyle or environment. In addition, failure to regulate genetic tests is likely to lead to burdens on the NHS when patients seek advice from their GPs – perhaps including medication - based on misinformation provided by commercial testing services.
20. Without regulation of claims for both clinical validity and clinical utility, there is also a risk of a major loss of public trust in genetic information. One of the main recommendations that emerged from the Royal Society's People's Science Summit on genetic testing in March 2003 was that a regulatory body be set up to oversee legislative and other issues surrounding genetic testing.<sup>15</sup> In 2007, the Science Horizons project (a deliberative panel, facilitated public events and small group discussions) also reported concerns about lack of regulation of personal genetic information.<sup>16</sup> Such engagement exercises are pointless unless Government is prepared to act on the concerns raised by members of the public.

#### **What impact will genomic data have on data emerging from projects such as UK Biobank, Generation Scotland and other biobanks?**

21. Large-scale population biobanks such as UK Biobank are being developed in a climate of controversy about the health benefits of a genetic approach to the prevention and treatment of common diseases and the scientific challenges of validating statistical associations – and quantifying interactions - between genes, environmental factors and disease.<sup>17</sup>
22. UK Biobank almost certainly lacks the necessary statistical power to quantify the gene-environment interactions it was intended to investigate and, in addition, without better environmental measures, including changing exposures over time, it will lose much of its supposed advantage over smaller, cheaper case-control designs.<sup>18, 19</sup> In addition, the potential for population biobanks to quantify risks for complex disease is limited by a 'multiple testing' problem caused by the large number of genetic and gene-environment interaction models that could fit existing data.<sup>5</sup> Because the number of hypotheses that could be tested is essentially infinite, sample sizes necessary to quantify the risks could "*plausibly be larger than the number of people that have ever lived*".<sup>20</sup>
23. In GeneWatch's view, identifying genes involved in complex diseases can be important in helping to understand disease mechanisms. However, it is much less

clear whether attempting to quantify risks and predict disease – the aim of UK Biobank - will be achievable or useful (see below).

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

24. *“Based on current evidence, an era of healthcare consisting of gene technology built on widespread predictive testing is not desirable from a health economic viewpoint”*. Rogowski (2007).<sup>21</sup>

25. Some geneticists have predicted a genetic revolution in healthcare: involving a future in which individuals take a battery of genetic tests, at birth or later in life, to determine their individual ‘genetic susceptibility’ to disease. In theory, once the risk of particular combinations of genotype and environmental exposure is known, medical interventions (including lifestyle advice, screening or medication) could then be targeted at high-risk groups or individuals, with the aim of preventing disease. This health strategy was strongly endorsed in the June 2003 White Paper ‘Our inheritance, our future: Realising the potential of genetics in the NHS’.<sup>22</sup> In his foreword, the then Secretary of State for Health stated: *“Above all, genetics holds out the promise of more personalised healthcare with prevention and treatment tailored according to an individual’s genetic profile”* and the White Paper includes the claim that: *“...the way external factors and genes interact to cause disease or protect us from disease will be better understood. This information will allow people with certain genetic profiles to avoid foods, chemicals or environmental factors, such as smoking, which are particularly risky for them”*.

26. However, there are also many critics of this strategy, who argue that it is likely to be of limited benefit to health.<sup>23,24,25,26,27,28</sup>

27. Although the identification of rare genetic mutations can provide useful information to individuals, including people at risk of (relatively rare) familial forms of cancer, the evidence that screening common genetic variants will prove useful to predict and prevent common diseases is extremely limited.

28. Recent papers, whilst confirming statistical associations between some genetic polymorphisms and common diseases, have shown very limited clinical utility. For example:

- Nine genes showing replicated associations with type 2 diabetes (HEX/IDA, SLC30A8, CDKAL1, CDKN2A, IGF2BP2, FTO, PPARG, KCNJ11 and TCF7L2) explain only a very small proportion of the aggregation of this condition in families<sup>29</sup> and testing for these genes does not appear to improve prediction of type 2 diabetes compared to measuring existing risk factors (body mass index and fasting plasma glucose concentration).<sup>30,31</sup>
- Of 32 candidate breast cancer susceptibility genes, all may be false, because the odds ratios from meta-analyses are reducing over time and converging to the null.<sup>32,33,34</sup>
- No region of the human genome has a uniformly large impact on hypertension and susceptibility genes for hypertension may be very difficult to detect.<sup>35</sup>
- An overview of meta-analyses of genetic associations for heart attack or coronary artery disease, concluded that even with large-scale evidence from statistical meta-analyses, significant associations may be subject to bias.<sup>36</sup> A recent study of nine common genetic variants (polymorphisms) associated with cholesterol

levels found that use of the genotype did not improve clinical risk prediction in 5000 subjects.<sup>37</sup>

29. Similar problems have plagued pharmacogenetic tests, which in general have also shown low clinical utility. A case for genetic testing before drug administration can perhaps be made for CYP2C9 and warfarin, but evidence for clinical utility is lacking; the evidence in favour of CYP2C19 testing is limited; and for CYP2D6 testing is poor.<sup>38,39,40,41</sup> In general, it is unclear why pharmacogenetic testing would be medically justified, except prior to prescribing a few specific drugs.
30. Early expectations for highly predictive tests were based on the common disease-common variant hypothesis (CD-CV), which states that the genetic component in the causation of common diseases is likely to arise from a relatively small number of genes. This now appears unlikely to be correct, except in special cases.<sup>42</sup> To be meaningful, multiple genes and gene-gene interactions need to be included in calculations of genetic risk and for these risk profiles to be useful, interventions must be proven more effective for individuals with certain genotypes.<sup>1</sup>
31. Scientists from the US National Cancer Institute and the University of Helsinki have questioned whether searching for common inherited genetic variants that increase susceptibility to cancer is worth the resources being spent.<sup>43</sup> They note that:
  - Evidence from biology, migration studies, and twin studies suggests that common cancer susceptibility genes are unlikely;
  - Even if susceptibility genes were identified, further large, expensive studies would be needed to show the clinical benefit of targeting the proposed intervention at those individuals with the genetic variant(s).
32. In general, twin studies exaggerate the importance of shared genetic factors in explaining why diseases run in families, because the classical method of analysing twin data assumes that there are no gene-gene or gene-environment interactions.<sup>5</sup> Nevertheless, several different situations may be identified from twin and family data, depending on the disease under consideration. These are:
  - Diseases or conditions with no significant heritable component, such as lung cancer.<sup>44</sup> Because no twin study has ever identified a significant heritable component to lung cancer, developing genetic screening tests for lung cancer susceptibility in the general population is clearly not worthwhile, because such tests will inevitably have poor predictive value and low utility. Testing smokers for supposed genetic susceptibility to smoking-related diseases could also mislead them about the risk of smoking and falsely reassure some people into thinking that they do not need to quit.<sup>45,46</sup>
  - Diseases or conditions where the assumptions of the classical twin study are known to be invalid, so a more complex explanation is necessary, for example, schizophrenia<sup>47</sup>. This might involve gene-gene interactions, gene-environment interactions and/or developmental effects. Although genetic research might help shed light on underlying disease mechanisms, genetic risk profiles must take account of multiple interactions and are likely to have low predictive value and low utility.
  - Diseases or conditions where the assumptions of the classical twin study may or may not hold, such as breast cancer. If the assumptions hold, more genetic factors have yet to be discovered to explain why breast cancer runs in families; however, even if these factors are identified, medical interventions would need to be developed for healthy people identified as genetically susceptible and tested in

large-scale clinical trials. However, if the classical assumptions do not hold – for example, if gene-gene or gene-environment interactions are important in breast cancer - familial aggregation of breast cancer may be largely due to non-genetic factors (shared environments or lifestyles), and common genetic variants will then have low predictive value for most women.

33. The usefulness of genetic information as a means to ‘personalise’ medical advice is therefore seriously questionable, because special conditions must be satisfied to achieve high clinical utility.<sup>5</sup> Although these conditions may be met for some diseases in some people, it seems highly unlikely that most common genetic variants will satisfy medical screening criteria for the general population.
34. A 2006 review found that conclusive evidence of favourable cost-effectiveness ratios for genetic testing is available only for few conditions.<sup>21</sup> With the whole population potentially ‘at risk’ and eligible for preventive medication, the cost implications of genetic susceptibility testing have been described as “staggering”.<sup>48</sup>
35. GeneWatch UK has repeatedly questioned the Government’s commitment to the vision outlined in the 2003 White Paper ‘Our inheritance, our future’, in the absence of any assessment of the likely benefits and costs of genetic screening in the general population. Sufficient data is now available to make a preliminary assessment of expected positive predictive values, numbers needed to treat, costs and cost-effectiveness of this proposed health strategy. Such an assessment is urgently needed.

**What are the implications of the generation and storage of genome data on personal data security and privacy, and on its potential use or abuse in employment and insurance? How should these be addressed?**

36. There are serious concerns about privacy, surveillance and discrimination, particularly by insurers and employers, should a system of health screening based on individual genetic make-up be implemented in the future. Although GeneWatch is sceptical about the extent to which genetic screening will be useful in the general population, people with rare mutations which predispose them to conditions such as familial breast cancer already face these issues.
37. There is currently no legislation to prevent insurers or employers using predictive genetic test results to refuse someone insurance or a job, although there is a voluntary moratorium on the use of most gene test results by the insurance industry. GeneWatch UK believes that legislation to prevent genetic discrimination is important because<sup>49</sup>:
  - People should be able to make the difficult decision about taking a predictive genetic test on health grounds alone, without the fear that it could affect their access to healthcare, the housing market, employment, pensions or travel insurance in the future.
  - Most members of the public are opposed to insurers using genetic test results. They feel it is unfair to discriminate against people for something they cannot do anything about. There are also widespread concerns from trade unions and some scientists that genetic screening and selection of workers could become a damaging alternative to reducing workplace hazards, or be used to try to cut employers’ pension or insurance costs.
  - The public has been promised that genetic research will bring benefits, not harm, to the people at highest genetic risk. Volunteers donating samples to genetic research are likely to feel misled if the results are used to discriminate against the

people that they are trying to help. Legislation would resolve the current uncertainty in which people do not know whether genetic tests taken now, or developed in the future, will one day be used to discriminate against themselves or others.

38. In 2007, the Science Horizons Deliberative Panel<sup>50</sup> raised concerns about the security, privacy and integrity of personal health information (IT- or genetically-based), and about safeguards against abuse of technologies by authorities or by criminals. People were also concerned about insurance issues relating to increasing genetic understanding and medical profiling.
39. Personal data security and privacy is inadequately protected by current legislation: a major area of concern is that the police will be able to access genetic profiles and DNA samples held by research projects such as UK Biobank, or in NHS or commercial health databases, provided they can get an access order granted by a court.<sup>51</sup> If genetic profiles are held in a searchable form in future, linked to each person's unique NHS number (allocated at birth), they could also be used by governments – or anyone who can infiltrate the system - to track individuals and their relatives. The rapid expansion of the police National DNA Database has raised widespread concerns about the potential for excessive Government surveillance. Stricter legal controls on the retention and use of medical data, including genetic information, are therefore likely to be necessary to maintain public trust in NHS medical records and associated data.

#### **Comments on research priorities**

40. 'Individualised' prevention, based on genetic screening, has long been advocated by the tobacco, chemical, food and nuclear industries, which prefer people to focus on internal, biological risk factors for diseases such as cancer and heart disease, rather than on their products or pollution. The pharmaceutical industry, and more recently the food industry, also favour individualised prevention, whether based on genes or other 'biomarkers', because this will allow them to market 'preventive' drugs and new 'functional' foods to the (rich, healthy) individuals claimed to be at high genetic risk. A relatively small number of 'genetic susceptibility' tests could classify the entire population as 'at risk' for life, making everyone a patient who can be sold 'personalised' products.<sup>52,53</sup>
41. In this context, it is not surprising that the 2007 Science Horizons project reported a "*striking trust deficit*" regarding whether research was being conducted in the public interest and that overarching issues raised by the Deliberative Panel included: "*trust in expertise - who can be trusted?*"; and "*fears about loss of the 'human touch' in everyday interactions, for example in relation to health, and in work*".<sup>16</sup>
42. GeneWatch UK recognises that the identification of common genetic variants (polymorphisms) can play a role in understanding the biological mechanisms involved in common complex diseases, such as heart disease and cancer. However, we are sceptical that genomic medicine will lead to valid, useful risk predictions for most diseases in most people.
43. In its 2003 White Paper and other documents, the Government has made a political commitment to implementing human genome screening in the NHS, in the absence of any evidence that genetic 'prediction and prevention' is a credible approach to tackling most major diseases. Concerns about the role of commercial companies in promoting this agenda have been repeatedly dismissed.

44. For example, in the context of the global epidemic of obesity, the food and biotech industries, and many of the scientists they fund, have widely promoted the idea that the ultimate goal of nutritional research should be personalised nutrition, involving individual diets based on a person's genes and, perhaps in the longer term, on other biological measurements and continual monitoring.<sup>54,55</sup> GeneWatch UK disagrees that personalised nutrition should be a research priority and questions the lack of public involvement in adopting this dubious commercial aim. In most cases, personalised diets are neither desirable nor achievable because:
- For most diet-related diseases in most people, the key to prevention lies not in individual biological differences but in tackling the politics of food and issues such as food industry marketing practices, socio-economic deprivation, health inequalities, transport and the lack of sports facilities in schools. Personalised nutrition is therefore a false solution to the problem of diet-related disease.
  - Personalised nutrition is about selling the idea of 'wellness', not about improving health: it is a marketing strategy, not a scientific concept. It seeks to 'medicalise' the problem of diet-related disease, by testing and monitoring the 'worried well' and marketing new products at a premium to the wealthy, supposedly to 'optimise' their health.
  - This marketing strategy involves personalising and privatising dietary advice, based on genetic tests (and perhaps other types of tests) sold by commercial companies. Some companies are already falsely claiming that public health advice is 'guesswork' and that genetic tests improve the accuracy of dietary advice. They are marketing misleading and inaccurate interpretations of people's genes and what they mean for their health. As this industry expands and provides multiple and conflicting dietary advice and products, there is significant potential to confuse and undermine healthy-eating messages. Some people may be falsely reassured that they are not at risk of particular diseases, with serious consequences for their health.
  - New 'value-added' products such as functional foods are expensive and unnecessary and may have unintended consequences for human health. The consequences of altering the food supply will be hard to predict and difficult to identify or correct should something go wrong. Controversial products are expected to be part of this marketing approach, including: genetically modified (GM) foods, foods designed to alter appetite or mood, and foods containing nanotech ingredients.
  - The idea of tailoring diets to genetic make-up is based on a false and outdated view of the role of genes. For most common diseases in most people, an individual's risk is not predictable, because multiple environmental and biological factors interact. What is predictable is the outcome of major shifts in diets on the health of populations.
45. GeneWatch UK is therefore concerned that the current inquiry has focused its questions on research funding and translation, not on who sets research priorities. If research funding is to be effective in tackling diet-related disease we suggest that ministers should:
- Prioritise public health (the social and economic determinants of health), rather than genomic medicine and personalised nutrition, and tackle the 'politics of food';
  - Tackle inequalities, empower people to change their diets and environments, and involve them in deciding what action and research would help to make a difference;

- End gene patenting, which distorts the 'knowledge-based' economy, and stop commercial interests from dominating the research agenda.

## Conclusions and recommendations

46. A 'genetic revolution' in healthcare has been widely promoted in the absence of any analysis of the cost-effectiveness, impact on health, or impact on the NHS, of genetic screening in the general population.
47. GeneWatch UK believes there is an urgent need for the Government to:
- commission an independent assessment of the costs and benefits of implementing genetic 'prediction and prevention' in the NHS;
  - end gene patenting, which distorts the 'knowledge-based' economy, and stop commercial interests from dominating the research agenda;
  - require medical oversight and statutory regulation of genetic tests – including an independent pre-market assessment of whether they are valid and useful for health;
  - adopt new legislation to prevent genetic discrimination and protect privacy.

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