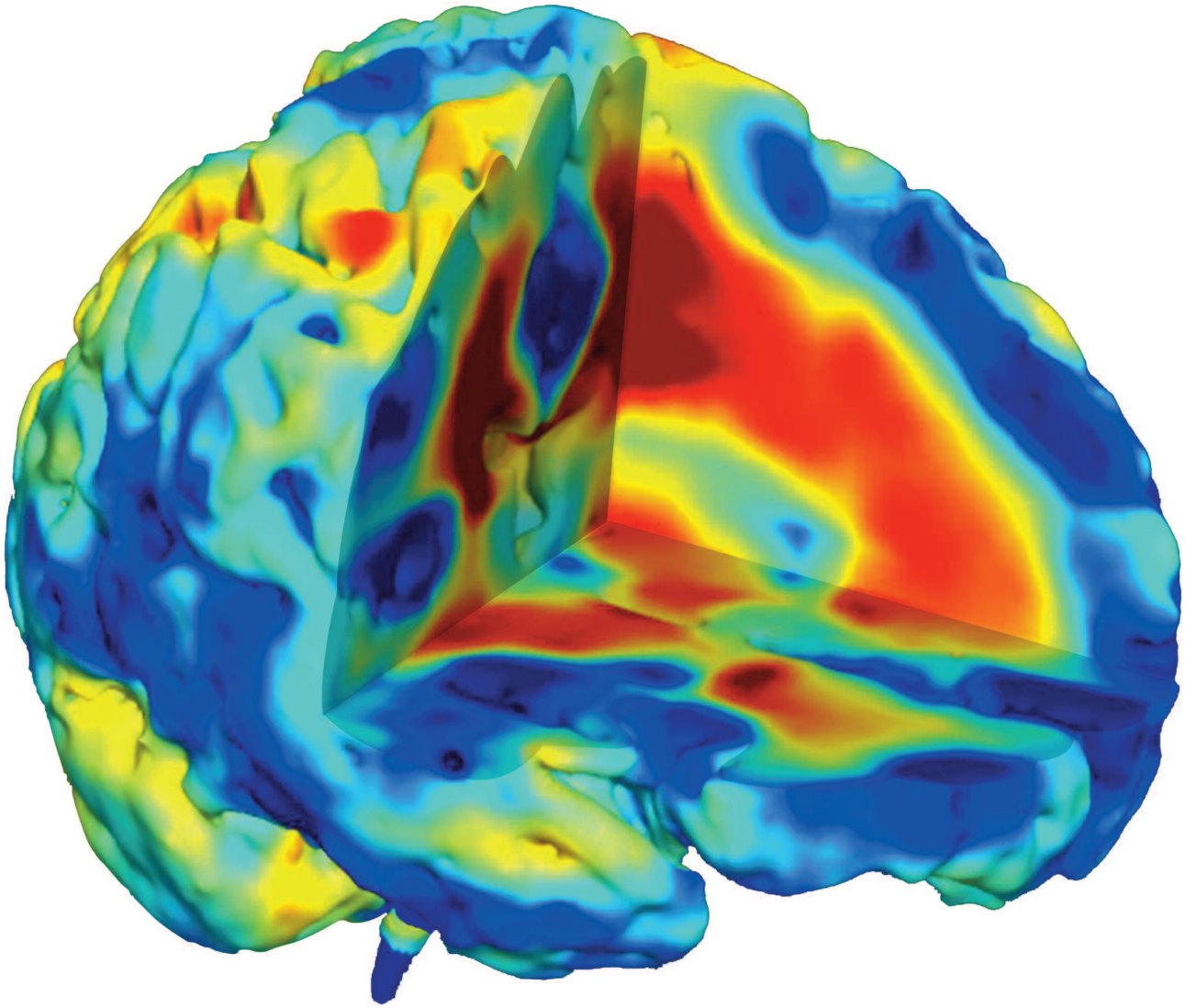
Health, humanity and justice:
Emerging technologies and health policy in the 21st Century.

Julia Manning
October 2010



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An independent review
commissioned by the
Conservative Party

Consultative Group
Professor Nigel M. de S. Cameron
Professor Noel Sharkey
Gregory Shenkman

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Contents

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Julia studied visual science at City University and became a member of the College of Optometrists in 1991. Her career has included being visiting lecturer in clinical practice at City University, visiting clinician at the Royal Free Hospital, being a founder member of the British Association of Behavioural Optometrists and working with Primary Care Trusts in south east London. She was a Director of the UK Institute of Optometry for 6 years, took post-graduate studies in diabetes and founded Julia Manning Eyecare, a specialist optometry practice for people with mental and physical disabilities which was bought by HealthcallOptical Ltd in August 2009.

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Executive Summary

It is a truth universally acknowledged that it can take a combination of monumental effort and good fortune to interest most people in any matter of science. The fact that only about seven percent of 'A' level students study any science subject illustrates the uphill task. But as with politics, science - particularly in the form of medical technology - has a huge impact on our lives. Our eyes may glaze over but we can't avoid this reality, and the opportunities and questions are only going to get bigger and bolder. This review aims to bring clarity and insight. As well as helping the reader to understand why 'emerging' technologies matter, we also aim to illustrate why these are not purely health and science issues, but issues of humanity and justice too.

Medical technologies are constantly changing and advancing - in many cases at lightning speed. It is extremely important both that a greater understanding of new emerging technologies is enabled, and also that we can make rational decisions about the direction of progress.

That's why a 'strengths and weakness' (SWOT) analysis of emerging technologies has been at the heart of this project. Four of the key areas were put under the microscope and examined for which were most imminent and relevant to health concerns. Full details are included in the appendices.

In Part 1 of this review we sketch the outline of the past and present situation with emerging technologies in healthcare. We wanted it to be an easily understandable introduction to the subject which sets out some of the implications and applications for human health and well-being. There are also significant questions to be asked about the boundaries of treatment, and we use the example of doping in sport as an illustration of the challenges that face us all. We conclude by emphasising the importance of our humanity and the need to make conscious decisions on priorities for health research based on the healthcare needs of the population.

In Part 2 we explain how we approached the analysis of emerging technologies and how we have begun to identify and frame the questions that will help with the process of risk assessment and policy formation. Intrinsic to this was thinking about legal, social and value questions - and these have been incorporated into a matrix for ease of comparison. As we cross checked the questions with the technologies we discovered that in many cases there was a straightforward, uncomplicated outcome. There were often myths that needed debunking, such as the more far-fetched notions of 'designer babies' but in a few other cases there was quite clearly a need for intense scrutiny.

Recognition of the importance of greater public engagement and confidence is both inherent in this paper, and emphasised throughout. Social and ethical discussion around the Human Genome Project demonstrated what is possible and health provides a

familiar platform on which to base democratic engagement. When so many potentially off-putting questions about technology are actually familiar issues of public health, privacy, human rights and justice, this can help both to engage the public and demystify science.

As a result of our analysis, we identify four particular 'emerging technologies' which could have far-reaching applications within the next 15 years, and which therefore deserve particular and immediate attention from government. These are:

1. **IT applications - neural implants and external devices, including deep brain stimulation and exoskeletons;**
2. **'smart' drugs;**
3. **synthetic biology; and**
4. **genetic prediction.**

We conclude that, although each of these technologies offers the possibility of real therapeutic advances, each also presents significant risks. In particular:

1. a) neural implants and sensors (which already provide huge therapeutic gains include enabling deaf people the transformational opportunity to hear again) are now beginning to enable people to communicate electronically without speech – raising issues of privacy that require serious regulatory consideration; and they are now also developing to the point where, through **deep brain stimulation**, they may have side-effects on mental functions and capacities which could one day raise issues about both coercion and 'enhancement' by wealthier people to 'buy' augmentation of their mental abilities;

b) exoskeletons (which have now developed to the point where they hugely enhance the physical ability of the person wearing them) could simply become the new car but could likewise become the new gun – offering those with evil intent a major new opportunity to engage in evil actions;

2. 'smart' drugs (which can have a significant therapeutic value for those suffering from diseases like Alzheimer's, ADHD and narcolepsy) can also be abused to provide the user with short-term gains in concentration and mental effectiveness, but at the cost of serious or life-threatening side-effects. As with steroids for athletes, there is a real danger of social and competitive pressure leading to such abuse if it is not highly regulated;

3. synthetic biology – the construction of new biological systems not found in nature – may offer great gains through reducing the cost of medicines, but also opens up the possibility of 'bio-error' or malicious use (even to the extent of creating new viruses to which we have no immunity); at present, these new biological systems could, in the wrong hands, be developed into unregulated biological weapons;

4. genetic prediction offers the possibility of a new range of preventative medicine solutions through the identification of those at risk from particular disorders and through better prediction of the safety and efficiency of new pharmaceuticals. But considerable thought needs to be given to the question of how we avoid people being subjected to gross manipulation through unsubstantiated or misleading results of commercially available genetic tests – and also to the question of how individuals can adequately control the use of test data by commercial firms and government agencies.

We conclude by urging the new government to establish a formal process to evaluate the benefits and risks of these and other emerging technologies. There are technological prospects ahead that will need public confidence if they are to be developed. There are research decisions to be made that must include profound consideration and analysis of their societal consequences. There is the opportunity to improve public health, reduce inequalities and affirm our humanity all at the same time. If there was ever a time when we needed clear and careful thinking about the way ahead, it is now.

Part 1
New technologies in plain English

Introduction

"And there, Mister Bond, I lost myself in the study of the human body and the human mind.

Why? Because I wished to know what this clay is capable of. I had to learn what my tools were before I put them to use on my next goal - total security from physical weaknesses, from material dangers, from the hazards of living."

Ian Fleming, Dr. No

Medical technology has transformed our lives and its pace of development keeps increasing. The curve gets steeper every year. Many of us are alive because of the vaccinations we received as children or before we went abroad on holiday. Some of us took medicine or put on moisturiser containing atom-sized particles to improve its absorption this morning. Some of us have been conceived through IVF treatment, or have parents requiring mobility assistance or an IT 'pacemaker' implant.

Advances in medicine and surgery, antibiotics, anaesthesia, vaccination, diagnostics and hygiene have revolutionised human lives – and made most of them a lot longer - in little more than a century. A better quality of longer lasting life has become the experience of the many, not the few (at least in the developed world). This progress brings new challenges to health policy, and health policy has implications well beyond healthcare provision. One in five of us who live to be over 80 can expect to suffer from dementia; in the past four decades, 30 previously unknown infectious diseases have emerged including MRSA and avian flu; fears are rising of a pandemic flu that could have effects as dramatic as the credit collapse (with the recent swine flu a wake-up call for many governments); meanwhile, malaria and HIV continue to rob millions of their health and lives.

The good news is that we live at a time where significant advances in medical research and technology are an almost daily occurrence. Knowledge of the human genome is raising the prospect of identifying and possibly eradicating causes of disease. Development of information technology (IT) including robotics and implants is offering the disabled new abilities that were previously closed to them. An understanding of brain science raises the possibility of improving memory function, maybe in everyone. Miniaturisation is allowing treatments to be targeted in a way that would previously have been impossible. Creation of artificial cells is meaning that we can begin to think about manufacturing new life or synthetic forms of existing varieties. Developments right across the spectrum of what are known as 'emerging technologies' – from IT to nano to the far reaches of synthetic biology – have an increasing role in shaping healthcare and the options we face for human well-being. The impact is not just on the health of our nation, but on our economy, culture, social justice and even the nature of our humanity. This opens up the basic question of politics: What kind of society do we want to belong to?

Now there are so many research opportunities open to us, we need to make decisions about what is desirable and what is permissible. If the research is successful, and there is an enormous demand for therapies, we will need a framework for deciding what and whom to prioritise. We need to decide how to balance our desire for the UK to continue to remain at the forefront of industry research and development with concerns about the possible impact on society and community of technologies that enable some of us to perform or live

beyond our natural abilities, especially if many or most cannot. Will everyone remain of equal value with the strong caring for the weak? Or will 'enhanced'[i] function and pursuit of perfection and strength exacerbate health inequalities as they create a polarised society such as portrayed in the gripping sci-fi film 'Gattaca' – in which DNA determines an individual's worth, and leads to a society composed of the superior 'valids' and the inferior 'invalids'?

This much is undeniable. The compounding impact of technological progress is going to have a vast influence on us all. We are observing the first stages of a quantum leap in our human capacity to develop and apply technologies in every area of our personal and community experience. The piecemeal approach to preparing for and handling these implications will no longer do. The genetically modified (GM) food experience over recent years has illustrated in one area of our life the profound impact of a technology and its public perception. This is just the beginning. The impacts of technology, which brought us the railways and the motor car and the aeroplane and the telephone – technologies that remain fundamental to our lives one or even two hundred years after they first appeared – are now becoming more pervasive and are changing very fast. The dramatic effect of the internet and mobile phones on our lives – technologies that did not exist when those of us in middle age were young – illustrates what is taking place right across the spectrum: rapid, disrupting change, the emergence of an amazing opportunity and the need to raise our awareness of what lies in store so we can handle it right.

These are vast questions, which will require prolonged debate. The purpose of this report is to identify some of the novel technologies that need particular consideration, to explore what they might mean for society, and to discuss some of the potential pressures and opportunities that they might create for the UK's system of public health protection and procurement. To provide a basis for orderly debate, we have constructed a risk analysis that aims to quantify the relative potential impact of some of the most promising technologies on health and human well-being and society.

Before we describe selected new and emerging health technologies, we describe below our methodology and approach.

1. Process

To compile this report, we spoke to experts in science and medicine, ethics and risk and undertook an extensive literature search. We held a series of discussion meetings, some with individuals and some with groups, as well as conducting many telephone interviews. Numerous professionals also commented on drafts of this report according to their area of expertise. We endeavoured to make it clear that this was an attempt at an introduction to the subject for policy-makers and commentators who have not had the opportunity previously to give these issues much thought.

2. Keeping it real

It was clear from the start that there was a mass of hyperbole about new technologies that reflects aspiration rather than fact. It has been our aim to keep our considerations grounded in reality, and to focus mainly on a time frame of 10-15 years; we felt that technologies likely to mature at later dates were too speculative to be relevant to this report. There are many people who enjoy predicting the future and there is a plethora of misleading media headlines that raise and dash hopes on a regular basis. We do not aspire to join the ranks of the soothsayers: our aim is to consider principally developments that are highly likely to become real within the span of the next three parliaments.

3. Opinion

The opinions stated are those of the author and consultative group. They are based on the research that has been undertaken and which is contained in more detail in the annexes. No opinion is without bias, but it has been our aim to depict as far as possible an accurate and balanced reflection of the new technologies, their potential and their risks, based on the evidence with which we have been presented. We have assumed that state supported health initiatives should place the raising of as many people as possible to normal in terms of health and lifespan (however defined) ahead of physical or mental 'enhancements' above normal and life prolongation beyond the norm. The aim is to open up the conversation.

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i 'Enhanced' can mean anything from wearing spectacles at one end of the scale, to remedying disease and disability problems to giving us superhuman powers of strength or memory. We use this term in inverted commas in this paper to highlight the diverse definitions.

Part 1
New technologies in plain English

Chapter 1
So what are these emerging technologies?

"I think you'll find this present a valuable addition to our modern lifestyle!

They're 'Techno Trousers'. Ex-NASA. Fantastic for walkies! All you do is attach the lead on here... then programme in. Walkies, ten minutes, twenty minutes... Oops! Ha ha ha! Have a nice walk, Gromit!"

Wallace to Gromit in 'The Wrong Trousers', Nick Park, Aardman animations

The term 'emerging technologies' is used to describe the new medicines, techniques, research and sciences that are – among other things - beginning to offer new ways of treating and preventing illness. They are usually described using the following terminology: nanotechnology, biotechnology, information technology (including robotics) and cognitive science. Hence, in much scientific literature these technologies are referred to under the acronym 'NBIC' ('nano-bio-info-cogno'). Here, we shall try to avoid jargon and to explain what each of the technologies means and what it offers. There are overlaps between these technologies, and they are 'converging' in the sense that they often come together in different applications.

Nanotechnology

Nanotechnology is the term that describes engineering and technology development on a tiny molecular scale. One nanometre is one billionth of a metre; the smallest thing anyone can see (with good eyesight) is about 10,000 nanometres; human hair is 50,000-100,000 nanometres in diameter. Nano-medicine is the application of this technology to the prevention and treatment of disease in the human body. Examples of applications include self-cleaning surfaces to improve hygiene, targeted drug delivery where the tiny particles only 'stick' to the diseased tissue in the body and in medicines where the small size means that they are more easily absorbed and can be used in lower, safer concentrations.

Specific concerns with nano-medicine arise from uncertainty over how the body gets rid of these tiny particles. They are so small that cells in the blood stream don't recognise them as 'foreign bodies' and their size means that they can move through blood vessel walls and into any part of the body.

There are already a few medicines licensed that use 'nanopharmacueuticals' and research is also underway, looking, for example, at how these nanoparticles can be used to treat cancer more effectively without damaging the surrounding tissues. It is also worth mentioning that some substances such as albumin, acacia gum and gelatine are naturally occurring nanoparticles and we have only realised this as we have become aware of this atomic scale.

Biotechnology

The term biotechnology covers the manipulation of living organisms, such as bacteria or yeasts, or biological substances (products made from living organisms) such as enzymes (which are complex molecules produced by living cells that make chemical reactions go faster) to produce useful treatments and diagnostic tools and processes. This is not a new science. Biotechnology has for decades allowed us to produce 'biologics' such as insulin, vaccines and human growth hormone.

However applications of this knowledge are increasing at an enormous rate with the expansion of disciplines such as genetics, stem cells and cloning.

Genetics is the science of inherited characteristics (traits) and how these relate to observable qualities in a given organism. This information is now being used to develop medicines targeted to an individual's genetic 'makeup', with the aim of providing treatments for genetic conditions such as cystic fibrosis and to identify embryos with defective genes – the basis of so called 'designer babies'. It is worth noting, however, that most of our features – the colour of our eyes, our IQ, our height are controlled by hundreds of genes (and probably unknown factors too) and it is currently impossible (no matter the claims in the press) to design your baby beyond eliminating one or two genes that are related to the most serious genetic diseases controlled by a single gene or via sex selection.

A technique that could expand the opportunities for genuine 'design' of babies is cloning. We mention this technology only in passing since, despite the success in cloning Dolly the sheep, the genetic defect problems encountered in cloning are huge and there is no prospect of being able to overcome them within the next 15 years. Human 'reproductive' cloning (leading to the birth of a baby) is banned in many countries including the UK, although experiments are allowed; any cloned embryos have to be destroyed after 14 days. The reality of the Dolly experiment was that it took 277 embryos to produce just one, live-born baby lamb which went on to die prematurely. But if scientists were able to overcome the problems of mutations in cloning, society really would be faced with the massive ethical dilemmas of designer babies, commoditisation and humans being designed to be genetically identical (with the issues of replacement or spare parts that this raises).

Stem cells receive a lot of coverage in the press as well. The use of adult stem cells has produced over 80 viable treatments already, recently enabling a Columbian woman to have a transplanted wind pipe covered in her own stem-cell grown cartilage, having lost her original one to cancer followed by similar operations in the UK and Italy. While embryonic stem cells have not produced any treatment, they are credited by scientists with increasing significantly their knowledge of embryo and cell development. As they can be grown, in principle, into any tissue in the body it is hoped that they will be a building block of 'regenerative medicine', where diseased or worn out body parts are replaced by new, healthy cells. Yet this seems a long way off, especially using the controversial technique of 'therapeutic cloning,' where stem cells would be culled from embryos cloned for the purpose. It is likely to be at least a decade away (some say much longer) before there are any viable, commercial applications that the NHS will have to consider. In all cases of stem cell research, the regulatory barriers to clinical trials are significant (see appendix 3) and warrant review if the UK is going to stay at the forefront of research and attract more investment in this technology.

In the meantime, regenerative medicine will still largely be defined by the continued research and development of artificial organs and applications of adult stem cells. The American Society for Artificial Internal Organs has been in existence for 55 years during which we have seen the evolution of kidney dialysis (first demonstrated in 1943), routine use of pacemakers and progression of artificial hearts (first totally implantable version achieved in 2001). Their annual conference is an international affair with Japan contributing on average 20 per cent of the research papers.

Synthetic biology is a more recent research area that combines biology with engineering principles to design or create new types of viruses or bacteria, or modify naturally occurring structures such as genomes (the full set of genetic information that we inherit from our parents). In some quarters it is known as 'extreme genetic engineering' and it has potential applications in energy, fuel and defence as well as medicine. This science is still in its infancy but it raises significant questions about both the potential dual uses of manufactured biologics and also about what kind of new or artificial life forms we want to create, if any. The most notable success so far has been the creation of artificial artemisinin for the treatment of malaria, which was first achieved in 2004. In a recent interview, one of the pioneers of this science, George Church of Harvard University, announced that he had engineered an artificial, self-replicating cell component [ribosome] but added, "It's not our intention to make an artificial bacterium, much less an artificial human. Being able to make a synthetic cell is a by-product." More recently Craig Venter and his team at the Craig Venter Institute generated the first bacterial cell which was totally chemically created by scientists and this is the first step to generating a totally synthetic organism. It should be of concern that there have been attempts by some to recreate dangerous viruses, and discernment over funding and the close monitoring of developments in this field are an essential role of Government.

Information technology and implants

In health there are both internal and external applications of IT and robotics that are already in use and are continuing to be developed. The internal applications include the installation and implementation of computer chips (implants) linked to our nervous system. Many people are familiar with cochlear implants, devices for the deaf which are attached directly to nerves in the brain and which have regenerated hearing for over 100,000 people. Electrodes placed in the brain have also been used to reduce tremor in people with Parkinson's disease and to provide pain relief in people with intractable nerve-related suffering. There are also implants that have been designed to release medication slowly from inside the body, or to provide a tracking signal. The former can improve dosage and

compliance; the latter was used by 'M' on James Bond in the second film (not the book) Casino Royale so that she could know where he was at any time. Sadly for him, the implant was dug out by the villain Le Chiffre. Medical applications include the use of a silicon chip as an internal method of storing health records that can be scanned, or for keeping tabs on a relative prone to wandering due to e.g. dementia. Recent research has been increasingly successful in providing the blind with electrodes that are implanted under the retina and convert light into signals that are sent to the brain.

Robotics and IT can also be used to provide remote monitoring of patients so that they can stay at home and have tests undertaken with portable home equipment that relays results automatically to clinicians. In Japan, work has been undertaken on robotic companions; and here in the UK, Lord Darzi is famous for his enthusiasm for robotic surgery and a mobile robot through which he can 'visit' patients. Newer applications include restoring abilities to disabled patients through 'thought' control. You can now buy a neck band that turns your thoughts into audible words on the phone and the first message on twitter posted using thought control was sent on April 1st 2009 (no April fool). Although 'bionic man', constructed through IT prosthetics (artificial body parts) which are linked to the nervous system, remains far off, much more imminent are 'exoskeletons'. These are external 'suits' that have been designed (among other things) to enable paralysed people to walk (Wallace in Aardman's 'The Wrong Trousers' was ahead of his time). A commercial version made in Israel is due to go on sale this year (2010).

Cognitive sciences

Cognitive science is the study of the mind, including artificial intelligence and brain (neuro-) science, but for the purposes of this paper, we have considered only drugs that work on the brain, by altering memory, emotions, behaviour or other performance. Current applications include medication to help retain and develop knowledge (cognition) in mental health patients and Alzheimer sufferers, and those that modify behaviour in children with attention deficit disorder (ADD). For a variety of reasons, more and more people in society are suffering from chronic conditions that affect their abilities to cope on a daily basis and there has been real concern expressed by many working in health and science that the investment in finding both prevention and cures is woefully inadequate.

The conditions to which these drugs apply range from the severe (e.g. dementia) to the mild (e.g. fatigue). The border between the treatment of ill-health and changes in 'lifestyle' is, therefore, becoming hazy. This is partly because over time it has been realised that drugs developed to treat a medical condition can be used in people who simply want to boost their performance. In the field of sport, this is nothing new; for years now, performance-enhancing agents have been ruled unacceptable. However, some of the very same medicines that are banned by sporting authorities are finding their way onto college campuses, into academia and the boardroom. Known affectionately by scientists as 'smart drugs', there is growing publicity (distracting from the original medical uses of the drugs), and a growing debate over whether these drugs should be allowed not just to make people well, but to make them 'better than well'.

It is open to question whether we can justify allowing 'enhancement' in everyday life, as is currently being demanded by some scientists, when they carry such a stigma in sport, and the risks of side-effects in healthy people, overdosing and dependency are usually not fully known. These performance-enhancing drugs also raise fundamental issues of equity, all of which need to be thoroughly investigated. These are pressing issues for Government and for the NHS.

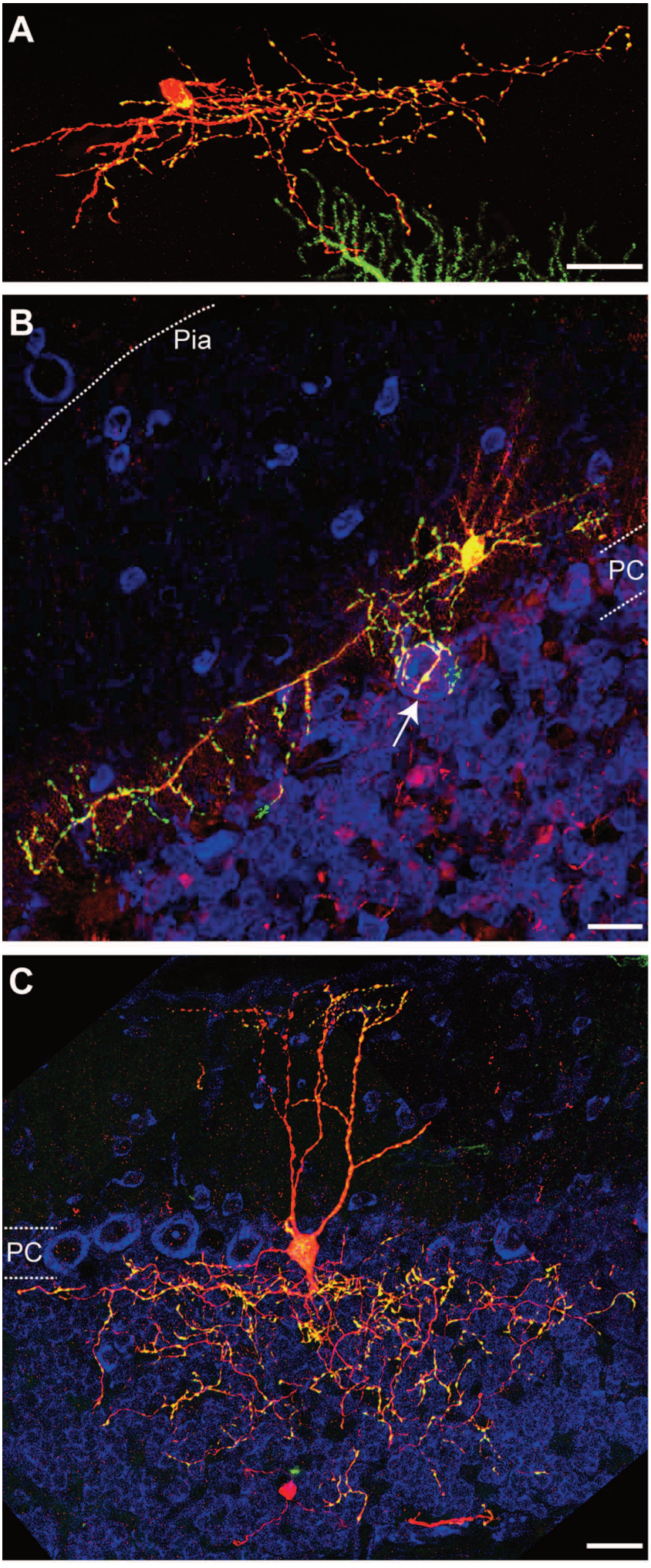

Fig 1: Morphology and presynaptic distribution in cerebellar interneurons.
(Li L, Tasic B, Micheva KD, Ivanov VM, Spletter ML, et al. 2010 Visualizing the Distribution of Synapses from Individual Neurons in the Mouse Brain. PLoS ONE 5(7): e11503. doi:10.1371/ journal.pone.0011503)

Part 1
New technologies in plain English

Chapter 2
Taking forward technology policy

When Dolly the sheep was cloned in 1996 (the result of investment sanctioned by former MP Ian Taylor, then the Conservative science minister), the headlines in the papers reflected the astonishment of the world. Suddenly, a whole new realm of possibilities seemed to have opened up. People were unsure and fascinated at the same time. How had this science fiction become fact? What was it all about? Newspapers helpfully ran reminders on biology lessons! There was a sense that the future had arrived.

As a result of this cloning and of subsequent developments in nanotechnology, biotechnology, information technology and cognitive science, a European Union High-Level Expert Group was set up to examine new health technologies in 2003. That Group concluded that these technologies would *'break through the boundaries of man, nature and technological artefacts'*.[1]

As our core group[ii] began to think about the issues raised by these same emerging technologies, we recognised that they do raise issues different from those raised by any previous medical advances. But, at the same time, we recognised that the emergence of given technologies is a matter of choice, not an inevitability, and that policy-makers need to create a framework for analysis in order to make informed, intelligent decisions. The results of our deliberations on the key questions were two matrices which are presented in chapter 7. These matrices identify what we regard as the ethical and moral, legal and social risks attaching to each of the technologies most likely to emerge in the near future as well as the likely importance of each of these technologies. The basis for our assessments was consideration of the impact on human health and well-being and on our existing culture, rather than any consideration of commercial feasibility or cost-benefit to the NHS; that is an important task but one for another paper.

We are united in our passion for science and progress. There is no doubt that there are amazing new opportunities to reduce the burden of disease and suffering both through prevention and treatment. The UK's standard and quality of living have benefitted hugely from the fervour and commitment of our scientists and health professionals. Although we make up only 1 per cent of the world's population, 8 per cent of the world's scientific papers originate here and in the last 50 years we have produced 45 Nobel Laureates. That is an achievement of which we should be rightly proud.

"What we call Man's power over Nature turns out to be a power exercised by some men over other men with Nature as its instrument."

CS Lewis,
The Abolition of Man

ii The consultative core group consisted of Professor Nigel Cameron, Gregory Shenkman, Professor Noel Sharkey, and Julia Manning.

However, we see very clearly that early consideration needs to be given to policy decisions, partly because of the complexity of the science and its consequences, but also in order to retain public confidence. The features of medical advance that most need investigation are, in our view:

- the fundamental shift created by the new technologies,
- the move to more personalised medicine,
- the potential for destructive as well as constructive use,
- the possible impact of the technologies on equality and social justice.

Fundamental shift

Many of the technologies described involve a fundamental shift in our conception of the world, because they begin to blur the line between human beings and artefacts. Many of these converging technologies open the way not only to therapy or restoration in the traditional sense of medicine, but also to changing, enhancing, improving and modifying the human body. Is this simply to be welcomed as the next step in our human and social development? Or is it dehumanising us, turning us into machines whose value is determined by their capacities rather than by their characters? In addition, these technologies frequently involve permanent change of a sort that we do not expect from medicine. Genetic selection cannot be undone. New artificial life once created cannot be uncreated. Once you've had a brain chip inserted to give you a sense of well-being, would you want to risk having it removed or give up the sensation it delivered, or even be able to make that decision from the position and identity of the old 'pre-implant' self?

Wholesale adoption of these advances would raise significant questions and consequences for humanity. The impact on the NHS too would be massive, both in treatment terms but also in the concomitant psychological management. The cost of many interventions is high, and some are already unclear about what constitutes an illness and what are simply lifestyle or happiness issues or part of the normal human variation spectrum. Some clinicians already question whether some of the procedures that are available at the expense of the taxpayer from the NHS are really medical in nature. The controversy over elective amputations for psychological reasons offers a striking example. But some are more mundane: tattoo removal, breast augmentation, protruding ears – though the NHS does require a psychological assessment before sanctioning the operation. Over time, as the quality of life has improved, there has been a shift in expectations of what the NHS should deliver – and some have come to regard medicine as something that can be used to assist conception, remove acne and relieve anxiety. We therefore have important questions to ask about the taxpayer funding of interventions that are based on the emerging technologies. If we decide that many new and very expensive techniques are only for those who can pay, will 'health inequalities' widen? Or can we draw a distinction between core health needs and lifestyle choices which is sufficiently robust to separate social from health inequalities? And should we object to social inequalities that are magnified by access to emerging technologies?

Personalised Medicine

'Personalised medicine' is the term that is used to describe healthcare that is increasingly designed for use by specific individuals. There have been many claims that our healthcare will be revolutionised by this focused approach as the knowledge of people's genetic make-up will mean they receive precisely the appropriate dose and type of medicine for them. We see this happening already in decisions made about which women with breast cancer will benefit from the drug *trastuzumab* (herceptin), in ongoing trials looking at the appropriate dosage of *warfarin*[2] for thinning the blood after, for example, a stroke, and in deciding which men will benefit from treatment for prostate cancer.

Yet, having undertaken extensive research for this report, we are unsure about the timing of this revolution, and even uncertain about whether it will be a revolution or more simply a refinement of medicine as we know it today.

Firstly, it will require the easy and cheap reading of the individual's genome. It is hoped by some of those involved in genetics that the first $1000 DNA screening test will be available by 2014, but the benefits of mass population screening are yet to be demonstrated. What value is there in knowing that you are 20 per cent more likely than the average person to develop heart disease? Won't this knowledge increase mental anxiety, cause a massive escalation in demand for health checks (with huge numbers of false positives) and jeopardise people's insurance chances or career choices? There is a moratorium on disclosing genetic information to health insurers until 2014, but what will happen after that?

Secondly, as the human genome was mapped, it became increasingly clear that most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in *hundreds* of genes and probably other factors too. Added to this, the whole process of gene expression – which is about the conversion of the information encoded in a gene – remains little understood.

The most promising developments so far appear to be in predicting adverse drug reactions. This could make a difference both in reducing the wastage of ineffective or inappropriate drugs, and also in enabling patients to get

the most efficient and suitable treatment. But it is not yet clear whether there will be widespread applications beyond this – and it is interesting to see some geneticists begin to express doubts on this score. Right now, we are finding out more about our complexity rather than our simplicity.

Dual use

'Dual use' describes the potential for research findings, new technologies and techniques to be used for both constructive and destructive purposes. Some processes designed to treat disease could also - if misused - facilitate the spread of disease, be addictive, harm the environment or endanger security.

There have been examples of this before. Morphine was first manufactured by Merck in 1827 and was used in pain relief. Refined to reduce side-effects and produced by Bayer as Heroin in 1898, the drug later found its way into the bodies of the of the pain-free until the resulting escalation in addiction and deaths led to it being made illegal in the USA (1923) and the UK (1955). DNA analysis today has enabled us to map the genetic sequence of the 1918 Spanish flu virus – great for research purposes – but there is the potential that this gives a rogue scientist the opportunity to recreate it. Special consideration therefore needs to be given to the funding and direction of research even before we get to the publication stages. In dealing with such risks, 'the precautionary principle' needs to be particularly carefully observed because of the potential for irreversible change.

Social justice

The final issue is whether technological advances might be the direct cause of injustice or coercion - for example, if they lead to discrimination against people who have a rare condition.

Companies that specialise in drugs for rare conditions and side-effects that afflict only the few are essentially being penalised by not having their medications assessed and endorsed by NICE ('National Institute for Clinical Excellence' - the medicine and devices assessment agency). Without this endorsement (as the numbers are too few to warrant appraisal) it is left up to local health trusts to decide who gets what. Is it fair and acceptable that some of the most needy will not get specialised medication because they have a rare condition or because their local health trust has had poor accounting oversight? Is it more important to ensure that all paralysed soldiers returning from combat are fitted with exoskeletons or to provide IVF for infertile couples? The 'credit crunch' and debt mountain remind us that we cannot afford everything and although covert rationing has operated in the NHS for decades, aren't we causing injustice and inequalities if the new technologies lead to overt prioritisation?

Already, the increase in demand both for women's eggs for stem cell research and IVF and organ donation has produced serious consequences for the poor. Advertisements on university campuses in the USA and in the papers in the Ukraine and other east European countries offer women the chance to earn money in return for a 'batch' of their eggs. In order to produce this batch (women only usually produce one at a time) they have to take high levels of hormone stimulant which carries with it the risk (on top of the egg retrieval process) of 'ovarian hyperstimulation syndrome'. The effects of this can include blood clots, kidney failure, fluid in the lungs, shock, and in rare cases, death and these eggs are irreplaceable as a woman only has the eggs with which she was born. They aren't produced, like sperm, throughout her life when wanted. Likewise, in poor villages in the developing world, selling an organ such as a kidney has been promoted to (mainly) women as a way of clearing their debts. Most end up with both a large scar and remaining debt. There is concern that we have entered an era of 'body shopping' that is already enslaving women in a new and extremely disturbing way.

If 'designer' babies become the norm, what of people who choose to conceive naturally and have a disabled child? Will they be penalised for not taking advantage of the latest technology? Logically, if the abortion of disabled foetuses is labelled as success, doesn't having a disabled baby become a failure? (We do not by this endorse the deliberate choice of a disabled embryo). How can freedom be safeguarded when technology enables developments of this kind, which a few disabled parents have claimed as a right?

If robotic 'carers' become the cheaper option for children or the elderly, will those people be demeaned and dehumanised by the reduced human interaction? Many sheltered housing units now have a part-time warden who doesn't visit each resident in the morning but contacts them through an intercom or video-phone. "Telehealth" will expand the possibilities of remote care further. Is this a clever use of technology that deals with the escalating demands of an aging population with more long term illness, or a system that could increasingly isolate the elderly?

iii The purpose of the precautionary principle is to create an impetus to take a decision notwithstanding scientific uncertainty about the nature and extent of the risk (HSE definition)

‘Smart’ drugs obviously raise the issue of equity, but if we allow this chemical ‘enhancement’, won’t we also be creating a new playing field for competition where it won’t be the brightest or fittest who succeed, but the richest (who can afford augmentation), the riskiest (who are prepared to take ever higher doses) and the genetically predisposed (who are most receptive to the chemical enhancer)? So is this simply part of our evolutionary process or the greatest risk to social equity that we face today? Do we want to continue supporting Wenger’s Arsenal against Ferguson’s Man United, or are we happy to move on to supporting pharmaceutically stimulated Team A against biotechnology augmented Team B?

Part 1
New technologies in plain English

Chapter 3
Principles - what should we welcome and what should we be cautious about?

"The Genetic Code of Human Life Is Cracked by Scientists...Today we are learning the language in which God created life."

New York Times, June 2007

Aspiration and a quest for excellence is good. It is a fundamental feature of our humanity that we strive to better ourselves. We describe children who underachieve as lacking in aspiration, for whatever reason, and rightly condemn this as a failure.

But side by side with the emphasis on achievement, there has historically been an accepted maxim: no matter how much we 'get and do', the most important thing is *who we are as human beings.* The very nature of performance reveals the fact that we all achieve at different levels in different fields according to our innate ability, training and determination. We marvel at the achievement of those who excel, precisely because of the way they have pushed their humanity to the limit. Sport gives the classic examples of this. For all the excitement of Formula 1 racing, isn't the athlete who runs for 26 miles without stopping deserving of more credit for their achievement because they did it alone? The success fully belongs to the athlete whereas there can be no doubt from the millions spent on car design that part of the 'win' of a motor race is due to the mechanical and aerodynamic design of the car.

However, if we become aware that athletes have enhanced their performance through anabolic steroids we deem them to have cheated; we intuitively know that a Jonny Wilkinson diet of lean chicken breasts is not the same as taking muscle bulking drugs. Some sportsmen have had laser eye surgery where the surgery has restored their vision to its natural potential. If new surgery became available (currently impossible) that enhanced vision beyond the normal range, then this would be considered cheating. No matter what we accomplish in life, no matter our age or our disability, although no two of us are the same we remain equal and human because of who we naturally are. And by natural we concur with other thinkers who have defined natural to mean our intrinsic bodily capacities, produced through time and work with any improvements the result of our own personally guided activities rather than a chemical dependence or taking agents that compromise our 'choosing and willing identity' itself.

Where emerging technologies repair, restore, heal or protect there can surely be no fundamental objection, although it is right to review the process of development which itself can have significant outcomes and implications. There will also remain an important role for the assessment body, the National Institute for Clinical Excellence (NICE) as it considers the real benefits and value to society overall of new technologies.

Yet taking what has been developed for therapy and using it in everyday life to 'enhance' or to augment our humanity threatens the notion of what it means to be human. To paraphrase the thinker Leon Kass: If we are intrinsically no longer the sole source or shaper of our identity; if we become indifferent to the source of our achievement or superior performance; if we try to transcend the natural limits of accepted normal diversity,

then who we are and what we achieve becomes less about making the best of what we have and more about the relentless pursuit of superhuman powers (and the power to surpass and defeat our rivals) that will accept no limits.

Added to this, the potential burden on the NHS and public health of those who are healthy becoming medicalised is enormous. With an ageing population, with the emergence of new infectious and resistant diseases and with the growing liability of lifestyle diseases such as obesity and alcoholism, the NHS is already facing unprecedented, some would say crushing demand. To increase this burden at the behest of those who want the licence to 'improve themselves' jeopardises our care for the sick and disabled. Modern democratic society has come to operate on the convoy basis in health advances. That is to say that, broadly, society as a whole benefits from medical advances, which are not reserved to the privileged few.

One of the fundamental questions to come out of the new world opportunities that lie ahead is 'why'? Where there are clear medical, therapeutic and regenerative benefits, the answer is obvious. When the arguments are for enhancement of the healthy, we need to be clear why we would want to change the status quo before we do so. We also need to be clear about what the priorities are for research, and these should be dictated by the greatest unmet health needs. They might not be as appealing as thought control or as fascinating as cloning, but conditions such as incontinence, dementia and macular degeneration blight millions of people's lives, yet currently receive proportionately very little research funding. We should also demand greater honesty and rigour when it comes to reporting of the research that is being done. Every health professional in the country could tell you of a time when a patient has come in clutching a newspaper or internet report proclaiming that a certain procedure can or will cure their disease. And each one of us has had to counsel that same patient on the prematurity of that claim and deal with the crushing blows of disappointment and increased anxiety that are the consequences of these frequent flurries of hype.

Most new technologies are still in the pipeline and we have time for the public debates, the discussions on prioritisation and risk analysis that are vital. We still have time to talk about the implications of extending our lifespan through medical intervention on the capacity of the NHS and Social Services, the economy, society and housing etc., and whether we can also extend our 'health-span' at the same time.

The social ideal of *'loving our neighbour as we love ourselves'* - encapsulated as it is in the ideas of human rights and freedoms that lie at the core of the modern world - demands that we strive to find ways to heal and restore our neighbour's afflictions. For all the debate about the NHS, the United Kingdom has a superb track record in medicine and technology. Future Governments should always be looking for ways to encourage invention and research and the uptake of innovation. We should remember that what we sanction here has repercussions across the world. Our strength will rise as a nation if our technology focus remains on healing the sick, bringing more people out of health poverty and preventing premature disease.

Part 2
New technologies and framing the questions

Introduction

In Part 2 of this report we look in more detail at the present and future technologies and the issues they raise. Technology is changing on an almost daily basis and so this is only a snapshot of the situation as seen and predicted today. In Chapter 4 we explain how we formulated our policy risk matrix as an initial framework to enable decision makers to assess and compare the overall risk of new technologies. We wanted to identify the relevant questions to ask of new technologies and explain why they are important. We outline how we compiled the matrix and the factors we considered as we allocated ranking of questions and risk scores.

In Chapter 5 we describe which technologies we chose to analyse and how we undertook this analysis. We look at examples of the benefits these technologies are bringing and cast doubt on the validity of some of the concerns that are raised in the press. However there are serious genuine concerns as well, and we detail these before making general recommendations. The matrix itself is presented in Chapter 7. It is a first attempt to quantify considerations of risk with respect to the technologies we describe. It was formulated as a means of informing policy makers and has deliberately been kept in summary form in order to be immediately comprehensible.

Appendix 1 covers the four major health technology areas that we thought warranted the most attention, and Appendix 2 summarises the other areas of technology that we felt were most relevant to the health of individuals in the near future. We did not include an appraisal of all the different diagnostic developments. Appendix 3 is an illustration in diagram form of the barriers that researchers face in the UK before they can begin to undertake their research, and Appendix 4, a list of most of the conditions for which there are genetic tests available.

Appendix 5 is the summary of the 'bottom lines' with respect to the major technologies. We have not gone into detailed recommendations in this first report but have been made aware during its compilation of the complexity of, and duplication within, the environment in which discussions are currently held, the multiplicity of often conflicting interests when it comes to decision making on research priorities, and the urgent need for much greater public engagement. As mentioned in Part 1, there is such rapid progress in what are increasingly converging technological fields that greater awareness and deeper and broader consideration of the opportunities and priorities for the health of our nation are urgently required.

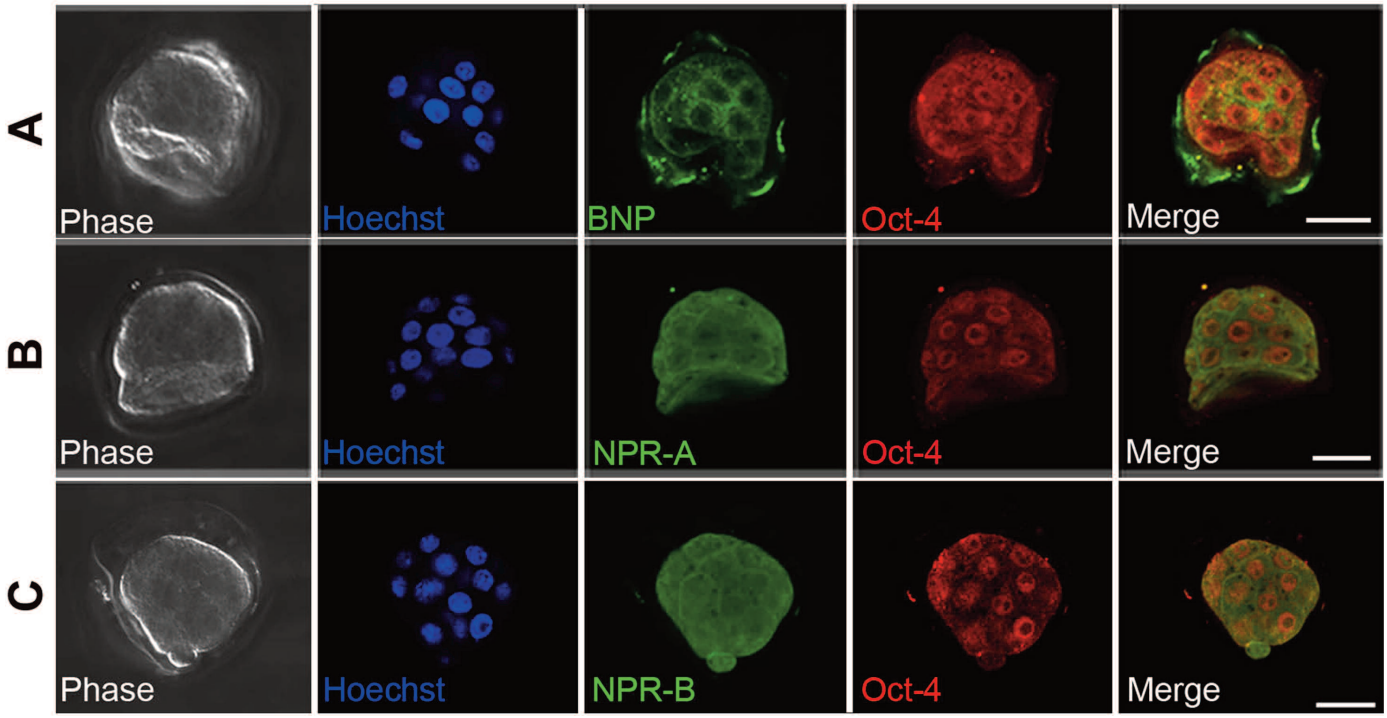

Fig 2: BNP and its receptors are expressed in pre-implantation embryos *(Abdelalim EM, Tooyama I, 2009 BNP Signaling Is Crucial For Embryonic Stem Cell Proliferation. PLoS ONE 4(4): e5341. doi:10.1371/journal.pone.0005341)*

Part 2
New technologies and framing the questions

Chapter 4
Risk and health

"Asking bioethical questions in the context of emerging science and technology is hugely important for our health, environment and ultimately our democracy."

Erik Parens, 'Do we need synthetic bioethics?' The Hastings Center, USA, 2008

Finding the 'risk' questions

As we argued in Part 1, we believe that government must rigorously examine new technologies for risk and be seen to do so. There has been a lot of discussion about the need to analyse and quantify risk but we did not come across any work which had begun to try to identify how this should be done, nor any systematic approach to risk. Some of the documents we reviewed referred to this need and set out some of the possible questions. Others took a purely procedural view and detailed how the process of research is overseen in order to inspire confidence in a thorough course of action. One example of the latter type of publication was the "Synthetic Genomics: Options for Governance," report produced by the J. Craig Venter Institute in the USA, which was funded by the Sloan Foundation charity. It came up with options for bio-security, lab safety and reducing environmental risk, all of which are valuable. There was no discussion however of the limits of the science or outcomes risk.

Our aim became therefore to devise a first draft risk framework for decision making that would help inform the political process.

In order to devise a comprehensive set of questions with which to scrutinise new technologies, we initially looked at the Human Genome Project (HGP) website and the 'ELSIs' (ethical, legal, and social implications) that had been raised as issues with respect to that project. The U.S. Department of Energy (DOE) and the National Institutes of Health (NIH) devoted 3% to 5% of their genome research budgets towards studying the ELSI implications of their genetics research. This represents the world's largest bioethics programme and it became a model for subsequent ELSI programmes around the world. We listed all the questions that they had identified in the different sections of their site and used them to prompt a generic set of questions that could be applied to any new technology. We then cross referenced this to all other significant questions we could find that had been raised in other publications, web or printed, about the other technologies that we reviewed. Many of these are listed in our bibliography. Our aim was to ensure that the most important issues are all covered by at least one of our generic questions.

As we deliberated about each question we assigned them into one of three categories according to their emphasis: Values, Legal and Social. There was often some overlap in nomenclature but we tried to select the dominant theme. The HGP uses the word 'ethics' as their first division instead of 'value'. We chose the word 'value' for all the primarily ethical and moral questions because we felt this related more directly to the process. Every policy question is also a 'values' question so our politics therefore is a collation, with authority, of the shared values of a community. And we define our values by the desired outcomes. Those questions that had more overt legal or social ramifications were assigned according to their principal application.

Why these questions are important

As stated in Chapter 3 of Part 1, the reason that new health technologies warrant careful scrutiny is that these emerging choices are no longer focused only on the world around us, but largely on ourselves. The fundamental shift that many of the converging technologies make is that they blur the line between human beings and commodities. Many applications do not so much address therapy or restoration in the traditional sense of medicine, but possible changes, enhancement, improvement and modification of the human body. So the consequences for humanity, let alone the NHS, are potentially enormous. Without seeking to hinder scientific progress, it is surely prudent that we take time to consider all the possible implications of the new technologies.

It is also important to raise the matter of the cost implications of some new therapies which are significant (even though we did not undertake a cost-benefit analysis). Quite apart from making a particular new procedure available, the concomitant costs of education, training and facilities could be vast. We now have an economic situation in which prioritisation and value for money are even higher considerations than they once were. The potential associated social costs such as those escalated by longevity, 'maintenance' (of for example a particular type of implant) or triggered health issues such as psychological disorders[3] cannot be ignored. We are not going to repeat here all the other concerns raised in the first section, but they influenced our thinking as we debated what questions allowed us to examine new technologies most thoroughly.

We did not include the direct question of whether the technology meets an unmet health need or seeks to alleviate a condition which is a major burden on the NHS and to individuals. This is not a risk question (except in political terms if the people disagree with the choices that have been made), but one of prioritisation. Therefore it does not belong in this assessment but is an issue that needs to be considered more publicly when it comes to deciding on the allocation of funding for research.

Deliberations

The 'deliberation' filter through which we debated the risk rating was one which included the following main considerations:

A. An appraisal of their applications in healthcare.

Therapeutic interventions that could either cure or prevent disease are obviously desirable subject to adverse side effects. In some cases, such as gene therapy, although the goal to restore normal function is the noble aim, results so far have shown that it is still a very high risk experiment. Also the prevalence of single gene disorders is relatively low compared to conditions such as Alzheimers. Interventions for the latter have been shown to be relatively low risk so far but are also currently very limited in what they can achieve in terms of therapy and there is as yet nothing so far that can prevent dementia. When it comes to considering urgency of need, this is a sensitive and inevitably subjective debate, but in objective terms a condition such as Alzheimers is an urgent health and societal burden because of the prevalence and predicted rise in incidence. Prioritisation of research is not addressed in this matrix but it is one of the most important discussions that we need to have and could be factored into this analysis in the future.

Applications of synthetic biology are on the whole far off apart from the new synthetic compound to treat malaria, but the evidence is already that there is a high risk of losing control over much of the process. However righteous the intention, it remains a potential danger.

B. A consideration of the current regulatory position

Despite the copious literature on regulation, it was not always easy to discern the current position, both due to untested statute and the convergence of these technologies. The recurring themes in each technology however were the issues of privacy, trust and awareness. With respect to privacy, whether it was applying genetic testing to children who couldn't understand 'consent', the use of implants in people with dementia or issues around health insurance, there are still many grey areas. The 20th century holds many warnings of both unintended consequences and the deliberate malevolent use of state held clinical data and, in a society that is still moving towards valuing capacity over character, this is a risk that we should take seriously.

We also came across grave concerns amongst defence experts that life scientists were not aware of conventions that regulate the development of biological and chemical agents. This lack of awareness increases the risk. And we are at the stage now where transparency in research is not enough to ensure trust and safety. Science cannot have a free rein. The respected thinker and scientist Bill Joy[iv] has said we need to accept "relinquishment: to limit development of the technologies that are too dangerous, by limiting our pursuit of certain kinds of knowledge". This is a historical concept. Usually we have put limits on our own capacity, through law and public opinion. Joy cites as a precedent the US Government's unilateral decision to relinquish the development of biological (1972) and chemical (1993) weapons. Likewise, the UN Declaration on Human Cloning calls on all states to pass laws to prohibit cloning for any purpose. 'What can be done' should not define 'what should be done'.

iv Bill Joy was a founder and Chief Scientist at Sun Microsystems. He wrote an acclaimed article in 'Wired' magazine in April 2000 on 'Why the future doesn't need us' *http://www.wired.com/wired/archive/8.04/joy.html*

C. The likelihood of becoming a commercial application within 15 years

We said from the beginning of this report that we wanted to consider authentic, achievable applications. This points to the reality that scores in the matrix will change over time as technologies become more or less promising. For instance we think that there will be progress in personalised medicine, although not to the degree of many of its proponents, and that it warrants a higher risk rating because of the associated resources required to deliver and sustain it. Likewise we anticipate greater demand for the lifestyle applications of 'smart' drugs by those with no underlying pathology, and that too carries a higher risk rating because of the related demands that this could create through addiction, side-effects and overdosing. Therapeutic neuro-drugs are lower risk, partly because there is an already established therapy record, but also because they are relatively low cost. Pre-implantation genetic diagnosis (PGD) is already commercial and as technology progresses, it should become cheaper, so there is limited risk of it not becoming more feasible. Implants likewise are already used, low cost and we think will have multiple health applications by 2025.

D. The impact on our culture

The values of our culture are reflected in our political decisions. Likewise, every decision made by scientists that contributes to the development of policy is neither value-free nor neutral because, simply by taking part, scientists are demonstrating that the policy makers will be better off with whatever information they are communicating. Added to this procedural value of their involvement, they then can (and they usually and rightly do) go on and suggest substantive action and policy measures. This is both desirable and important, but the point is that in almost all circumstances, the integration of science and values is inevitable and to be encouraged. As a result, policy making can more effectively take risk into consideration.

The logical starting point for the applicable values base should be the United Nations Declaration on Human Rights (UNHR). The nations who forged this agreement 52 years ago probably never dreamed of the progress that technology would achieve and could offer us today. Nevertheless, the principles are timeless and, in the post-war world, both sensible to human fragility and appreciative of the public health gains already made in medicine, it articulates for us the global frame of reference that we colloquially refer to as the UN tradition of 'fundamental rights and freedoms'. The shared enlightenment traditions of humanitarian tolerance and universal human rights mean that, as we think about technology policy, we must take into consideration amongst other things:

- the inherent dignity and the equal and inalienable rights of all members of the human family
- that everyone has the right to life, liberty and security of person
- that all are equal before the law and are entitled without any discrimination to equal protection of the law
- and that everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including… medical care… and the right to security in the event of … sickness, disability etc.

Some will say that the last point is more an aspiration than a right. We include it here because it is part of the UNHR declaration and relates to health.

The overriding themes are those of equality of treatment, respect and freedom. They do not imply that we should aim for homogeneity, but they do convey with it the sense that our concern should be for those who are under-resourced or restricted; the poor in health or less-able. It is one of the defining statements of social justice. Therefore as we consider the vast array of possibilities before us and the impact on our culture of these decisions, we should be cautious when faced with technology that could exacerbate inequalities and be bold when offered opportunities to reduce them.

E. The potential for misuse

There is increasing recognition that progress in innovation and research in biotechnology to transform health outcomes could lead to not only off-license use of drugs to treat disease, but also to the spread of disease, harm to the environment and threats to our security. The particular concern acknowledged on all sides is that the freedom requested by scientists would make the possibility of 'dual use' technologies a more credible threat. This 'dual use' term describes the potential for research findings and techniques to be used for both constructive *and* destructive purposes.

Some scientists have issued 'statements of responsibility' which have sought to assuage our concerns through reassurances of accountability and conscientiousness. These include the Journals and Authors Group 2003 agreement to analyse submissions for publication through the lens of 'the potential harm of publication outweighing the potential societal benefit'. Added to this are the WHO's *Life Science research: Opportunities and Risks for Public Health,* the UK's BBSRC[v], MRC[vi] and Wellcome Trust's *Managing risks of misuse associated with grant funding activities,* the AMA's[vii] *Guidelines to prevent malevolent use of biomedical research* and the US NSABB[viii] *Draft criteria for dual use research of concern.* Yet in Brian Rappert's paper *'The benefits, risks and threats of biotechnology'* which lists the above risk documents, he also highlights that self-censorship is extremely rare and that it is very unusual for these groups to advise that a publication be turned down or funding refused because of dual-use concerns.[4] Therefore we have already available in print the genetic sequence of the 1918 Spanish flu virus, the artificial chemical synthesis of poliovirus and how to overcome the normal genetic resistance in mice to the deadly mousepox. We are not necessarily advocating publication censorship, but there should definitely be deeper consideration of the funding allocation in the first place for different avenues of research which takes into account the risk of misuse. If it were mandatory, not just that research trials had to be registered before being given the green light, but also which parameters were going to be assessed, this too could go a long way to embedding more confidence. While we believe that we can and should have free and open scientific enquiry, the framework for that analysis needs to acknowledge the values base, and there is a strong case for revisiting the questions that form the risk-benefit calculations if virtually no research or publications are being declined by the existing governance mechanisms.

Compiling the Risk Matrix

The matrix sets out our relative weighted risk assessment for the new technologies on a 0-5 scale.

The values on the scale indicate their relative risk. They are not to be thought of as absolute values or interval data. They represent rank orderings. That is, a risk factor of 4 is greater than a risk factor of 2 but it should not be thought of as indicating exactly twice the risk.

A higher risk score (between 3 and 5) was allocated where there was greater uncertainty, more significant consequences, additional complexity, substantial regulation required or greater potential burden on the NHS. Those of less concern were graded between 0 and 2. It is worth noting again here that this matrix did not look at the value of the technology to society in economic terms, nor its commercial feasibility overall (although we ask the question about cost-benefit analysis in the matrix, it needs in depth study). That is a task for another paper.

We then also considered the 'rank' of each question in terms of its overall importance and used these rankings to weight the risk scores. For instance the question of whether the technology would challenge what it means to be human was given the highest importance of '3' and a question on whether the technology would indicate the presence of a disease for which there is no known cure is given the lowest rating of '1'. The first matrix that shows the assigned scores is Table 1. The second matrix, Table 2, shows the combined risk score weighted by importance factors. The purpose of the risk weightings is to give a clearer indication of the relative risk scores and therefore the difference between the risk profile of different technologies, in order to highlight those raising the most concerns.

The questions that we felt were most important and given the highest weighting of '3' were the following.

1a. Does this technology threaten to change or challenge the essential nature of what it means to be human?

1b. Does this technology threaten to move people outside of the normal limitations of being human?

It's worth noting here that we at first thought these two questions were interchangeable, but when using them to interrogate different technologies we realised that there was a fundamental complexity. Achieving beyond normal human limitations wouldn't necessarily challenge the nature of our humanity, but it could create a debate about our essential nature.

v Biotechnology and Biological Sciences Research Council
vi Medical Research Council
vii American Medical Association
viii National Science Advisory Board on Biosecurity

6. Is there a potential for the loss of control of the technology?

13. Is this technology or the effects of the technology non-reversible?

14. Are confidentiality of information and privacy affected?

18. Could a patent be granted and, if so, to what extent would the grant of a patent restrict the availability or affordability of the technology to most people?

19. Will there be a need for legislation pertaining to reciprocal obligations?

23. Could there be an impact on fundamental human equality or on social justice?

26. Will the use of this technology produce abilities beyond normal human capabilities?

27. Will this science cause a permanent effect on the unborn or the next generation?

Those that were important but not in the top category are listed below.

2. Could this technology cause inequity?

3. Will there be the possibility of coercion or oppression as a result of the development of this technology?

5. Could malicious use of the technology outweigh the potential gains?

7. Will the introduction of this technology result in an increase in resources required from the NHS professionals and training?

10. Is it likely that this technology will lead to an increasing challenge to core values?

11. Does this design (for industry / health applications) blur the distinction between machines (artificial) and humans (natural)? Does it have implications for treating humans more like commodities?

12. Could this technology create new species?

15. Will it be difficult to create regulations to ensure accuracy, reliability and utility?

16. Will regulation need to be put in place to prevent information being used in a discriminatory manner?

17. To what extent is it difficult to determine who owns and controls the information, technology or tissues acquired in this process?

20. What will be the impact on the lifespan of the individual or the overall population?

21. Could this technology affect medical tourism to the UK?

22. Will there be a need for pro-active planning and specific public engagement before the introduction of this technology?

24. Might this technology result in stigmatisation or will there be a specific societal impact?

25. Might this technology reduce diversity?

28. Could this technology cause an adverse behavioural impact in either the individual or their community?

Questions that we should ask but which are of least importance on this scale and weighted 1 are just the following two.

8. To what extent would a cost-benefit analysis on this technology show low feasibility?

9. Might this technology indicate the presence of a disease for which there is no cure?

This risk scoring and risk weighting methodology was applied to the four technologies that we identified as being the most significant. Three out of the four (genetics, ICT / Implants and neuro-therapeutics) we further subdivided into different examples. In genetics this was to differentiate between the already available PGD therapy and other largely aspirational aspects of personalised medicine, including gene therapy and pharmacogenomics. With both neural implants and ICT devices and neuro-therapeutics, we wanted to distinguish between therapeutic applications and those which could enhance 'normal' human capabilities. How we set about analysing these technologies is set out in the next chapter.

Part 2
New technologies and framing the questions

Chapter 5
Specific technologies: Opportunities and risks.

Choosing the technologies to scrutinise

Having decided on the policy questions and their importance in Chapter 4, we examined 10 developing technologies. These were genetics and personalised medicine, nanotechnology, robotics and artificial intelligence, information technology and implants, synthetic biology, neuro-therapeutics, neuro-imaging, stem cells and regenerative medicine and RNA interference. Four of these significant convergent technologies we believed were sufficiently far advanced to be most worthy of immediate consideration (although we acknowledge that the science of spotting the fastest developing technology is in itself imprecise!) These are detailed in Annex 1 with the others reviewed more briefly in Annex 2. Whether they will have the greatest impact on health is hard to predict. As mentioned at the end of the last chapter, three of them were further subdivided giving a total of seven technologies to which we applied the matrix framework. In the case of each of the seven most significant convergent technologies, Annex 1 identifies the following aspects:

- how the technology is commonly defined, some examples of applications including illustrations of their use or development internationally;
- the nature of the strengths of the technology with a focus on the UK;
- the nature of the known weaknesses with the expertise and functions;
- the nature of the opportunities, particularly with respect to the UK and health improvements;
- the type of threats that this technology or its application raises, as well as highlighting some of the unfounded fears that have previously been raised.

Process of scrutiny

The analysis of each technology in Annex 1 began with the comprehensive *'2005 Delta Scan: Future of science and technology 2005-2050'* project which was undertaken by the Horizon Scanning Centre (part of Foresight in the UK) and the Institute for the Future (California). This piece of work looked at 16 fields of science all of which we examined for their relevance to healthcare. We identified 23 technologies that we considered relevant and devised up to date summaries of each and researched their status. There had been some quite significant changes over the years, demonstrating that it is a constantly shifting environment. The status summary was achieved with a review of the literature, reviews and reports undertaken by learned societies, scientific and academic institutions, charities and NGOs. We also looked at governmental committees and councils that had been set up over time to review some of the technologies and their output. We communicated too in person, by phone or on email with scientists both in the UK and USA who are specialists in the field of one or

other of these disciplines. Inevitably there were at times conflicting opinions.

Once we felt that we had a realistic view on the status of each subject, we had several meetings to discuss the stage and significance of each, and out of this process we selected four core technologies (again with three of them subdivided further) that we felt were the most advanced or were potentially most significant. A further six we felt should also be included in our appendices. We also found that a significant amount of media reporting, including specialised press, of novel research or discoveries makes vigorous claims for breakthroughs, potential cures or regeneration. The sources may be very senior but on closer inspection, the evidence base often points to something more on the scale between aspiration, exaggeration or at times pure fantasy. Of course, giving a very long time line (50 years in the case of the Delta Scan) allows all manner of prophecy. But sometimes it is the expert themselves who are the source of more immediate excited assertions. One classic case of this was the statement made in 2006 by Andrew Von Eschenbach, head of the U.S. National Cancer Institute, that thanks to advances in nanomedicine we shall "eliminate suffering and death due to cancer by 2015." Thankfully he was corrected by the eminent scientist Sir Paul Nurse. Quoted in the New Yorker magazine, British Nobel prize-winner Sir Paul Nurse's sharp criticism of these claims were that they "cannot be justified even as a statement of aspiration... because when we fail to deliver, as we surely will... we will lose the confidence of both the politicians and the public."[ix] Not only is confidence lost, but some of the exciting progress that is being made in treatments and research gets lost in the fog of inflated claims. A significant challenge for the government is determining who are the 'honest brokers' when it comes to discerning the truth about the realities of progress. All scientists want to attract further funding to their field and many have reputations to defend when it comes to previous pronouncements. Vested interests are a challenge to policy makers and bias must always be scrutinised for its evidence base.

The four core subjects were subjected to more in-depth research and each paper, including the shorter summaries in Annex 2, were commented on by relevant experts. The bibliography at the end of the document will give some idea of the publications reviewed. It was our aim through setting out our 'swot' analysis on the four core subjects to enable the reader to get a greater sense of the scope of these technologies without getting into too much complex detail. However it was important to give enough information to enable an understanding of how, from this data, we would then allocate the scoring when it came to the risk assessment. The subdivisions reflect either significantly different applications of the same converging technology, or applications of the same technology for therapy and 'enhancement' e.g. the neuro-therapeutic drug Ritalin has an application for therapy (to treat ADHD), and also allegedly for 'enhancement' (to boost memory skills in academia or the workplace).

We are in no doubt that this first attempt to quantify generic risk questions can be refined and will need to be developed further. There may be crucial points that we have omitted and there is inevitably going to be disagreement over the allocation of risk and rank numbers. However, the matrix highlights the *key issues* in a direct manner which invites debate and resolution. This approach also raises the awareness of funding issues both because the realms (and therefore costs) of what can be done are expanding, and because it highlights the difference between spending on therapy and enhancement. It seeks as well to raise awareness of decisions that have, are, and will be taken in this field and bring them into the public domain in a new, and we hope clearer way. We feel that heightened public awareness is essential. There needs to be (much) greater transparency and consistency when it comes to decision making in research not least because it is concerned with both our health and the allocation of taxpayers' money.

Significant benefits to society

In each case, we have found significant potential benefits for society. Several examples based on our research include the following:

1. Genetics was an obvious subject to include in this review. We have known about DNA for over 50 years. Phrases such as 'in your genes' have become part of modern parlance, and there's often an unquestioning acceptance that our genetic make-up has a very significant part to play in our lives. But in reality the impact of genetics in medicine has made slow progress. So although it is a term with which we are all familiar, it is still very much an emerging technology as the detail has proven even more complex than originally thought. That said, through advances in genetic testing we have been able to identify people who would benefit from particular drugs, or who would be at danger from taking a particular drug. An example of the former is a test for patients with a form of cancer called myelogenous leukemia. Those showing a positive result are known to benefit from taking a medicine called imatinib, which is an important consideration at £17,000 per year's treatment. Conversely abacavir was developed to treat HIV but in 5% of patients it was found to cause a severe, potentially fatal reaction.

ix Paul Nurse, NEW YORKER, March 13, 2006 at 69 quoted in Nanotechnology, Medicine, and the Human Condition: A Perspective from the United States, The European Group on Ethics in Science and New Technologies to the European Commission submission by Professor Nigel M. de S. Cameron, Roundtable, March 21, 2006.

A test for variations in the HLA-B gene was developed that indicated those patients who would be at risk from taking this drug. Trials are continuing for the much more widely used blood-thinning drug warfarin; pharmacogenomics has been used to predict more appropriate initial doses for people requiring low and high doses than from a clinical algorithim and new trials are under way to see if side-effects can be prevented as well.[5]

2. The benefits of cochlear implants are already well known but neural implants are increasing in their potential applications. They are being successfully used in diverse patient conditions such as chronic pain, epilepsy, incontinence, tremor from Parkinson's and more controversially, depression. More implantable devices have been developed that can monitor vital signs, and some well known devices such as pacemakers have shown that they work out cheaper than their medicinal alternatives. Outside the body, specially formed electronic suits known as exoskeletons are already commercially available in some countries, giving people with paralysed limbs the opportunity to move and walk again.

3. Patients with mental illness, dementia, epilepsy and behavioural difficulties have been able to benefit from advances in neuro-therapeutics i.e. 'brain-drugs' for some years. Donepezil HCl (Aricept) is a memory loss drug that was designed to assist people with the Alzheimer's form of dementia and Ampakines are a class of drug which, it is hoped, will also restore mental functioning in patients with dementia. Modafinil is a stimulant that was designed to help people with narcolepsy, where they suffer from excessive sleepiness during the day.

4. Synthetic biology is the newest technology that we studied, and because of its infancy there are few applications. However one treatment that was expected to be in commercial production by 2010 (but this may be postponed) is a synthetically formed Artimisinin compound which has been a crucial ingredient in malaria therapies for some years, but which is difficult to extract from its natural source.

Misplaced Public Concern

The media hype that has surrounded some of these technologies has swung between exaggerated claims for cures and frightening scenarios of outcomes. However we have frequently found that there is little cause for concern. Scaremongering is a serious issue in itself – the fraudulent MMR vaccine cause of autism claim is a testament to this – and finding a way to disseminate the truth to the public is still a challenge for government and society. We explain below four of the more high profile examples.

Firstly, 'designer babies', in terms of current technologies, are largely a myth. Genetic medicine has allowed us to pinpoint some genes that cause specific disease. These are known as single gene disorders, and there are about 6000 of them, with tests in the UK available for about 10% of these. Most of our features and traits are controlled by multiple genes as well as other known and unknown factors. Gene therapy is still experimental but through pre-implantation genetic diagnosis, (PGD) embryos which carry a single 'rogue' gene can be identified and only healthy embryos implanted via *in vitro* fertilisation. The spectre of designer babies whose parents select the traits that they want their offspring to have is – with one important exception - unfounded. This is because there is only a 1 in 4 chance that any one gene will be identified in an embryo (so you need a minimum of four embryos to have the chance of finding the one gene), so the probability of being able to select an embryo where there were say just three different genes involved would be 1 in 224 and already it is impossible to obtain that many eggs to fertilise and analyse. Added to this, IVF is a very expensive, invasive treatment. There is simply not the capacity or capital to begin to offer embryo selection on the NHS to couples who can conceive normally. Private clinics abound, but even they are limited for the above reasons, and in the UK, sex selection for social reasons is illegal, fundamentally because it is sex discrimination, but also out of practical concerns about issues of gender imbalance. There have been two exceptions in the news where the term 'designer baby' has been used by some commentators, whose excuse for the term lies in the fact that in the process of *in vitro* fertilisation certain embryos may be discarded and others implanted on the basis of the genetic identity of the embryos concerned. While this is generally for the purpose of discarding embryos carrying inherited diseases, itself a controversial subject, it can of course be done to ensure that embryos with particular traits are implanted. There has been controversy here around the desire of some deaf people to use these techniques to ensure that they have congenitally deaf children. We consider this merciless. The second is the case of so-called 'saviour siblings', where a baby can be brought into being through the IVF process with the aim of providing tissue that will cure another child in the family of an inherited disorder. The psychological impact on the 'saviour sibling' is as yet unknown. Views on both these issues vary widely, but these practices suggest that the 'design' idea is not irrelevant – even if we are far from having technology that could build in desired traits.

Second, genetic testing. There have also been concerns about the personal information that genetic testing would reveal, and the consequential impact on life opportunities and issues of privacy. It was thought that genetics would allow us to predict, with certainty, risk factors for particular conditions such as heart disease, diabetes and cancer. Worries were expressed about the effect of such predictions on health and life insurance, job prospects and training, mental health and education. However genetic testing has not yet delivered the anticipated ability to predict the vast majority of common diseases. The House of Lords science and technology sub-committee July 2009 report *'Genomic*

Medicine' recommends that in the future NICE's remit should extend to a programme for evaluating tests. This would be valuable, but we must not lose sight of the fact that research is revealing increasing complexity of causality (including the role of interaction of just simple bacteria)[6] and genetic tests should not be given inappropriate authority.

Third, artificial intelligence. For years there has been a lot of speculation about artificial intelligence and computers 'taking over' from humans. In reality there has been little progress for some decades in the creation of 'thinking computers' but this has often been confused with the speed of processing, which, in accordance with Moore's law, doubles in rapidity every 18 months. The world's largest computer – IBM's Blue Gene – can now simulate a network of 22 million neurones connected to the web of half a billion links, but several hours of this computer activity corresponds to one second's worth of brain activity! We are still a long way from 'uploading' people's minds or even understanding how the human brain really works.

Artificial life had had a lesser amount of press until this year when Craig Venter declared that he had created a synthetic bacterial genome. As it was a copy (albeit a very impressive one) of a pre-existing genome and utilised a live 'host' bacterial cell, we consider this an impressive synthetic recreation but not artificial life. Artificial life has been the goal of many biologists and engineers, as time has progressed we have found that we are more intricate with greater complexity of interactions than we previously realised. It's worth remembering that a single cell is made up of about 100 billion atoms, some of which constitute the (on average) 100 million proteins of 20,000 different types. It would take about 200 of those cells to form the dot on the letter i. Some scientists, however, were following the approach of trying to work out the minimum requirements to produce a free-living organism. The research is revolving around identifying the smallest set of genes that allows for replication of an organism in a particular environment.

Fourth, internal IT implants. These implants have become familiar to us through the use of the pacemakers and cochlear implants. As artificial components that allow us to regain or replace former functions they have rejuvenated the lives of many, but have not turned us into 'bionic' man or human-robotic hybrids like the Borg out of Star Trek! The cost-benefits to health, independence and activity have been very positive. As materials develop and remote monitoring becomes possible, both the potential personal and societal benefits and applications will increase.

Appropriate public concerns

In some cases, however, we believe there are real grounds for concern. This is where the questions we identified in Chapter 4 became helpful. We set out these questions in a matrix, along with examples of the seven converging technologies. In the matrix we rank the level of concern caused by each specific convergent technology in relation to each specific criteria. Crucial to this allocation is consideration of whether there is, for the purposes of this paper, a realistic concern within the next 15 years or so.

As the matrix shows, we have identified four specific technologies with high and important risks. These are:

1. the use of IT implants including brain computer interface (BCI) or brain machine interface (BMI) and external IT devices to enhance human capacities;
2. the use of neuro-therapeutics (smart brain drugs) for lifestyle purposes;
3. the use of synthetic biology to create artificial life;
4. genetic prediction.

The principal issues arising from these four technologies are described below.

Case Study 1

The use of IT implants including brain computer interface (BCI) or brain machine interface (BMI) and external IT devices for therapy and to enhance human capacities.

Description

Implants are man-made tools that are inserted into the body, for example for drug delivery, communication or control purposes. Neural implants are IT devices that connect directly to the nervous system for a variety of medical and non-medical purposes. Emerging applications include the insertion of 'brain pacemakers' to manage brain dysfunctions (such as tremors) or control artificial limbs.

There is also a rising number of IT devices that can be connected to the outside of the body to read the electrical signals from the brain or nervous system.

In April 2009 the first 'twitter' message was posted that had used thought control alone, and in 2008 a 'voiceless' phone (Ambient Corporation) went on sale that could determine what you wanted to say by a neck band that picked up on nerve signals being sent from the brain to the vocal cords. BrainGate (Brown University, USA) was the precursor of these achievements and consists of a surgically implanted sensor that records the activity of dozens of brain cells simultaneously. The system also decodes these signals in real time to control a computer or other external device. Initial trials enabled a paralysed man to operate lights and his computer and open emails

just by thinking.[7] The longer term aim is to allow control of prosthetic limbs or even real limbs through a muscle stimulator system.

It should be emphasised that these devices are not reading thoughts. They are reading the electrical activity of neural signals in the brain from the surface of the cortex and are calibrated during particular motor movements. This is the method behind the Emotiv thought controlled computer game using the EPOC neuro-headset released in 2009 that detects electrical signals from the brain, based on electro-encephalograph (EEG) technology which has been refined and licensed from biosensor company NeuroSky. It is calibrated by the player who first thinks about the moves e.g. move left, move right, move up and move down. The device records these signals and the player can then move elements around in the game.

Using a similar device, this year Honda demonstrated that its advance humanoid walking robots could be controlled directly by electrical signals in the brain of the controller.

These technologies – both BCI and implantable medical devices (IMDs) - can be used for important therapeutic purposes. For example:

- **cardiac resynchronisation therapy (CRT)** involves implanting a pacemaker in the patient's chest in order to improve the efficiency of the heart rhythm, or a device, for example an implantable cardiac defibrillator (ICD), to shock the heart out of a rhythm incompatible with life. These are currently available in the UK and are provided by the NHS.[8] Costs seem to be up to £10,000 per quality adjusted life years ('QALY'), and about 70% of the eligible population have them, though this is one of the lowest figures in Europe;

- **encapsulated cell technology (ECT)**[9] are non-neural implants made of 6mm semi-permeable hollow-fibre membranes containing modified cells that produce a biological agent to treat inner eye disease; and

- **cochlear implants** are used to restore hearing to those who are deaf or severely hard of hearing. Unlike hearing aids they do not amplify sound, but pick up sounds using a microphone and then send an electrical signal to functioning auditory nerves. NICE is currently reviewing the use of cochlear implants, but patients can get them if their local Primary Care Trust (PCT) agrees funding. Due to the large cost of the procedure, many areas have waiting lists.

Other important therapeutic uses of this technology for (e.g.) pain management and tremor control are described in Annex 1.

Example of therapeutic use

Deep Brain Stimulation – Matrix column D

We have found that the risks from some implant technologies, even when applied to therapeutic uses, are increasing in breadth and impact. One example is deep brain stimulation.

Definition

Deep brain stimulation (DBS) is an example of brain-computer interface technology in which an electrode is implanted to alter neuronal activity in the thalamus or basal ganglia.[10] Although the exact mechanism of action is not fully understood this technology can be used to treat tremor in those with or without Parkinson's (up to 10% of patients are thought to be suitable). This therapy has been approved by NICE (the National Institute of Clinical Excellence) although at a cost of up to £30,000, it is not routinely available across England. It is being trialled as a treatment for depression.

As with all neural surgery, DBS entails several anticipated risks. As well as the usual risks of general anaesthesia, there are the surgical risks of haemorrhage and infection. Visual defects, speech problems, and other complications can be caused by faulty positioning or inappropriate stimulation settings. Because a device is left implanted in the body, there is the risk of malfunction or a reaction to it such as scar tissue build-up as the body reacts to the 'invasion'. All of these are normal therapeutic risks.

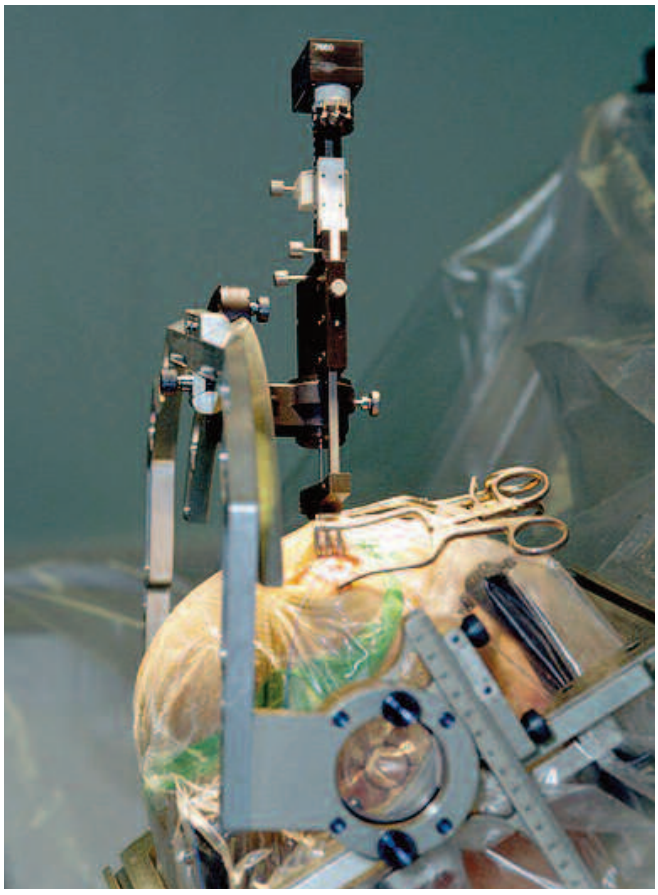

Fig 3: Insertion of an electrode during deep brain stimulation for Parkinson's disease.

However other less obvious risks come into view once this therapy is interrogated through the medium of our matrix questions. A study in 2007 of bilateral hypothalamic DBS used to treat a patient with morbid obesity showed, quite unexpectedly, that stimulation evoked detailed autobiographical memories.[11] This memory improvement was not outside normally expected levels – so there is no credible assertion yet that this could be an 'enhancement' – but it was an unexpected side effect. Memory augmentation is a subject of research interest and we consider that it could raise a series of important questions of inequity in the next 10-15 years.

Given that 'Brain Computer Interface' technology is an area of major research interest and development and is already stimulating the computer-gaming industry, major issues also arise about control – not just of the device but also of the person in whom it is implanted. Neurosecurity has been defined as: "the protection of the confidentiality, integrity, and availability of neural devices from malicious parties with the goal of preserving the safety of a person's neural mechanisms, neural computation, and free will".[12] Neurosecurity is a discipline that has grown because of the awareness that within the next 15 years, implants will be deployed that will require security and privacy settings that protect the user from hackers and the risks of oppression. It was demonstrated by a US team in 2008 that it was already possible to hack into a pacemaker.[13]
Opinion was divided at this stage as to whether any manipulative application of DBS should prevent or outweigh its therapeutic use. However we agreed that it will be very important that the development of internal IT devices has security and privacy at the centre of utility and safety design; and current self-monitoring by academics needs to be reviewed. Responsibility in publication, such as that shown by the research team behind the ICD hacking who didn't publish the details of their methodology, should be the norm. Nor should we be naive about the possible dangers of using DBS devices to cause behavioural changes. This has already been shown to be possible.[14,15,16]

In terms of NHS resources, we rate this technology as quite high risk. The implant devices themselves are expensive and the expansion of applications and monitoring could be very costly. Neuroscientists such as Kevin Warwick at Reading University have also voiced concerns about the potential for neurological 're-wiring' due to the presence of the implant. The complexity of the brain and how little of it we can examine at a microscopic level should not be forgotten – one trillion neurones each with 10,000 synapses giving 10 quadrillion connections – it would currently take 190 million days to electron-scan one brain's worth of neurological tissue.

Example of 'enhancement' use

Artificial exoskeleton – Matrix column E

In the time frame we have set, we don't think that there is the realistic possibility of seeing neural IT Implants leading to any kind of 'enhancement'. Even the triggering of autobiographical memory is within the normal range, and we don't know of any experimentation involving intentional 'enhancement' via DBS. But by contrast there is reason to suppose that exoskeletons and external IT devices to enhance individual capacities may soon be available for 'enhancement' of human capabilities.

Definition

An exoskeleton is an externally worn device that is used to increase the body's capabilities. Powered exoskeletons have been used for years in industrial, medical and more recently defence settings, but will probably be increasingly used to develop devices that interact with the human body in the home. Prototypes for people with disabilities (just the 'leg' versions) began to be available domestically from 2008. Argo Medical technologies in Israel hoped to have a complete body suit commercially available by 2010 at a cost of about £10,000.[17] The therapeutic use for such suits e.g. Cyberdyne HAL exoskeleton, is to enable the elderly and disabled to walk by reading neural signals travelling to the legs and moving the legs of the suit in real time.

There is no doubt that this technology allows people to perform beyond normal human limits. Exoskeletons have been developed to enable soldiers to walk for longer and in industry they have been used to allow people to lift heavier loads. We rate this as a moderate risk because of the impact such enhancement could have on equality and social justice. We are also concerned about the risks of the individual losing control and hence of malicious applications. These risks are intensified by the fact that prices are likely to drop over time, possibly creating a significant demand for commercial products which would be difficult to regulate. There will be no way of determining who wants to use a 'strong arm' for leisure purposes and who wants it to wield power over others. Exoskeletons could be the new car or they could be the new gun, and the regulations and control issues could be very similar.

We acknowledge that as exoskeletons are an external technology, they do not carry the risk of irreversible changes. They are highly visible and the physical enhancement carries with it no surgical or neurological dangers. But we feel that the overall risk, as indicated by the scoring in the matrix, outweighs the advantages of enhancement in the domestic setting: any gains from super-strength are outweighed by the risks that unregulated development and use of this enhancement poses.

Case Study 2

The use of neuro-therapeutics (smart drugs, mental 'viagra') for lifestyle purposes

Description

Drugs that work on cognition to alter memory, learning, attention, emotions and other aspects of cognition[18] are variously known as neuro-therapeutics, neuro-cogniceuticals, psychoactives or cogniceuticals. These drugs can be used for treating neurological conditions ranging from the severe (e.g., Alzheimer's disease) to the mild (e.g., fatigue),[19] and the border between medicines used to treat ill-health and lifestyle 'enhancement' is hazy.

Examples of therapeutic applications of psychoactive drugs in conditions that affect the central nervous system, include use to treat:

- **Alzheimer's disease** - the most common form of dementia, accounting for up to 70% of all cases and has an incidence of up to 20% in the over 80's. The first symptoms are impaired memory, then impaired thought and finally complete dependency. The average duration of the disease is 8 years between onset and death.[20] The main treatments in the UK are cholinesterase inhibitors such as Aricept or Exelon which stop the breakdown of acetylcholine (a messenger chemical) in the brain;

- **mental illness** - exhibiting as some level of abnormal behaviour or inability to cope, affecting up to 1 in 4 of the population at some point in their lives with 50% of episodes beginning in children under the age of 14 years.[21] A wide range of neuro-therapeutic agents (usually described as anti-depressants) are currently available which seem to stimulate transmitter chemicals in the brain and have a success rate of up to 65%;

- **narcolepsy** - a sleep disorder characterized by sudden and uncontrollable episodes of deep sleep. Amphetamines were once used as wake-promoting agents but they had significant side-effects; they have now been replaced by non-amphetamine neuro-therapuetic stimulants such as modafinil, (e.g. Provigil).

When taken for lifestyle purposes, these drugs are called 'smart drugs' or 'mental viagra' or 'cosmetic neurology'. These include drugs which boost performance in otherwise healthy brains or address non-medical conditions.

Medications originally designed for a particular therapeutic purpose are increasingly being used off-license and off-prescription in normal people to boost performance. For example, Ritalin - the same drug prescribed in children since the 1980s for attention deficit hyperactivity disorder (ADHD) - has been taken for memory enhancement among students in the USA and UK. Peter D Kramer dubbed the concept 'cosmetic pharmacology' in his 1993 book 'Listening to Prozac', in which he raised the policy issues for and against the increased use of drugs by people who aren't ill.

Example of 'enhancement' use

Methyphenidate e.g. Ritalin, as a lifestyle drug – Matrix column G

Ritalin was first noted as being used by adults, off-prescription, in the 1970s. It's unclear when it was first used as an agent for 'enhancement' of performance in students. In the UK, Ritalin is a class B drug which can be prescribed only under the supervision of a specialist in childhood behavioural disorders. In the USA, the Drug Enforcement Administration classify it as a schedule II drug, in the same category as cocaine: taking it after the age of 12 disqualifies you from serving in the military.

When Ritalin is used off-licence (i.e., for a purpose or age-group not specified in the original licence) by people without ADHD it has a stimulant effect, resulting in suppressed appetite, increased concentration, wakefulness and euphoria. Regular use can result in both addiction and "tolerance" (requiring higher doses to produce the desired effect). Adverse side effects can include *"convulsions, anxiety, paranoia, head-aches, malnutrition due to decreased appetite, and irregular heartbeat and breathing, which may be life-threatening."*[22]

The unrestricted use of Ritalin and other lifestyle or 'smart' drugs to 'enhance' performance creates four significant risks:

1. the damaging side-effects mentioned above, which alone are sufficient to warrant retaining strict controls over the use of this drug;

2. the potential impact to the economy of treatment and support remembering that already the cost to the economy of job loss and inability to work from alcohol abuse is documented at £2.3bn;[23]

3. the issues that arise from fairness if some 'runners in the race of life' choose to put themselves at risk by using an external agent to improve their performance (just like athletes using drugs) while others choose not to do so;

4. connected with (3) above, the serious risk that individuals will come under coercive or competitive pressure to improve their performance (and put themselves at risk) by taking substances of this sort.

We must never forget where pursuit of perfection has led us before, and the resulting inhuman behaviours. Michael J. Sandel calls the overall threat the 'drive to mastery'.[24]

We conclude that these drugs should remain strictly controlled. The contrast with the drugs of the 1960s is an interesting one: then it was about escape and leisure. Today, although some reduce inhibitions, these drugs are largely about competition, compliance and work.

Case Study 3

The use of synthetic biology to create artificial life

Description

Synthetic biology (synbio) is the design and construction of new biological systems not found in nature. It aims at creating novel organisms for practical purposes but also at gaining insights into living systems by re-constructing them.

Synbio has already produced an artificial therapy for the treatment of malaria, and the underlying science is progressing rapidly. Artificially replicated viruses such as polio have already been recreated; and the risk to public health and the environment of novel, engineered, synthetic toxic bacteria or viruses is real.

Advocates see no limits to this technology and talk not only about creating new, artificial life but also of being able to design the next generation of human beings. This is however at an extremely early stage. Synthetic biology may well produce new artificial life forms but not within our 15 year timescale. (See page 91 for a more detailed explanation of why we don't consider the replication of a bacterium as artificial life.)

Analysing Synthetic Biology as a concept

Matrix column C

Applying the questions from our matrix within a 15 year time frame, we do not see a risk to our humanity or to equity arising from synthetic biology. And in the meantime if more artificial compounds are synthesized, we would expect to see a reduction in cost over time of medicines with a positive medium term impact on the NHS.

However the cost of a potential public health crisis in the face of 'bio-error' could be unprecedented. There is at least a medium risk arising from the unintended consequences of an artificial agent being released into the environment. Intended, malicious use of this technology poses far greater dangers: we rank synbio as high risk for possible malicious application and loss of control (including irreversibility), even before 2025.

There are three big issues: the creation of new viruses to which we have no immunity; the difficulty in controlling this technology; and its irreversibility. Biological weapons experts are concerned that 'life scientists' do not realise the significance, or even the existence, of current treaties that limit biological experimentation in order to ensure our safety. We need to ensure that relevant aspects of synbio are brought firmly within the scope of those treaties and within the corresponding national controls.

In short, although synthetic biology is not yet sufficiently advanced to cause a major threat to society, the GM crop debacle could look in the medium term like a picnic in comparison if this technology is not handled with the highest level of precaution.

Case Study 4

Genetic Prediction

Description

Genetic testing can be used for a wide variety of purposes, including diagnosis and/or carrier testing for genetic disorders; pre-symptomatic testing for late-onset genetic disorders or pre-disposition testing for familial cancers; genetic susceptibility testing for risk of common diseases or behaviours; ancestry and paternity testing; and prediction of the safety and efficacy of medicines.

We have included genetic prediction as a case study as we are aware that there is a huge amount of interest in it. The public already have easy access to genetic tests both run by labs and over the counter ("direct to consumer" (DTC) kits). With respect to these kits in particular, we do not believe that the risks have been adequately set out.

Direct to consumer kits were the subject of a Human Genetics Commission consultation which developed "principles" that manufacturers should adhere to on a voluntary basis, with no system for monitoring put in place. However the premise of the consultation was that it sought to facilitate the marketing of DTC kits, rather than asking what are the genetic tests which are actually valid and which should be available to the consumer. Companies are under no obligation to ensure that minimum criteria are being met before being allowed to market their kits. So we have taken the situation as it now is and applied the questions from our matrix to highlight the risks of these genetic prediction tests.

Example – Predictive, over-the-counter genetic testing

Matrix Column B

Our concerns about the negative impact of DTC predictive genetic tests arise from:

1. the high risk of misinterpretation of the results;

2. the still small evidence base for valid gene associations. This is because the tests are only as good as their accuracy, which is dependent on analytic validity (has the right sequence been identified?), clinical validity (whether the gene is really associated with the claimed disease and how predictive it is of that disease?) and clinical utility (whether the testing is useful to improve health outcomes?); and

3. the issues around privacy and confidentiality.

1. Misinterpretation

An example cited recently in the New Scientist[25] shows how difficult it is to interpret the statistics:

"Picture yourself, for example, in the doctor's surgery. You have just tested positive for a terminal disease that afflicts 1 in 10,000. The test has an accuracy of 99 per cent. What's the probability that you actually have the disease?

It is in fact less than 1 per cent. The reason is the sheer rarity of the disease, which means that even with a 99 per cent accurate test, false positives will far outweigh the real ones. That's why it is so important to carry out further tests to narrow down the odds."

"99% accuracy" in the jargon of the profession does not mean what any lay person thinks it will mean (i.e. that you have a 99% chance of being told the truth by the test). What it means is that one person in every 100 tested is a false positive i.e. someone that tests positive but doesn't actually have the disease.

As a result if you happen to be tested and found positive, the so called "99% accuracy" tells you only that there are not likely to be any other false positive results in a group of 100 testers. It does not imply that you have a 99% likelihood of having the disease. Indeed, if 1 million people are tested, we would expect 100 of them (from an incidence of 1 in 10,000) to have the disease and 10,000 (1%) to be false positives. So it is 100 times more likely that you will be a false positive than that you will actually have the disease. In short, in ordinary language, the test is 99% inaccurate!

2. Valid gene associations

In addition there are many tests available for conditions for which there is no cure, and even apparently simple one-gene diseases can have many mutations, some of which cause varying degrees of severity or no symptoms at all. What is the point of promoting tests for diseases which cannot be cured? The uncertainty and lack of understanding created by tests which talk about accuracy, probability and penetrance (the number of people who develop the disease when they have the gene) is already leading to unnecessary demand on NHS services and some people may be left with anxiety for no good reason, either because they won't develop the disease or because there is no cure for it anyway.

There is particular concern among geneticists about proposals to market tests which are poorly predictive of serious psychiatric conditions such as schizophrenia. There is also the possibility of undermining public health by confusing people about the need to eat healthily or quit smoking regardless of what genes they have.

3. Privacy and confidentiality

For adults there are the potential issues on work, insurance, life assurance etc., which is of all the greater concern as test results can be so inaccurate and misleading. If this is not addressed and the drive to patient-held electronic records becomes a reality, there is a real danger of considerable confusion and error over the recording of findings that try to quantify risk. Likewise, if significant numbers of genetic profiles were stored in the NHS in a manner which created a searchable database, this would lead to concerns about potential access by other government and non-government agencies. This contrasts with the UK Biobank which stores DNA samples anonymously. On the issues of DTC genetic test kits the recent House of Lord's Genomic Medicine report did not recommend any compulsory changes to protect the public. This is baffling as the same report states that the insurance industry considers these tests currently so vague as to be irrelevant (which is good news, so the public should not be mislead).

Public engagement has already been undertaken by the Royal Society and Science Horizon's projects and one of the recommendations was for proper regulation of genetic testing, which is not being delivered by the current HGC consultation. We consider that there should be much higher profile engagement and publicity and that the government should show leadership on the need for quality information and public protection.

Part 2
New technologies and framing the questions

Chapter 6
Conclusion

"Perhaps it is always hard to see the bigger impact while you are in the vortex of a change. Failing to understand the consequences of our inventions while we are in the rapture of discovery and innovation seems to be a common fault of scientists and technologists."

Bill Joy, 'Why the future doesn't need us'. Wired, 8.04

The four case studies we have highlighted – IT implants, neuro-therapeutics, synthetic biology and commercial genetic testing – indicate clearly that large and troubling issues (as well as possible major therapeutic advances) arise from these emerging technologies; but there has been little public focus on the advances, the risks or the measures that might be taken to control the risks. This is part of a general pattern. The 2007 Science Horizons report is one of several that have highlighted the fact that there is still far too little public engagement in science and scientific decision making. Lack of engagement with the public results inevitably in loss of trust, lack of awareness, ignorance of progress, anxieties about privacy and concern over the possible 'dual use' of technologies that are capable of use for evil as well as for desirable purposes. Public ignorance can and often does result in resistance at grassroots level to valuable scientific progress, as well as an undesirable and dangerous absence of public scrutiny. We believe that a more public debate is overdue.

There is already the 'European Group on Ethics in Science and New Technologies to the European Commission' (EGE) formed in 2003 which produces excellent and substantial opinion papers on new technologies and which makes them available to all via their website. Not infrequently these papers remind us that no development is inevitable. We highlight in this paper that one of the fundamental shifts that these technologies create is that many of them raise value questions about human character versus human capacity. But the UK does not have a strategic council which performs as an overarching body that can ponder the implications, opportunities and threats of new emerging technologies and research avenues in the UK. The current 'Council for Science and Technology' has an esteemed membership which advises on taking science and innovation forward, but not on risk, values and policy. We think there is a case for a forum which focuses on future technology and what Baroness Greenfield calls the 'why' question: Why are we undertaking this research? Why are we developing this technology? At the same time, it would be naïve to conclude that the establishment of any single new body would solve the problem. With the advancement of these new technologies, many existing public bodies will need to engage with the policy implications with greater enthusiasm.

This report has sought to introduce the subject of emerging technologies, in particular in relation to healthcare. We wanted to work towards a framework to help us both question and understand the opportunities and risks that are opening up to society. Because these are technologies which are converging and overlapping and because there are significant sociological and anthropological implications, they are relevant to us all. We have demonstrated that there are rapid advances in many fields and have described scenarios that reveal just how crucial it is that we spend more time considering what is desirable and what is permissible. The topics of

efficacy, priority and affordability need much scrutiny as well as the overarching framework within which they should be considered. Should we not be focusing on improving the norm for health across our nation and the ability of everyone to reach it before allocating time and funding to enhancements and improvements for the privileged minority?

We believe that the crucial distinction is between new technology that is used to cure or prevent disease and new technology that is used to 'enhance' individual human capacities. We cannot afford to be luddites automatically rejecting technologies despite the possibility that they may offer the prospect of preventing or curing debilitating illnesses with a focus on the common good. But this should not lead us unthinkingly to accept the case for 'enhancement'. 'Enhancement' can be taken to imply many things, all the way from enabling us to remedy disease and disability problems (e.g. spectacles) to giving us superhuman powers of strength or memory. In the latter sense it raises fundamental problems for equity, justice, and the freedom of the individual. For the former, there are huge challenges ahead in simply meeting existing health needs. Spending public money on research to facilitate enhancement i.e. to make individuals 'better than well' would be in our view, an immoral diversion of precious NHS and medical research resources. We also reject the idea that 'enhancement' is an inevitable or a necessary or desirable evolutionary step.

We fear that the unconsidered use of emerging technologies to 'enhance' the individual may threaten social justice and social cohesion, and may also threaten the special status of human beings, leading to the idea that the individual is a machine which can simply be improved like a car, aeroplane or computer by external physical interventions. The long term effects on our culture, our society and our politics if that idea were to be widely accepted would be very serious.

We hope that our report will increase the awareness of decisions that need to be made in a rational and balanced way so that our society neither ignores the benefits of these powerful new technologies nor pretends that they are without risk.

Part 2
New technologies and framing the questions

Chapter 7
Risk matrix 1

Questions	Risk analysis at January 2010 Values
1a	Does this technology threaten to change or challenge the essential nature of what it means to be human?
1b	Does this technology threaten to move people outside of the normal limitations of being a human?
2	Could this technology cause inequity?
3	Will there be the possibility of coercion or oppression as a result of the development of this technology?
4	Does the possibility of dual use of this technology raise questions about the potential benefits?
5	Could malicious use of the technology outweigh the potential gains?
6	Is there a potential for the loss of control of the technology?
7	Will the introduction of this technology result in an increase in resources required from the NHS professionals and training?
8	To what extent would a cost-benefit analysis on this technology show low feasibility?
9	Might this technology indicate the presence of a disease for which there is no cure?
10	Is it likely that this technology will lead to an increasing challenge to core values?
11	Does this design [for industry / health applications] blur the distinction between machines [artificial] and humans [natural]? Does it have implications for treating humans more like commodities?

Key

Technologies

0	none or not applicable
1	unlikely/low
2	maybe/low
3	maybe / medium
4	yes / moderately high
5	definitely / high
?	too early to say or no concensus reached

	Genetics		C: Synthetic Biology	Neural Implants & ICT devices		Neuro-therapeutics	
	A: Gene Therapy	B: Over The Counter (OTC) / Direct to Consumer		D: Therapy e.g. Deep Brain Stimulation	E: Exoskeleton Enhancement	F: Therapy	G: Enhancement e.g. Ritalin
	1	1	1	0	2	0	4
	0	0	?	3	4	?	0
	2	3	1	0	5	1	4
	5	4	4	3	3	1	4
	1	3	4	1	3	1	2
	2	3	5	2	3	1	2
	1	4	5	3	3	1	3
	3	5	5	4	3	3	5
	0	2	1	0	2	2	0
	4	5	0	0	0	0	0
	1	4	5	1	4	1	5
	1	0	5	0	3	0	0

continued overleaf

Part 2
New technologies and framing the questions

Chapter 7
Risk matrix 1

Questions	Risk analysis at January 2010 Values
12	Could this technology create new species?
13	Is this technology or the effects of the technology non-reversible?
	Sub-TOTAL
	Legal
14	Are confidentiality of information and privacy affected?
15	Will it be difficult to create regulations to ensure accuracy, reliability and utility?
16	Will regulation need to be put in place to prevent information being used in a discriminatory manner?
17	To what extent is it difficult to determine who owns and controls the information, technology or tissues acquired in this process?
18	Could a patent be granted and, if so, to what extent would the grant of a patent restrict the availability or affordability of the technology to most people?
19	Will there be a need for legislation pertaining to reciprocal obligations?
	Sub-TOTAL
	Social
20	To what extent will there be an impact on the lifespan of the individual or the overall population?
21	Will this technology affect medical tourism to the UK?

	Genetics		C: Synthetic Biology	Neural Implants & ICT devices		Neuro-therapeutics	
	A; Gene Therapy	B: Over The Counter (OTC) / Direct to Consumer		D: Therapy e.g. Deep Brain Stimulation	E: Exoskeleton Enhancement	F: Therapy	G: Enhancement e.g. Ritalin
	1	0	5	0	0	0	0
	5	3	5	2	1	0	2
	27	37	46	19	36	11	31
	3	5	0	3	2	1	3
	1	4	5	2	5	2	4
	5	5	0	3	3	3	4
	1	3	1	3	4	0	1
	4	4	4	0	3	3	2
	1	1	5	1	4	1	1
	15	22	15	12	21	10	15
	3	3	2	1	2	2	3
	2	0	1	2	2	2	1

continued overleaf

Part 2
New technologies and framing the questions

Chapter 7
Risk matrix 1

Questions	Risk analysis at January 2010 Social
22	Will there be a need for pro-active planning and specific public engagement before the introduction of this technology?
23	Could there be an impact on fundamental human equality or on social justice?
24	Might this technology result in stigmatisation or will there be a specific societal impact?
25	Might this technology reduce diversity?
26	Will the use of this technology will produce abilities beyond normal human capabilities?
27	Will this science cause a permanent effect on the unborn or the next generation?
28	Could this technology cause an adverse behavioural impact in either the individual or their community?
	Sub-TOTAL
	Totals

	Genetics		C: Synthetic Biology	Neural Implants & ICT devices		Neuro-therapeutics	
	A: Gene Therapy	B: Over The Counter (OTC) / Direct to Consumer		D: Therapy e.g. Deep Brain Stimulation	E: Exoskeleton Enhancement	F: Therapy	G: Enhancement e.g. Ritalin
	1	5	5	0	5	2	5
	3	5	1	3	5	1	5
	4	3	2	1	3	1	5
	5	2	0	0	1	2	0
	0	0	2	1	5	1	2
	5	0	2	0	0	0	1
	1	3	5	2	4	0	5
	24	21	25	8	27	11	27
	66	80	86	39	84	32	73

Part 2
New technologies and framing the questions

Chapter 7
Risk matrix 2

Questions	Importance	Risk weighted by importance at January 2010 Values
1a	3	Does this technology threaten to change or challenge the essential nature of what it means to be human?
1b	3	Does this technology threaten to move people outside of the normal limitations of being a human?
2	2	Could this technology cause inequity?
3	2	Will there be the possibility of coercion or oppression as a result of the development of this technology?
4	3	Does the possibility of dual use of this technology raise questions about the potential benefits?
5	2	Could malicious use of the technology outweigh the potential gains?
6	3	Is there a potential for the loss of control of the technology?
7	2	Will the intro of this technology result in an increase in resources required from the NHS professionals and training?
8	1	To what extent would a cost-benefit analysis on this technology show low feasibility?
9	1	Might this technology indicate the presence of a disease for which there is no cure?
10	2	Is it likely that this technology will lead to an increasing challenge to core values?
11	2	Does this design [for industry / health applications] blur the distinction between machines [artificial] and humans [natural]? Does it have implications for treating humans more like commodities?

Key

Importance
1 Low
2 Medium
3 High

Technologies
0 no or not applicable
1 unlikely/low
2 maybe/low
3 maybe / medium
4 yes / moderately high
5 definitely / high
? too early to say or no concensus reached

	Genetics		C: Synthetic Biology	Neural Implants & ICT devices		Neuro-therapeutics	
	A: Gene Therapy	B: Over The Counter (OTC) / Direct to Consumer		D: Therapy e.g. Deep Brain Stimulation	E: Exoskeleton Enhancement	F: Therapy	G: Enhancement e.g. Ritalin
	3	3	3	0	6	0	12
	0	0	?	9	12	?	0
	6	9	3	0	15	3	12
	15	12	12	9	9	3	12
	3	9	12	3	9	3	6
	6	9	15	6	9	3	6
	3	12	15	9	9	3	9
	9	15	15	12	9	9	15
	0	6	3	0	6	6	0
	12	15	0	0	0	0	0
	3	12	15	6	12	3	15
	3	0	15	0	9	0	0

continued overleaf

Part 2
New technologies and framing the questions

Chapter 7
Risk matrix 2

Questions	Importance	Risk weighted by importance at January 2010 Values
12	2	Could this technology create new species?
13	3	Is this technology or the effects of the technology non-reversible?
		Sub-Total
		Legal
14	3	Are confidentiality of information and privacy affected?
15	2	Will it be difficult to create regulations to ensure accuracy, reliability and utility?
16	2	Will Regulation need to be put in place to prevent information being used in a discriminatory manner?
17	2	To what extent is it difficult to determine who owns and controls the information, technology or tissues acquired in this process?
18	3	'Could a patent be granted and, if so, to what extent would the grant of a patent restrict the availability or affordability of the technology to most people?'
19	3	Will there be a need for legislation pertaining to reciprocal obligations?
		Sub-Total
		Social
20	2	To what extent will there be an impact on the lifespan of the individual or the overall population?
21	2	This technology will affect medical tourism to the UK

	Genetics		C: Synthetic Biology	Neural Implants & ICT devices		Neuro-therapeutics	
	A: Gene Therapy	B: Over The Counter (OTC) / Direct to Consumer		D: Therapy e.g. Deep Brain Stimulation	E: Exoskeleton Enhancement	F: Therapy	G: Enhancement e.g. Ritalin
	3	0	15	0	0	0	0
	15	9	15	6	3	0	6
	81	111	138	60	108	33	93
	9	15	0	9	6	3	9
	3	12	15	6	15	6	12
	15	15	0	9	9	9	12
	3	9	3	9	12	0	3
	12	12	12	0	9	9	6
	3	3	15	3	12	3	3
	45	66	45	36	63	30	45
	9	9	6	3	6	6	3
	6	0	3	6	6	6	3

continued overleaf

Part 2
New technologies and framing the questions

Chapter 7
Risk matrix 2

Questions	Importance	Risk weighted by importance at January 2010 Social
22	2	Will there be a need for pro-active planning and specific public engagement before the introduction of this technology?
23	3	Could there be an impact on fundamental human equality or on social justice?
24	2	Might this technology result in stigmatisation or will there be a specific societal impact?
25	2	Might this technology reduce diversity?
26	3	Will the use of this technology will produce abilities beyond normal human capabilities?
27	3	Will this science cause a permanent effect on the unborn or the next generation?
28	2	Could this technology cause an adverse behavioural impact in either the individual or their community?
		Sub-Total
		Totals

	Genetics		C: Synthetic Biology	Neural Implants & ICT devices		Neuro-therapeutics	
	A: Gene Therapy	B: Over The Counter (OTC) / Direct to Consumer		D: Therapy e.g. Deep Brain Stimulation	E: Exoskeleton Enhancement	F: Therapy	G: Enhancement e.g. Ritalin
	3	15	15	0	15	6	15
	9	15	3	9	15	3	15
	12	9	6	3	9	3	15
	15	9	0	0	3	6	0
	0	0	6	9	15	3	6
	15	0	6	0	0	0	3
	1	3	5	3	4	0	5
	70	57	25	33	73	33	71
	196	234	208	129	244	96	209

Part 3
New technologies under the microscope

Appendix 1
The four most significant converging technologies

1. Genetics & Designer Babies

Definitions and Description

A Gene is a section of DNA that is responsible for a particular physical and inheritable characteristic (or phenotype) of an organism. It also specifies the structure of an RNA molecule which in turn guides the production of a protein.

The human Genome is the complete sequence found in each set of chromosomes.

Gene therapy is the insertion of a normal copy of a gene into a cell containing a defective gene in order to treat a disease.

There are two types:

- somatic cell gene therapy, where the genetic changes are made in the body but not in reproductive cells;

- and germ-line therapy, which involves making changes to the fertilised egg. Germ-line changes are common in plants and animals but illegal in humans.

Genetic testing can be used for a wide variety of purposes, including diagnosis and/or carrier testing for genetic disorders; pre-symptomatic testing for late-onset genetic disorders or pre-disposition testing for familial cancers; genetic susceptibility testing for risk of common diseases or (more controversially) behaviours; ancestry and paternity testing; and to attempt to predict the safety and efficacy of medicines. Inherited mutations in genes can lead to increased risk of diseases such as cancer. Non-inherited (somatic) mutations also occur in cancer cells.

- Germ-line testing - genotyping or gene sequencing - tests the genetic make-up with which individuals are born.

- Gene expression is the process by which a gene is switched on and turned into first (RNA) and then the protein during a patient's lifetime.

- Biomarkers are any biological measure that can be used to assess risk or stage of a particular disease (e.g. protein or metabolite levels): they can be used to measure disease process or treatment effects.

Pharmacogenomics refers to the general study of all of the many different genes that determine drug behavior. Pharmacogenetics refers to the study of inherited differences (variation) in drug metabolism and response. The distinction between the two terms is considered arbitrary, however, and now the two terms are used interchangeably.

Personalised Medicine is the use of genetic testing to prescribe and develop drugs. Rather than 'blockbuster' drugs the idea is that medication will be 'customised'. Personalised medicine introduces the promise that it is possible to give the appropriate drug, at the appropriate dose, to the appropriate patient, at the appropriate time[26] and that will accentuate the move towards the individualisation of healthcare.

'Designer Babies': Pre-implantation Genetic Diagnosis (PGD) is the identification of embryos with defective genes. PGD involves the testing of embryos produced through in vitro fertilisation (IVF) for the presence of a range of genetic disorders. It may be considered an early form of prenatal diagnosis and has led to the term 'designer babies'. Genetic engineering of humans is not possible. The technique is also used to identify suitable tissue donors for existing sick children (so-called 'saviour siblings').

Background

Having started as a dream in the 1980s, the race to map the human genome was completed in April 2003 (following the initial draft in April 2000). It was an incredible achievement, as 3.1billion letters of the DNA code spread across 24 chromosomes. With this information came new knowledge about the genome function, including how little of the genome is used for coding proteins – with only about 20,000 to 25,000 genes.[27] In addition came the data that humans are 99.8% the same – there is remarkably little variation. The original theory was that any genetic disease could be identified and could be treated ("predict and prevent"). In reality, most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis and diabetes, are caused by the combined effects of variations in hundreds of genes and other factors, such as diet and smoking. Socio-economic factors also play an important role. Added to this, the whole process of gene expression – which is conversion of the information encoded in a gene first into messenger RNA and then to a protein – is still little understood.

There are about 6,000 known single gene disorders. 90% of human genetic variation is found in differences in single nucleotide polymorphisms or 'SNPs' (pronounced "snips"). These are DNA sequence variations that occur when a single unit of nucleic acid (i.e. A,T,C,or G) in the genome sequence is altered. For a variation to be considered a SNP, it must occur in at least 1% of the population.

The theory is that some SNPs could predispose people to disease, although many have no effect on cell function and finding a SNP variation does not mean that the development of a particular disease is inevitable. The driving force has been efficiency. "According to GlaxoSmithKline, 90% of today's drugs work for only 30% to 50% of the people for whom they are prescribed.

Furthermore, adverse drug reactions account for a surprising number of hospitalizations and deaths: one analysis published in JAMA (Journal of the American Medical Association) in 1998 found such reactions to be responsible for more than 2 million hospitalizations and 100,000 deaths in the US in one year".[28]

Examples of applications and International Scene

Gene Therapy

Applications of gene therapy remain experimental.

Examples include:

- For a rare genetic disease called ADA deficiency, the first condition approved for human gene therapy trial,[29] gene therapy has been declared a safe and effective treatment.[30]

- At Moorfields Eye Hospital, a man with Leber's Congenital Amaurosis, a type of inherited childhood blindness caused by a single abnormal gene, showed some improvement in detection of light when treated in April 2008.[31,32] Phase 2 trials are underway

- For advanced heart failure, phase 2 trials of *Mydicar* in 'cupid' trials in the US showed statistically significant improvement.[33,34]

PGD & Genetic Screening

An indication of the number of PGD tests that are available in the UK is provided in appendix 4, although this list is incomplete. Altogether the HFEA has authorized tests for around 60 diseases. Until 2006 only testing for serious genetic conditions was permitted but this was expanded to include cancers and each application is considered individually. Genetic screening is mostly post-natal [see below].

Pharmacogenomic Testing

- A test used in patients who have chronic myelogenous leukemia can show which patients would benefit from a medicine called Gleevec *(imatinib)*.[35,36,37]

- Another test is being developed to screen non-small cell lung cancer (NSCLC) tumours to determine which ones are the right candidates for a new cancer therapy.[38]

- *Abacavir* is used to treat HIV but it causes a severe reaction in about 5% of patients with a particular genetic variant. The Food and Drug Administration (FDA) now 'urges' on the drug label that people must be tested for variations in the HLA-B gene before being prescribed this drug.[39]

Examples of International Activity

At the 8th International Symposium on Pre-implantation Genetic Diagnosis in 2008, 34 countries took part.

European Union

PGD: Spain led the way with PGD with the fastest expansion of PGD clinics in Europe.[40]

On July 7th 2010 the German Court of Justice ruled that PGD should be made legal.

Research: alongside publication of the latest in research findings in their journal, the European Society of Human Genetics [ESHG] offer a very balanced perspective on the potential and problems.

Genetic testing: EuroGenTest is an EU-funded network looking at all aspects of genetic testing. It aims to develop the necessary infrastructure, tools, resources, guidelines and procedures that will structure, harmonize and improve the overall quality of all EU genetic services at the molecular, cytogenetic, biochemical and clinical level. In addition, the Council of Europe added a protocol to the European Convention on Human Rights and Biomedicine (ECHRB) concerning genetic testing for health purposes. This prohibits discrimination, puts human individual welfare above other concerns and confirms the right to privacy[41].The UK is not a signatory.

Therapeutic cloning: made legal in the UK in 2004 but outlawed in France[42] in 2005.

USA

- The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) is part of the Office of Science Policy within the National Institutes of Health (NIH). An open letter in 2008 to the then HSS Secretary asked for registry of commercial genetic testing laboratories, information from the FDA on pharmacogenomics and the inclusion of family history for Medicare patients who could benefit from genetic counselling.[43]

- The 'March of Dimes' was originally founded by Roosevelt to eradicate polio, but it is now an international US-based campaigning charity that tackles preventable birth defects and disabilities.

- President Obama established the 'Presidential Commission for the Study of Bioethical Issues', replacing George Bush's President's Council on Bioethics in early 2010.

- Multiple genetic testing at birth is already happening in New York State, where babies are mandatorily screened for 44 genetic diseases[44] at birth, the most of any US state.[45] Francis Collins, past head of the Human Genome Project, thinks that the costs will have fallen sufficiently in 5 years' time so that everyone could be offered a full DNA screen (Collins F, oral communication, 2009 February 7).

- '23andMe' is a genetic testing company funded by Google. 23andMe's mission is "to be the world's trusted source of personal genetic information". You pay for your test and get feedback on your (supposed) genetic predisposition and the chance to share the data that you paid for with researchers. However the service has been criticised by a number of geneticists as it does not provide medical advice.

- In 2006, the US Government Accountability Office published a report critical of Direct-to-Consumer (DTC) genetic testing[46]. In 2008, an investigation of DTC tests published in the American Journal of Human Genetics criticised the reliability of DTC genetic tests.[47]

- The University of Berkeley, California announced its plans to send in the summer of 2010 DNA swab kits to all new students, on the same day that the FDA announced it was halting the sale of DTC kits by Walgreens.[48]

India
IVF has become a significant tourist attraction because of the low costs, but it has also become popular due to infertility levels of up to 20% among Indian couples.[49]

China
Commercial genetic predisposition testing is widespread and poorly regulated, leading to dubious advertising and misleading medical advice.

Israel
The Israeli Defence Force authorities have initiated legislation to establish a genetic database of all army recruits for personal identification.

Iceland
DeCode genetics was the first company to offer genetic profiling but filed for bankruptcy in November 2009, having been criticised for some years over its approach to the issues of privacy and consent.

Strengths

General

The UK has

- Enabling regulation

- Global reputation for innovation and research

- Strong clinical trials base and United Kingdom Clinical Research Collaboration (UKCRC)

- The Health Professions Council which is recommending to Government that Genetic Counsellors become a regulated profession.

The government signalled its commitment to utilising the progress of genetics in the NHS in its 2003 Genetics White Paper and its 2008 review. It is advised by the Human Genetics Commission (HGC which succeeded the Human Genetics Advisory Committee and is jointly sponsored by the Departments of Health and Business, Innovation and Skills and devolved administrations), but there are other key organisations that have an interest in this field. These include the Human Genomics Strategy group, the Primary Care Genetics Society (gives support to Primary Care Professionals), the Foundation for Genomics and Population Health (PHG Foundation which grew out of the NHS run Public Health Genetics Unit), the Genetic Interest Group (GIG - an umbrella organisation for charities involved in genetic disorders), the Joint Committee on Medical Genetics (JCMG), Association of Genetic Nurses and Counsellors, the NHS UK Genetic Testing Network, the Clinical Genetics Society (CGS), Pegasus (Professional Education for Genetic Assessment and Screening) and GenewatchUK.

Gene Therapy

Of gene therapy trials, 63% have taken place in the USA, 12% in the UK (in second place) and 4.9% in Germany[50]. Most trials (64.5%) have concerned different forms of cancers.

While there are no commercial applications of gene therapy the UK was central to the trials for Leber's Congenital Amaurosis [see above]. Between 1993 and 2008 the regulatory body in the UK, the Gene Therapy Advisory Committee (GTAC) approved 155 trials with 126 actually going ahead[51]. This includes, for example, trials supported by Genzyme in the treatment of Parkinson's disease and macular degeneration.

Pharmacogenomics

- Increasing use of this science to help predict adverse drug reactions (ADRs).
- The House of Lords' Science and Technology Committee published towards the end of 2009 a comprehensive Genomic Medicine[52] report which also highlights carrier identification and sub-division of diseases which it is hoped will help researchers to develop more specific, personalised therapies.
- Testing of patients before chemotherapy revealed patients' sensitivity to drugs and thereby enables doctors to reduce potential toxic side-effects.[53]
- A growing number of drugs tailored to gene-expression testing of various cancers (e.g. Herceptin, Gleevec, Iressa)
- Clinical trials at the Mayo Clinic have revealed that a drug in trial turned on a tumour-suppressing gene - highly unusual as drugs typically target genes and proteins that are already turned on (over-expressed) and turn them off.[54]

PGD

In the UK there are 14 centres licensed to carry out PGD out of 72 IVF clinics.[55] Compared to the rest of the EU the number of cases where PGD is used in IVF is small. In 2004 it was used in 285 cases (HFEA figures), compared to 1,960 in Spain and 1,420 in Turkey (not in the EU but which is included in the figures collected by the European Society of Human Reproduction and Embryology [ESHRE]).[56]

There are two types of testing: exclusion testing which traces which grandparent's DNA has been inherited and selects the unaffected embryos without revealing the patient's genetic status; and non-disclosure testing where embryos are tested directly for a genetic condition. The 2010 HFEA 8th edition of the Code of Practice recommends that where possible, only exclusion testing should be offered. At present, PGD for chromosomal disorders is increasing across Europe and in 2005 (latest published figures) was used in 5846 treatment cycles out of a total of 418,111 of all assistive reproductive technologies including IVF [ESHRE figures]. There is no therapy involved, simply the elimination of embryos that are 'substandard'. While this is an accepted procedure in the UK, it was illegal in other countries (for instance Austria, Germanyand Switzerland). This procedure is controversial as some still regard it as the termination of a life, but it is also used by parents who wish to avoid being faced with the decision whether to terminate a foetus that is found during pregnancy to have a genetic disorder.

A similar technique called pre-implantation genetic screening (PGS) is increasingly being used to determine aneuploidy in IVF (abnormal number of chromosomes in the nucleus), as this affects implantation and miscarriage rates, but it's efficacy in doing so is being questioned.[57]

NICE guidelines on fertility currently don't cover PGD treatments and it's not clear whether they will be covered in the revised guidelines in 2011.

UK Success

Assisted Conception Unit (ACU) at University College London (UCL)

Paul Serhal, medical director of the ACU, oversaw the birth of a baby who had been screened for BRCA1 gene early in 2009.[58]

Women with a defective BRCA1 or BRCA2 gene are up to seven times more likely to develop breast cancer than those without the mutations; these genes also increase the risk of ovarian and colorectal cancer.

Scientists and doctors at the ACU and the PGD group at the UCL Institute for Women's Health have pioneered and successfully applied this technology to avoid transmission of cancer predispositions in a whole host of cancers. This includes a genetic form of bowel cancer (adenomatous polyposis coli, or APC) and a genetic form of cancer of the retina (retinoblastoma).

NHS

- The NHS will pay for genetic tests, after a GP referral, in families where there is a serious risk of any of a range of inherited diseases.

- Primary Care Trusts will consider whether to pay for the PGD procedure on a case by case basis. For those with fertility problems the IVF stage can be charged to the NHS. Cost to the NHS is about £5,000 per 'round' of IVF and PGD.

- As there are no commercial treatments, all patient involvement in development of genetic-based therapy is funded by research grants. The cost implications for the NHS of a successful gene therapy are enormous – the cost of the development of the gene therapy for retinoblastoma was $124 million with the US phase 1 clinical trial costing $3.7million.

Weaknesses

General

- The causation of disease is much more complex in most cases than simple genetic aetiology. Added to this, protective mechanisms of 'rogue' genes have been illustrated by, for instance, the gene for sickle cell in younger children. For children under 10 years old with a combination of one normal gene and one sickle cell gene (they don't have sickle cell disease as they have one healthy copy of the gene) there is a 60% protection rate from malaria. This drops to about 30% in older children and adults, adding to the puzzle.

- Genetics is being used prematurely or inadvisably by other agencies e.g. the UK Border Agency's Human Provenance Pilot Project. Here genetic tests are being used to give an indication of an individual's 'nationality' and 'country of origin', yet nationality is a legal concept and not the same as ancestry. Genetic tests cannot give the answer being sought, yet they are still being used.

- There is an incredibly complex regulatory environment before genetic research can even be initiated [seeAppendix 3].

- The lack of funding for translating research into development and actual therapy and therefore loss of innovation to UK for commercialization is a significant loss.

- The lack of public/private funding partnerships and uncertainty around return on investment (ROI) is a deterrent.

- There seems to be no guiding sense of prioritization around research and grant making decisions. There is a brain drain to the USA and Far East.

- Globally there is uncertainty around Intellectual Property and/or the potential (disputed) negative effects of expanding the IP regime to include genes, proteins etc.

Gene Therapy

This suffers from the law of unintended consequences. In 2007, a child who had been treated for X-SCID, (x-linked severe combined immunodeficiency), often known as 'baby in the bubble syndrome' where boys are born with no immune system, was found to have developed leukaemia 2 years after the successful treatment[59]. There have been no other reports in the medical literature of illness in the other 9 children treated at the same time, however four of eleven children previously treated in France also developed leukaemia[60]. Overall it has not yet delivered the hoped for breakthroughs.

Pharmacogenomics

- Over-estimation of the importance of genes in determining the reactions to medicines, most of which are complex though a few are clear cut. Some initial successes are now being shown to be optimistic interpretations.[61, x]

- Claims of a revolution in medicine are unsubstantiated but pharmacogenomics might improve differential diagnosis and risk prediction.[62,63]

x For instance the test that looks at a liver enzyme within cytochrome P450, which breaks down certain types of drugs, was originally thought to show that people with a less active form of the enzyme might get too much of a drug. In some cases this is disputed as being the most significant factor

Genetic screening

There is a good paper by 'Sense about Science: Making sense of testing' which touches on the general reasons why screening healthy people is not always a good idea. Specifically on genetic screening some of the problems are:

- the predictions are poor and commercial kits (see case study 4 and below) can give misleading results due to the complexity of the testing process, which is affected by mutations, and interpretation of the findings. Some papers have recommended that other family members should be tested before results can be confirmed;

- genetic susceptibility uncertainty.
  For instance NICE has not proposed screening the whole population for breast cancer BRCA1/2 mutations, but only high-risk families, because the mutations are rare, the penetrance (the number of people who develop the disease when they have the gene) is between 40% and 80% (i.e., it depends on the family history and is not the 'over 80%' stated by *Genomic Medicine*)[xi, 64,65,66] and the treatment intervention is very drastic.

- there is currently a dispute in the press and scientific literature about whether future predictions will significantly improve and, if so, what research would be needed to achieve this.

Commercially available genetic tests

There is incomplete regulation overseeing commercially available kits in the USA. The "kit" marketed to laboratories to conduct their own testing is regulated by the FDA. For tests that are conducted in house (so-called "home brews"), CLIA regulates analytical validity, but not clinical validity or clinical utility. Likewise in the UK they are regulated under the In-Vitro Diagnostics Directive, but this only covers analytical validity (has the right sequence been identified), not clinical validity (whether the gene is really associated with the claimed disease) or utility (whether the testing is useful to improve health outcomes). The Human Genome Commission (HGC) have drafted a code of conduct but as far as the public are concerned, their information is incomplete and potentially misleading.

People in the UK don't know whether their insurance will be affected after 2014 which is when the industry moratorium ends. In the U.S., the Genetic Information Non-discrimination Act (GINA) is a permanent protection against discrimination both for insurance and employment purposes. GINA, passed under the presidency of George W. Bush with very wide, bipartisan support was designed to protect Americans from discrimination based on their genetic information when it comes to health insurance and employment. France, Sweden and Finland have similar laws. The House of Lords Genomic Medicine report argued against it partly because healthcare in the UK is 'free' through the NHS (and not supplied by employers) and also because the information from testing is 'of little value'. However the latter is precisely why we feel we should have legal protection: undue authority could be given to tests taken by the public under the misapprehension that the tests are useful! This legal protection could be achieved by the UK becoming a signatory to the Council of Europe Convention on Human Rights and Biomedicine[xii] - the only binding international instrument on technology, policy and ethics.

There is no clear legislation in the UK that prevents employers from using gene-screening in pre-employment health tests[xiii]. Minutes from the an HGC meeting at the end of 2008 indicated that genetic testing in the workplace isn't widespread, but it went on to comment: *"The Information Commissioner's Employment Practices Code advises employers to inform the HGC of any proposals to use genetic testing for employment purposes. There are concerns that this existing mechanism for monitoring genetic testing in the work place may not be sufficiently robust and so there are plans to explore further, how the HGC can monitor genetic testing in employment".*[67]

Francis Collins, former head of the Human Genome Project, said when interviewed for this paper, *"The clinical validity of tests is improving and giving you information that is correct, but the tests currently give you less information on utility. I would like to see a public database initiated, with objective information on clinical validity and utility provided for each commercial test. Manufacturers would be required to comply, or the operating company could be shut down."*

xi Page 15 para 2.9 states 'The breast cancer genes BRCA1and BRCA2 are examples of genes with "high penetrance" because over 80 per cent of individuals who carry a mutation in one of these genes will develop breast or ovarian cancer, or both, in their lifetime.' This is not backed up by the published evidence.

xii Chapter IV, Article 11 prohibits any form of discrimination against a person on grounds of genetic heritage.

xiii There are different opinions on this, but the fact these differences exist demonstrate that this is a grey area, whereas in the USA there is specific legislation that outlaws such discrimination

PGD

There have been calls for the harmonization of regulations across Europe to eliminate the problems of medical tourism which result from PGD still being illegal in some countries.

Academic and Industry Hype

[see Media Hype below]

In compiling this report it was impossible to avoid many hugely inflated claims (many of which are now being modified) of what genetics could mean and when it could deliver to healthcare. Gary Pisano in his book 'Science Business – the promise, the reality and the future of biotech'[68] critiques the biotech industry and attempts to explain why on the whole it has not yet delivered economic benefits. However it can do, he says, if a long-term view is taken along with a willingness to integrate over short-term monetization of intellectual property. There is a role for a government review of regulation and assistance to business here.

Insurance

There is a moratorium until at least 2014 preventing insurance companies (brokered by the BIA, the trade association for British insurance) from using the results of predictive genetic tests.[69] It was introduced so that no one would be put off being tested for hereditary diseases. In the future it is possible that the moratorium will be lifted, in which case premiums could go up or down depending on a person's genetic make-up. However with the utility of genetic tests increasingly being questioned, concerns about this are receding, except for predisposition testing for the relatively rare familial forms of cancers. A number of patient groups have argued that women taking BRCA1/2 mutation tests for predisposition to breast cancer need greater certainty about whether their insurability will be affected in the future.

Public Engagement and Testing

There is testing of newborns in the UK for up to five inherited disorders,[70] but this testing remains optional and there has been little public engagement on the issue. The State of New York's policy is that, *"When a healthy child is at risk for a paediatric-onset disorder, predictive genetic testing to confirm or allay disease risks may be in the best interests of the child, even if preventive or therapeutic interventions are not available"*[71]. However they have not defined 'best interests' and there is concern in the UK and EU about this too. The ESHG recommends that genetic testing should only take place in minors when a genetic mutation has been found in a related adult.[72]

Even then, genetic testing often only gives a level of probability, not certainty about disease development. Testing where there is no cure allows public health data to be collated, but the concomitant risks include personal and family anxiety, the potential for coercion and discrimination and the implication that personal health data is the property of the State, not the individual. In relation to children, there was a public meeting in 2007 on the subject of 'Genetic testing in children' organised by Genetic Interest Group, Clinical Genetics Society and others. One key statement was that 'In the absence of childhood onset or the availability of medical interventions, that predictive testing for an adult-onset disorder should not be offered'.[73]

Opportunities

- The presence of the NHS should mean that clinical applications when they arise should be translated more easily. There is still much to be done, however, when it comes to persuading 'conservative clinicians' to improve uptake of new techniques and medicines.

- The Genetics and Insurance Committee (GAIC) which advises government have now produced their 6th report. The Committee has allayed fears within the insurance industry about the impact of widespread genetic prediction.[74] (This Committee is apparently now going to be disbanded).[75] In reality there is little of concern as the ability to make significant predictions has not materialised for most diseases in most people. There is now an opportunity to reassure the public in the same way. Concern about the future insurability of individuals taking predisposition tests for familial cancers could also be addressed, without significantly affecting the insurance market.

- Pharmacogenetic testing is indicating that a more accurate dosage of warfarin can be achieved though not yet the improvement in control of anticoagulation or complications.[76,77,78]

- Our international reputation is still attracting foreign skilled workers to the UK.

- Intellectual property benefit to the UK.[xiv]

- As the pace of change is slower than anticipated, there is more time to invest in the education of the public and regulation of publically available genetic tests. These are particularly important as the market is growing while public knowledge is static.

xiv The patenting of biological inventions is governed by the Patents Act 1977 as amended by the Patents Regulations 2000, which entered into force on Friday 28 July, 2000. The Patents Act 1977 was amended to bring it into line with the European Directive (98/44/EC) on the legal protection of biotechnological inventions. The Directive was adopted in July 1998 with the support of the UK to harmonize national patent laws of the Member States of the EU that concern

- The European Patent Office (EPO) ruled on 27 November 2008 against allowing a patent on developing human stem cell cultures whose preparation involves the destruction of embryos. This decision was made as it was felt that 'commercial exploitation would be contrary to public order ("ordre public") or morality'. It also allows research to proceed unhindered.

- As new techniques and research emerge, there is the chance for more informed discussion of priorities for research.

- Patient-directed (and possibly remunerated) electronic records that allow individual details and genetic information to be used by commercial organisations for research have been suggested in the USA. As electronic patient records (EPR) have yet to take off in the UK, we should have a discussion over who owns the data and who has the authority to make it available for research purposes.

Threats

Privacy - Genetic discrimination

The 2003 Genetics white paper included the idea to screen every baby at birth. The not-for-profit policy research group GenewatchUK called this "barcoding babies"[79] and produced a helpful critique of the value of doing so, backed up by research from the ESHG. For immediate post birth testing there are the issues of confidentiality and privacy concerns around test results being kept by the NHS, the derogation of the principle of informed consent and the inability to offer genetic counselling before tests are undertaken (as is currently the case with adults in the NHS). In addition the NHS is still reviewing the IT 'Summary Care Record', which could essentially form a national DNA database that mirrors the last government's scrapped National Identity Card Scheme. This potential invasion of privacy is poorly understood by the public due to a lack of open debate about plans to incorporate genomic information into electronic medical records. The Human Genetics Commission's report into the White Paper proposals also raised a wide range of issues including effectiveness, cost-effectiveness and ethical concerns about testing babies for susceptibility to adult-onset conditions without their consent.

Accuracy of Pharmacogenomics

There is increasing awareness of the complexity of factors relating to any one disease, but there is possibly a danger of neglecting the relevance to adverse drug reactions of the:

1. increased toxicity of some medicines;

2. limitations of safety testing and need for monitoring of new medicines;

3. increasing use of medicines, including multiple medicines and more 'over the counter' sales.[80]

Patenting

- Nobel Laureate James Watson resigned from NIH over others wanting to patent 'raw' sequences of DNA. More than 20% of our human genes are already patented and many of these patents are concerned with claims for utility, for example as diagnostic tests for cancer.

- There are strong arguments for and against patenting in biotech. The US Human Genome Project lists nearly twice as many arguments against patenting as for. There have been several examples of drug development that has been curtailed by companies 'sitting' on their patents and not developing therapeutic agents. Also where families have been involved in tissue donation, others have been denied the benefits of the therapy due to the complexities of rights and patents.[xv] Affymetrix are unusual in being a company that oppose genetic patents as their technology tries to analyse multiple genes. Their approach inspired a review paper in 2002 by the John Marshall Law School on 'Who owns the genome?'

- Also in 2002 the Nuffield Council on Bioethics launched a discussion paper on patenting which concluded that patenting should be the exception rather than the rule and that tests of inventiveness and usefulness should be more rigorously applied.

- According to the DNA Patents Database there are 49,366 DNA Patents in the USA and 67,451 published applications.[81]

- In 2004 the Department of Trade and Industry (DTI – now DBIS) published 'Patents for genetic sequences: The competitiveness of current UK law and practice'. It concluded that the UK patent system was 'working satisfactorily'. However a number of subsequent reviews in the EU and elsewhere have questioned the economic and health benefits of expanding the patent system.

xv This subject is explored extensively in Professor Donna Dickinson's book Body Shopping (Oneworld, Oxford, 2008).

- Following the Gower's Review of 2006[xvi] the UK Intellectual Property Office ran a consultation in the autumn of 2008 on the 'Patent Research Exception' which permits use of a patented invention for experimental purposes without infringing the rights of the holder. A government response could not be found at the time of going to print.

- The American Civil Liberties Union has recently filed a legal challenge to gene patenting in the US. This case could have profound implications for legislation in this area.

- A US Federal Judge has recently invalidated two patents for genes linked to breast cancer, saying that they *"are directed to a law of nature and were therefore improperly granted."* This ruling is likely to call into question thousands of the patents granted as human genes.

Use of investment

One of the key drivers behind the NHS IT programme and electronic patient record (EPR) was the hope that it would enable population screening for genetic 'prediction and prevention'. The failure of the EPR part of the National IT programme so far has distracted from this but there are concerns that this hope is also hampered by the lack of emerging evidence of utility.

The whole area of cost-benefits of developing new therapies and pharmacogenomics has not been the subject of this paper. However it needs mentioning as the case for sufficient commercial benefits for much of the pharmaceutical and biotech industry to take research into actual therapies is still to be made.[82,83,84]

Loss of confidence

The HFEA website still states that, "It is expected that PGD will only be available where there is a significant risk of a serious genetic condition". However in 2007 they allowed PGD to be used to prevent the birth of a baby with a family history of squint.[85] There is concern that PGD will be expanded to more superficial imperfections which will rock public confidence in the authorities who are sanctioning these procedures.

Media Hype

While selection of embryos is possible, genetic engineering of humans is not. 'Designer babies' are created by genetic changes selected by their parents to produce a made-to-order offspring. However traits that it is feared parents may want to enhance are generally controlled by multiple genes. For any given single gene there is a 1 in 4 chance of getting the required 'best version' embryo from the parents. Yet if just two genes are to be optimized there is on average a 1 in 16 chance of finding one embryo that meets the requirements.

Given that a woman usually only produces one egg per cycle, she has to take follicle-stimulating hormones to produce extra eggs simultaneously. On average, IVF institutions then surgically remove up to 5 ova in order to have a choice over how many to implant. In the recent case of the baby born free of the BRCA1 gene, 11 ova were removed for analysis. The point here is that to even have a choice over two genetic traits, a significant number of eggs would have to be surgically removed, and this becomes both impractical and dangerous for the mother. Higher levels of hormone stimulant are needed to produce more eggs and this brings with it the risk of ovarian hyper-stimulation syndrome, which if severe can cause blood clots, kidney failure,[86] fluid in the lungs and shock,[87,88] and in rare cases death.[89,90] These figures mean that currently, no parent could practically choose more than two genetic traits and these would have to be classified as 'serious' in order to qualify for NHS funded PGD.

In addition, none of these genes operate in isolation and there is some evidence for the biological impact of parental experiences (their nutrition, behaviour, environment, etc.) on the genetic make-up of a child. In other words, their experiences can change the genes passed on to their offspring, a theory first described by Jean-Baptist Lamarck 50 years before Darwin, and what we now call 'transgenerational epigenetic inheritance'.[91] Then again, many scientists dismiss these findings and blame 'Lamarkism' for holding back medical progress. The debate continues.

The other point to make here is that 'designer babies' will only become a real issue if reproductive cloning (made illegal in the UK in 2001) is developed to the point of making viable embryos. The first grants for therapeutic cloning, where the intention is that stem cell lines are produced for therapeutic purposes, were given in 2004. This was particularly controversial for several reasons: Only four other countries had sanctioned the creation of embryos purely for research; it is the foundation of reproductive cloning and would help this to happen in other countries even if outlawed here; and huge numbers of eggs are required with low indication that this will result in viable therapies compared to other research areas. In addition, claims made by Korean researchers that they had successfully cloned human embryos were exposed as fake.

xvi Andrew Gowers undertook a review of Intellectual Property in 2005 and reported his findings to the Government in December 2006. On the patent research exception, the Gowers Review reported that it was "not entirely clear what uses fall within the scope of the experimental use exception" and the lack of case laws "leads to uncertainty as to its scope".

The Bottom line

- There have been some exciting triumphs in genetic medicine but in most cases these constitute incremental changes rather than any transformation (acknowledged by the Wellcome Trust in the Lords' Genomic Medicine report). A number of technology experts have argued that the government has pinned too much hope on a biotechnology revolution.

- Genetic medicine seems to be taking longer than anticipated to deliver the hoped-for revolution in personalised, tailored medicine. Some feel that progress in genetics has revealed more about our complexity and our unrealistic expectations of what this field of medicine could deliver. Others feel however that the current course of clinical implementation is as expected and still have high hopes for 'personalised medicine'.

- The most progress and potential is in the domain of prediction of drug responses. Most successful applications have been in the field of cancer gene-expression testing.

- The UK is at the forefront of research, but in part this is controversial. The UK is not a signatory to the one binding international instrument in the field, the ECHRB (Oveido 1997) which, among other things, outlaws therapeutic cloning. It has also not signed or ratified the European Convention on Biomedicine and its protocols, which set ethical and clinical standards for genetic testing and research.

- Genetic screening is currently a relatively weak predictor of disease and may increase stigma, anxiety and discrimination. There is currently a dispute in the scientific literature about whether predictions will significantly improve. The public are not being adequately protected or informed about the serious limitations of 'direct to consumer' genetic tests and kits.

- The cost, the nature of the invasive procedure of IVF and the complexity of 'simple' traits such as blue eyes mean that while PGD will not result in designer babies in the near future, an increasing interest in sex selection and the principle of design raises fundamental questions for long-term policy review.

- As new treatments are found for genetic conditions, the use of PGD should be reviewed.

2. Neural Implants and bodily IT devices

Definition and Description

Neural implants are IT devices that connect directly to the brain for a variety of medical and non-medical purposes. Emerging applications include the insertion of 'brain pacemakers' to manage brain dysfunctions (such as tremors) or control artificial limbs. Other implants are man-made tools that are inserted into the body for example for drug delivery or communication.

There are also a rising number of IT devices that can be connected to the outside of the body to read the electrical signals from the brain or nervous system.

IT augmentation is the use of external technology devices to restore or enhance function.

Examples

In addition to those in the case study, examples include:

Implantable programmable drug delivery pumps

1. Intrathecal drug delivery for chronic pain - morphine delivered directly to the spinal fluid.[92]

2. Administration of baclofen for the treatment of spasticity, particularly in patients with multiple sclerosis.

3. Insulin pump for diabetes.

Implantable neurostimulation devices

Neurostimulation implants deliver electrical stimulation to the spinal cord or nerves. They can be used for the following purposes:

1. spinal cord stimulation for chronic pain management. NICE have recommended this for patients who fail to respond to ordinary treatment for at least 6 months. Cost of the implant is £5,000-10,000 but there is evidence that devices become cheaper than other therapies after 2.5 years;[93]

2. sacral nerve stimulation. This can be used to treat intractable urinary urge incontinence, bowel incontinence or chronic constipation. It has been found to be a cost-effective method of treatment under NICE guidelines;[94]

3. vagus nerve stimulation (VNS) -

i. In the teatment of epilepsy this has been used in about 43,000 patients worldwide[95] with up to 50% reduction in treatment costs compared with medical costs in patients without the neurocybernetic prosthesis;[96]

ii. To treat depression[97] its use was recorded in Scotland 2005[98] but after initial approval it was turned down by the FDA in the USA in 2007;[99]

4. gastric neurostimulation (GN) to treat gastrointestinal motility disorders. In a sample of patients with gastroparesis for 3 years, GN appeared to be more effective than medical therapy in improving long-term gastrointestinal symptoms and costs, and decreased use of healthcare resources compared with intensive medical therapy.[100]

Deep brain stimulation

In deep brain stimulation (DBS), an electrode is implanted to alter neuronal activity in the thalamus or basal ganglia,[101] although the exact mechanism of action is not fully understood. There are many different applications of this therapy including:

- tremor control in Parkinson's disease[102]; Initial treatment for Parkinson's disease is with the drug *levodopa* but the side-effects can eventually be worse than the condition itself;

- essential tremor; Patients with essential tremor have no symptom other than tremor, which may occur in their hands, head, legs, trunk or voice. As for patients with Parkinson's disease, they can be helped by DBS. Cost to NHS per patient was found in 2006 by the NHS EED study to be £31,942;[103]

- treatment of dystonia; a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures.[xvii]

Artificial chip-controlled leg

This is the first sort of artificial limb to interact with the human. It adjusts the dampening effect in the knee in response to the patient's movement. It is very expensive and there are very few in the world.[104]

Radio frequency identification device – 'Verichip'

This is a microchip implanted under the skin. When read using a scanner it gives a unique identifying number that can be used to retrieve records. It has been suggested that it could be used to store medical records or to help identify patients with Alzheimer's disease. Extension of this technology could be useful in the prevention of fraud, reduction of medical error and improvment of capacity to meet medical emergencies.[105]

Smart pills

Pills embedded with an edible communications device which sends wireless signals through the body when it comes into contact with stomach fluids are under development.[106] The signal goes to another chip on or just below the skin which forwards data to a smart phone or direct to the GP via the internet. This informs the doctor if the patient is complying with medication, although another company is investigating how to link this technology with a patient controlled computer game.

Examples of International Activity

EU

1. Comprehensive analysis on the '*Ethical Aspects of ICT Implants*'[107] was published by the European Commission in 2005 and details further examples of IT applications. In Germany and the USA artificial retinas are being developed.

2. European Technology Platform on Smart Systems Integration (EPoSS)

USA

1. Artificial biomorphic controlled limbs.[108]

2. US Governments artificial retina programme[109] and Johns Hopkins University, North Carolina State University and the University of North Carolina-Chapel Hill development of the artificial retina component chip (ARCC).

3. Development of BrainGate [see above], a direct brain-computer interface to communicate with and control a computer.

Israel

Exo-skeleton. [see above]

Japan

The Halo-3 Exoskeleton 'Robosuit' was trialled 2005 by Cyberdyne[110] and went on sale to the public in Japan in 2008 but is not yet available overseas. Honda was also involved in this technology.

Korea

The Delta Scan Foresighting Project[111] predicted in 2005 that *"Korea may exhibit the greatest uptake of these new technologies. There, high broadband use plus the world's highest rate of plastic surgery provide the medical technology infrastructure and the demand necessary to drive development".*

xvii Different abnormal posture problems include: Failed Back Syndrome (FBS) or low back syndrome or failed back; Radicular pain syndrome or radiculopathies resulting in pain secondary to FBS or herniated disk; Postlaminectomy pain; Multiple back operations; Unsuccessful disk surgery; Degenerative Disk Disease (DDD)/herniated disk pain refractory to conservative and surgical interventions; Peripheral causalgia; Epidural fibrosis; Arachnoiditis or lumbar adhesive arachnoiditis; Complex Regional Pain Syndrome (CRPS), Reflex Sympathetic Dystrophy (RSD), or causalgia.

In December 2008 the European Commission through EPoSS and the South Korean Ministry of Knowledge Economy got together in Belgium for the 2nd EU-Korea cooperation forum on ICT research, in which 290 organisations participated.

Strengths

Developments in IT mean that there is increasing potential for them becoming part of us - implanted into our bodies. In the NHS there are a variety of commercially available IT and neural applications, some of which are available on the NHS but at the discretion of the PCT. [see above]

Professor Kevin Warwick of Reading University made history as the first person to have a microchip inserted into his forearm. The benefit to health of such research is unclear but he is at the forefront of wanting to merge humanity with IT and create cyborgs.[112]

The largest centre in the UK for VNS is Kings College Hospital in London.[113]

Other UK activity is ongoing in Cybernetics and IT Centres at Reading, Warwick, Bradford and Hull

Weaknesses

Breach of Body and infection risk

Significant resistance to implantable devices may persist due to social, moral, ethical, and religious objections. Even Bill Gates, speaking about chip implants at a Microsoft seminar in July 2005, said, 'One of the guys that works at Microsoft always says to me "I'm ready, plug me in." I don't feel quite the same way. I'm happy to have the computer over there and I'm over here'.[114]

The risks related to IT implants were highlighted by the Order of the US FDA in respect of the subcutaneous "VeriChip": *"adverse tissue reaction; migration of the implanted transponder; compromised information security; failure of implanted transponder; failure of inserter; failure of electronic scanner; electromagnetic interference; electrical hazards; magnetic resonance imaging incompatibility; and needle stick"*. Dr Robert Benezra of the Sloan-Kettering Cancer Center in New York said that, *"There's no way in the world, having read this information, that I would have one of those chips implanted in my skin, or in one of my family members."*

However, Professor Warwick said that, *"Perhaps in some people's eye, the use of deep-brain stimulators for the treatment of Parkinson's disease, epilepsy, or Tourette's syndrome is perfectly acceptable because of the improved standard of living … However long-term modifications of brain organisation can occur … there can be considerable long-term side effects in the use of such technology"*.[115]

Necessity

People who are averse to the idea of implants will probably be able to achieve many of the same benefits through externally worn devices. While implants are likely to be widely available in 20 years, the majority of human computational extensions may be more like an exoskeleton.

There are concerns about the control of technology and its use for augmentation rather than therapy; will it really deliver improved health outcomes?

Ownership

There was a recent divorce case where the husband wanted compensation for his wife's breast implants. This bizarre case raises the more significant question of ownership of technology when it is implanted.

Opportunities

The health potential of the convergence of neurology, systems biology, tissue engineering and IT are enormous. The challenge will be to identify the truly promising avenues and marry them up with the greatest healthcare needs. Opportunities will include:

- the increasing prevalence of Parkinson's disease and depression will provoke a greater demand for these therapies;
- development of biosensors or Micro Electro-Mechanical System (MEMS), are implantable devices that can be used to monitor parts of the body such as blood pressure or blood glucose levels, or to deliver drugs at an appropriate time (smart pill drug delivery system);
- further development of implants to enhance or restore memory, for instance the artificial hippocampus;
- progress with the artificial retina and more advances in cochlear implants;
- determination of the regulatory situation ahead of further advances. The legal situation was outlined in the European Group on Ethics in Science and New Technologies to the European Commission's (EGE's) 'Ethical Aspects of ICT Implants' pages 13 - 19.[116]

Threats

Regulation and Privacy

Currently, non-medical IT implants in the human body are not explicitly covered by existing legislation, particularly in terms of privacy and data protection.[117] The existing relevant regulations are mentioned in the EGE's Ethical Aspects of IT Implants study. The EGE makes the general point that non-medical applications of IT implants are a potential threat to human dignity and democratic society.

Costs

1. None of this technology is cheap. Demand for restorative technology for the disabled will increase as advances are made. The NHS will need to prioritize and decide which are the greatest needs.

2. What level of investment is needed? Do the high costs mitigate against progress in the UK? Will we lose valuable researchers if we don't increase investment?

'Enhancement'

The control of technology and its use for augmentation rather than therapy could be a threat to or part of human evolution. Either way there needs to be much more public debate.

Development

The UK has a deficit of maths and physics students [and teachers], and those there may be unwilling to cross the medical-technology divide, which could hamper the UK's progress in this area.

International patents

Was the issuing of US Patent 6,754,472 to Microsoft in June 2004 for a 'method and apparatus for transmitting power and data using the human body' the ultimate level of commoditisation?

The Bottom Line

- Implants and IT developments are developing rapidly and needs to be taken seriously; these devices are no longer in the realm of science fiction but relevant to all of us.

- In our 'Age of technology' there is a huge amount of interest and enthusiasm for new IT applications.

- We are familiar with certain applications such as pacemakers without really thinking about them as 'implants'.

- Some interventions will have medicinal alternatives that are cheaper or less risky. Others, like heart pacemakers (CRT) are cheaper than a lifetime on medication.

- Many are a novel and unique way of tackling a problem (e.g. paralysis) that allows technology to undertake the task that can no longer be undertaken by the individual.

- However the development of thought and emotion control through implants or sensors raises huge issues about the loss of independence, privacy and freedom.

3. Neuro-therapuetics - therapy and lifestyle drugs

Definition and Description

Drugs that work on cognition to alter memory, learning, attention, emotions and other aspects of cognition[118] are variously known as neuro-therapeutics, neuro-cogniceuticals, psychoactives or cogniceuticals. These drugs can be used for treating neurological conditions ranging from the severe (e.g., Alzheimer's disease) to the mild (e.g., fatigue), and the border between which medicines are to treat ill-health and which are for lifestyle is hazy.

When taken for lifestyle purposes these drugs are called 'smart drugs' or 'mental viagra'. They are those taken to satisfy non-medical conditions that have been developed with a specific other application in mind.[119] These include drugs which boost performance in otherwise healthy brains or address non-medical conditions.

Examples

Neuro-therapeutics

1. Psychoactive drugs are used in conditions that affect the central nervous system, including:

dementia
Alzheimer's disease is the most common form of dementia, accounting for up to 70% of all cases and has an incidence of up to 20% in the over 80's. The average duration of the disease is 8 years between onset and death;[120]

parkinson's disease
Parkinsonism is characterized by tremor, rigidity and akinesia (loss of movement) and affects 120,000 people in the UK. It is associated with degeneration of dopaminergic neurons in the nigrostriatal pathway. Treatments are currently chemical antagonists or agonists to try to stem dopamine loss. Parkinson's disease research suggests that it is not directly inherited but that some people may inherit a genetic susceptibility;

mental illness including depression and psychosis
Mental illness affects up to 1 in 4 of the population at some point in their lives and 50% of episodes begin in children under the age of 14 years;[121]

epilepsy;

attention deficit hyperactivity disorder (ADHD, hyperkinesias) ;

narcolepsy (excessive day time sleepiness).

2. Lifestyle applications

Behavioural issues
ADHD is characterized by inattention, impulsivity, and hyperactivity. There are those who say it is a behavioural issue, those who see it as a medical condition. Either way, there has been at least a 65% increase in the prescribing of drugs for the condition in the last 4 years, costing the NHS £31m.[122]

New recreational 'smart' drugs
Medications designed for a particular deficit are increasingly being used off-license and off-prescription in normal people to boost performance, for example, Ritalin for memory enhancement among students in the USA. Peter D Kramer dubbed it 'cosmetic pharmacology' in his 1993 book 'Listening to Prozac', in which he raised the policy issues for and against the increased use of drugs by people who aren't ill.

Strengths

We have a much greater understanding of brain chemistry and the relevance of the control of levels of the naturally occurring neurotransmitters such as serotonin, dopamine, epinephrine (commonly known as adrenaline) and others which impact our feelings of happiness, self-esteem, aggression, nervousness, fear, depression, fearlessness and wellbeing.

Examples

Neuro-therapeutics

Alzheimer's disease
New papers are being published every week and the Alzheimer Research Forum provides a list of latest research published.[123] Research avenues are vaccination, genetics and anti-amyloid drugs and mono-clonal antibodies. In the UK the Alzheimer Research Trust Network links 15 universities including Cambridge (Addenbrooks), Ulster, Newcastle, Dundee, Southampton, Cardiff and Bristol.

Parkinson's disease
In UK universities and hospitals, 96 research projects worth £13 million are underway. Research funding has gone up fourfold in the past 4 years (causes £7 million; treatments £3.8 million), but this is still only one-third of what is spent on Alzheimer's disease research in the UK.

Mental illness
A wide range of agents are currently available. There are five main types -

- TCADs (Tricyclics)
- MAOIs (Monoamine oxidase inhibitors)
- SSRIs (Selective Serotonin Reuptake Inhibitors)
- SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors)
- NASSAs (Noradrenaline and Specific Serotoninergic Antidepressants)

They have a well-established positive impact in up to 60% of patients on antidepressants.[124] *Modafinil*, which was developed for narcolepsy, has been shown to improve memory in patients with schizophrenia.

Narcolepsy
Modafinil, a selective, non-amphetamine, wake-promoting agent, doesn't have the side-effects of anxiety, palpitations and hyperkinesias seen with other CNS stimulants.

Lifestyle

Performance
Antidepressants can change behaviour in normal people, with Prozac (for well-being – not just depression) being a classic example.[125]

Modafinil has been shown to allow a person without any pathology to stay awake for 3 days and this is already used by the military.

Memory loss drugs such as acetylcholine system enhancers (e.g., Aricept) that were designed to boost memory recall for early memory loss in Alzheimer's disease have been claimed to boost memory in healthy patients.

None of these drugs have been licensed for use by the general public for performance purposes.

Behaviour
Drugs for ADHD include Ritalin (methylphenidate), Concerta, Equasym XL, Straterra, Dexedrine and Adderall. Treatment in the UK must be under the supervision of a specialist in childhood behavioural disorders.

Examples of International Activity

USA
The National Institute on Aging Alzheimer's Disease Centers (ADCs) links 30 universities.[126] Massachusetts General Hospital's Lars Bertram collaborated with Alzforum to develop the AlzGene database, which lists every published genetic association study to help researchers compare results across multiple studies on the same genes.

The Parkinson's Disease Foundation is based at the Columbia University Medical Center and Cornell Weill Medical Center in New York City and Rush University Medical Center in Chicago.

Global
The 'Dominantly Inherited Alzheimer's Network' (DIAN)[127], a 6-year $16-million programme, was launched in July 2008 at Washington University for the early onset, genetically inherited form of the disease. It's a consortium involving Harvard University, Massachusetts General Hospital and Brown University, Columbia University, Indiana University, the University of California at Los Angeles, the University College of London's (UCL's) Institute of Neurology at Queen's Square, and a consortium of the universities of Brisbane, Perth and Sydney in Australia.

Weaknesses

There is general concern about the medicalisation of some conditions, especially the increasing focus on drug-based 'solutions' for performance. This has been progressively more on the radar since the introduction of Prozac, which generated the debate around 'cosmetic pharmacology' and the implications of 'remaking of the self'. An example of this is the development of a drug for shyness that is dubbed 'social viagra' - the race to produce a commercial product is underway.[128]

Funding

Dementia

In 2007, public funding of dementia care research was £7 per head of population in the UK, whereas the USA spent £52 per person. An extra £100 million was promised by 2008 by the UK Government (an increase of £1.60 per head). However the comparison with the spend on cancer in startling. In 2007-08, the Medical Research Council (MRC) and Department of Health (DH) gave cancer research £248.2 million, while dementia research received £32.43 million.[129] Yet some say the overall morbidity and mortality figures for cancer have changed little over the past 40 years despite an estimated global investment of £3 trillion.[xviii] In the UK 700,000 people live with dementia with an estimated cost to the economy £17 billion a year, more than the cost of cancer and heart disease combined.

Orphan drugs

These are at risk of neglect and being denied to patients as they are not assessed by NICE due to their small potential market, and are left to management decisions by PCTs. The move to clinician led commissioning and value-based pricing may improve the situation. For example, Myozyme, which is used to treat patients who have a confirmed diagnosis of the very rare Pompe disease[130] (not a neurotransmitter but an example of a drug designed for a very rare disease). Myozyme is an artificial enzyme which replaces the deficiency in alpha-glucosidase experienced by people with this disease.

Off-license use

Performance

When used off-licence (i.e., for a purpose or age-group not specified in the original licence) by people without ADHD, drugs such as Adderall, Ritalin and Dexedrine have a stimulant effect, resulting in suppressed appetite, increased concentration, wakefulness and euphoria, effects that are similar to the illegal amphetamine. Stimulant abuse can lead to *"Convulsions, anxiety, paranoia, headaches, malnutrition due to decreased appetite, and irregular heartbeat and breathing, which may be life-threatening ... Mixing the drugs with alcohol or other drugs, especially decongestants, exacerbates these dangerous side effects. Those who inject the drugs risk infection, HIV, hepatitis, and blood vessel blockages. Moreover, injecting the drug may deliver a toxic overdose to users. Those who abuse prescription stimulants regularly may become addicted or develop a tolerance to the drug".*[131] According to a study published in January 2005 in the journal 'Addiction', up to 25% of students at some US colleges report non-prescribed use of these stimulants.

Information deficit

Performance

The stimulants mentioned above and other medicines that are being used to stimulate performance have side-effects, but these are not widely known. For instance the side-effects of Ritalin include nervousness, insomnia, anorexia, raised blood pressure, angina and weight loss. For Aricept, they include diarrhoea, insomnia, fatigue and depression. The potential increase in health problems that would increase demand on NHS resources is not insignificant.

Conflicting opinions – Diagnostic drift

Mental Illness

Overprescribing in mental health is the subject of Charles Barber's book 'Comfortably Numb'.[132] In a study published in October 2007, Benjamin Druss and others[133] found that nearly 40% of people who received mental-health services, including medications prescribed by a family doctor, did not meet diagnostic criteria for illness. 'Diagnostic drift' is a term that describes the changes in diagnostic methods and classification over time, so what might have been seen as 'just feeling low' is now diagnosed as depression. This can have both positive and negative outcomes.

Other considerations

- 'Smart drugs' – will they actually deliver what manufacturers claim they will? How will we be able to control dosage? How will we address the lack of knowledge of side-effects. For instance some, such as Ritalin, have known side-effects, while others, such as Modafinil, do not seem to.
  [see threats below]

- Side-effects of some current drugs such as those for Parkinson's disease cause compulsive gambling or hyper-sexuality.

- An Alzheimer's disease research meta-analysis paper suggested that there are no significant new agents in trials and "it will probably take one to two decades before a major breakthrough in secondary prevention of Alzheimers can be expected".[134]

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xviii Eric Low, the executive director of the International Myeloma Foundation, said in the Scotsman's 2003 Cancer Research supplementary, "In the last 40 years, there has been something like $3 trillion invested in cancer research globally. If you look at outcome per dollar, it is not a fantastic result. "We are not making huge strides on the back of major investment. We have to prioritise what the important parts of the research are and ensure the money is going into the right projects."

Opportunities

There is a difficult and hazy line between what are appropriate and inappropriate uses for neuro-therapeutics, but there is no doubt that they offer to some people the chance to overcome debilitating problems.

New agents in development include:

- ampakines, which are small molecules that positively modulate certain glutamate receptors, and thereby enhance fast, excitatory transmission throughout the brain. Possible applications are restoration of mental function in people with dementia, relief of the effects of sleep deprivation, poor memory and, according to the website, stupidity;[135]

- asenapine (Saphris), a potential new agent for schizophrenia associated with bi-polar disporder that has fewer side-effects;

- drugs being designed for people who have had bad experiences,[136] including post traumatic stress disorder[137] that would erase specific memories.

The incidence of neurological disease means that there is an increase in demand for 'brain' drugs from society. The greater awareness and prevalence of conditions such as dementia should stimulate research in this field. This situation and the interest from the media and academia in 'smart drugs' means that there is an opportunity for:

- in-depth review of the regulatory situation and engagement of doctors[138] and the public in the debate on the costs and benefits;

- appraisal of funding and support for R&D into neurological conditions that are increasing in prevalence with the ageing population;

- attracting more doctors into neuroscience and determining how more academic-NHS partnerships can benefit patients;

- government funding of research and how to strengthen the UK's pharmaceutical industry base to facilitate investigation - there is a growing interest in 'psychopharmacology' and the potential profit and benefit to the UK economy could be considerable;

- development of market incentives to encourage treatments for addiction.

Threats

Unpopular areas neglected

- Mental health: there is a dichotomy between increased reliance on medication as a first line of treatment and a lack of development of new drugs for mental health conditions.

- Development of orphan drugs for rare diseases is jeopardized by the haphazard uptake of what can be life-changing therapies.

- There is a tension with the claimed underinvestment in alternative therapies such as talking therapies. A 'brain' framing of pathologies could promote drug interventions at the expense of social and environmental prophylaxis.

Costs

- Cost to the NHS: Misuse of current 'recreational' drugs already cost the economy £13 billion, with an addicted population estimate of 350,000.[139] The increased cost to the NHS of treating addiction, overdoses and concomitant social harm at a time when facilities for treating and dealing with current addictions is woefully inadequate should not be underestimated.

- Social equity: If only the wealthy can afford lifestyle drugs or the 'prime' versions of them, what will be the impact be on school grading, access to university places, career progression, etc.? Likewise the increased interest in pharmacogenetics indicates that people will respond differently to these drugs but there is currently little progress in diagnostic tests for existing drugs.

- Medicalisation of behavioural issues: For instance if shyness and further levels of hyperactivity become medical conditions there will be an increase in NHS appointments and prescribing.

- Increase in dementia: The prevalence will rise from 700,000 people in the UK today to over 1.4 million in the next 30 years. Unless research is made a greater priority and is better funded, the costs of care will be prohibitive. The current cost to the NHS is estimated at £3 billion.

Risks of lifestyle 'smart' drugs

To industry

The lack of public debate is a risk to industry as without sufficient public debate and consensus, pharmaceutical and biotech companies are vulnerable to public reactions like that seen to genetically modified (GM) crops and food. Not only does there need to be an upstream public engagement process [see below] for retaining confidence, but there is the linked economic risk. Obviously it is much safer to invest in technologies that the public know about, are comfortable with and are open to.

Lack of Regulatory Framework

There is nothing in place to manage the control and distribution of 'lifestyle' drugs. Will people get them for off-label uses, and to distribute to others? If so, how should prescribing be managed?

To individuals and the NHS

- Early reporting of 'lifestyle' effects that could lead to consumer demand before adverse drug reactions (ADRs) are fully investigated. The impact on the NHS and healthcare professionals needs to be considered, such as the use of antidepressants to change behaviour in normal people to 'better than well', as covered in various publications on Prozac and in the journals. For example, it has been claimed that improved business negotiations were an outcome of 'normal' people taking antidepressants.[140]

- Demand/false information/unreal expectations – the case of Seroxat highlighted both the addictive qualities of a drug introduced as a non-addictive replacement for previous addictive agents (e.g., *lithium*) as well as the (disputed) incomplete publication of trials that would have showed the risks of both addiction and aggression resulting from this drug.[141] It has also been successfully cited in a defence case where the defendant blamed the drug for his criminal behaviour.[142]

- Unintended consequences of memory erasure from drugs designed to block unpleasant memories.

- No stigma of illicit street drugs, but this helps to convey the misperception that they are all safer.

Lack of engagement

Public

In December 2008, Nature published an editorial by seven leading bioethicists and neuroscientists stating that, ' *"Society must respond to the growing demand for cognitive enhancement. That response must start by rejecting the idea that 'enhancement' is a dirty word", argue Henry Greely and colleagues'*.[143] This story was then picked up by TIME magazine, in January 2009,[144] which published a balanced piece on the pros and cons of liberalising prescribing guidelines. In the UK, it is legal for a physician to prescribe a medication for a reason not given in its license, but they would have to be able to justify their action medically.

TIME quoted the well-known appraisal by Leon Kass, Member of the President Bush's Council on Bioethics, in a 2003 report on enhancement that, *"We must live, or try to live, as true men and women, accepting our finite limits, cultivating our given gifts, and performing in ways that are humanly excellent. To do otherwise is to achieve our most desired results at the ultimate cost: getting what we seek or think we seek by no longer being ourselves."*

Professional

Since prescription stimulants are prescribed by doctors they are easy to obtain. There is little evidence that doctors are fully aware of the lack of regulatory framework. [see above]

Confusion and conflict with doping in sport

The current strict regulations against the use of any enhancing drugs in sport could be undermined by the acceptance of performance-enhancing drugs in everyday life.

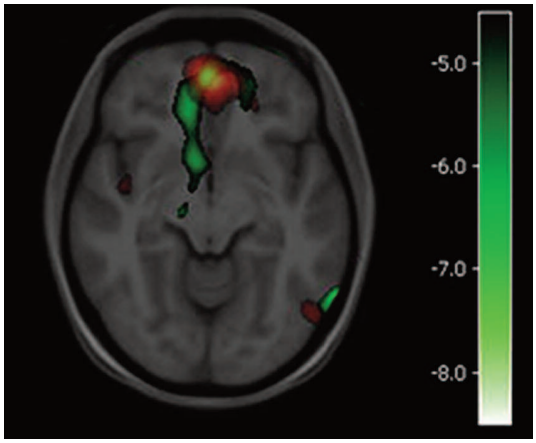
It's worth noting that drugs that enhance performance have not traditionally been brain drugs, but those that boost muscle bulk or oxygen supply, such as erythropoietin (EPO).[xix] CERA (Micera) is a third-generation EPO not yet licensed in the UK. It has a slower release rate and is harder to detect, but is the drug implicated in the recent Olympic drug scandals.

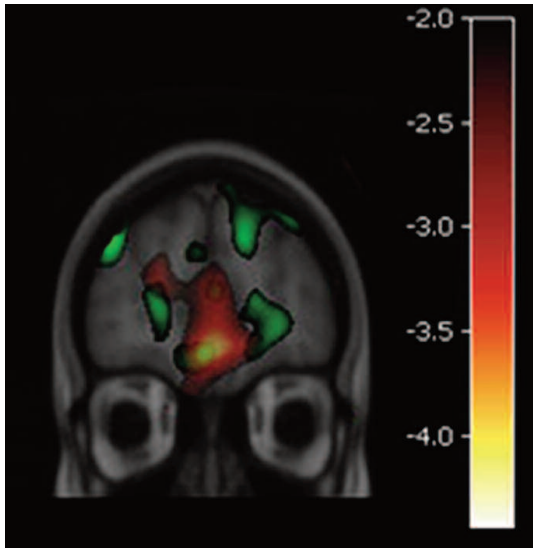
How will we prevent an 'arms race' of performance drug use? In its Opinion N° 14, the European Group on Ethics stated that, *"There is an urgent need for policy to take into account the profound change that has taken place in sport in this century due to the influences of growing economic interests and of the mass media on an increasingly global scale. These influences have accelerated medical and technological developments in sport and related industries as well as increased the pressure put on the sports person. As a result, all action concerning doping must take into consideration, in accordance with this change, the realisation that today performance and victory prevail over competition and participation. The Group thus intends to stress the tension that exists between anti doping measures and an unlimited demand for enhanced performance"*.[145]

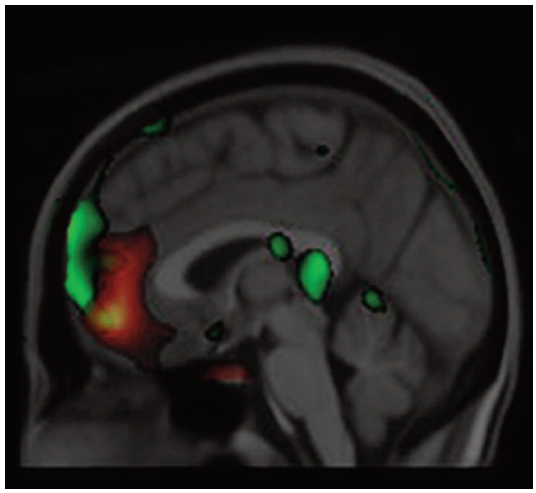
xix Semi-synthetic EPO, pioneered by Amgen, is more often in the press as the performance boosting drug misused by endurance athletes. It increases oxygen delivery to muscles and has been shown to improve performance by up to 15%. However this also causes thickened blood and an increased risk of heart attack and stroke in dehydrated athletes with some subsequent fatalities. Naturally occurring EPO concentrations can be increased by altitude training.

The Bottom Line

- There is a growing market for neuro-therapy and lifestyle drugs.
- There is no expected breakthrough in the prevention or treatment of dementia in the next 20 years, although if there is an increase in investment in R&D for dementia this may change.
- We need to plan for an increased demand for services in dementia over the next 20 years, which will have a significant impact on the cost to the country of the NHS and Social Services.
- There is a lack of investment in the development of therapeutic treatment for mental illness.
- The debate lines are being drawn between those who think that performance-enhancing drugs should become a part of everyday life and those who think they should be banned, just as they are in sport.
- There is an immediate need for Government to build on the work of Foresight Drugs Futures 2025? and the Academy of Medical Science's Brain Science, Addiction and Drugs [2008], including increased consultations on lifestyle drugs and developing a high-priority plan for public engagement.
- 'Lifestyle drugs' are being increasingly sought by the public; there is a need for a professional consultation on prescribing of psychoactive substances by health professionals.







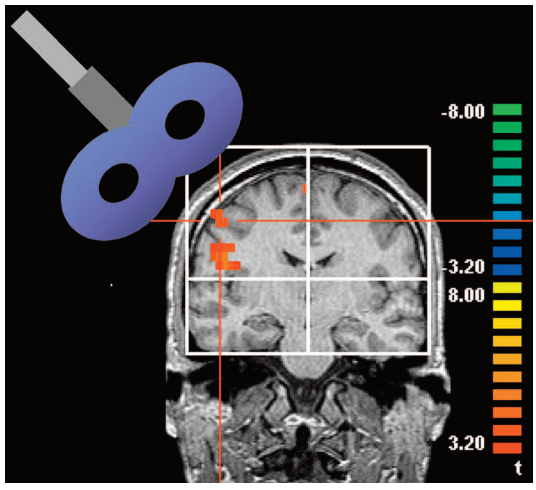


Fig 4: (top three images) Sites of significant correlation of emotional impact and blood flow changes by deep brain stimulation (Gjedde A, Geday J, 2009 Deep Brain Stimulation Reveals Emotional Impact Processing in Ventromedial Prefrontal Cortex. PLoS ONE 4(12): e8120. doi:10.1371/journal.pone.0008120)

Fig 5: (bottom image) Transcranial magnetic stimulation alters sensory perception and activity in sensory cortical areas (2005 Stimulating the Brain Makes the Fingers More Sensitive. PLoS Biol 3(11): e408. doi:10.1371/journal.pbio.0030408)

4. Synthetic Biology

Definition and Description

Artificial life on this planet won't start with cyborgs but with a tiny, artificial, single-celled organism. The best understanding of synthetic biology ('synbio') can be summarized as *the deliberate design of biological systems and living organisms using engineering principles.*[146] All the components are familiar, but advances in the speed[xx] and scale of existing technologies have moved theories of biological re-creation closer to reality.

Classroom biology largely consists of gaining understanding through reductionism – how does it work? - the analysis of animal, mineral and vegetable into their smallest components, moving from the functioning whole to a gross understanding of the physiology (interactive networks and cells, tissues, organs, organelles) to the fine underlying networks and pathways to the baseline DNA, genes and chemicals.

Synbio takes the ingredients above and asks what can we make? It starts with the individual subunit bases of DNA, adenine (A), cytosine (C), guanine (G) and thymine (T), or the full gene (a locatable genomic sequence of DNA on a particular chromosome) and an understanding of the information encoded in the gene. It is now possible to computer design the DNA sequence and synthesise it in the lab. Short sections of sub-gene length DNA are called oligonucleotides ('oligos' for short). Some researchers are concerned with using these oligos to reengineer existing life forms, others with making 'minimal' cells – cells with the minimum number of genes required to function. DNA building blocks called 'biobricks' can be created or existing natural genetic components used to design novel genetic sequences.

Balmer and Martin[147] have 'crudely' grouped the major areas of synbio research under the following headings: making minimal genomes; designing modular components; pathway engineering; expanding the genetic pool; production of artificial cells; and creation of synthetic biomolecules.

Examples

This complex science is in its infancy, but the potential applications are enormous. Much investigation and research is being undertaken by non-medical organisations because of the prospective industrial applications. Despite this there is already significant promise for health through the production of synthetic forms of molecules, more targeted drug delivery and vaccines.

Chemical synthesis

In 2002, Eckard Wimmer successfully completed a 3-year effort to create a polio virus from scratch[148] using published DNA sequence information and mail-ordered raw materials.

Engineered bacteria

In 2004 man-made *Artemisinin*[xxi] [149] for the treatment of malaria was produced. The significance of this is that 'artimisinin combination therapies' (ACTs) are the drugs of choice to treat malaria but they are much more expensive than traditional monotherapies such as Chloroquine partly because of the unpredictability of the parent plant crop Artemisia annua. It was originally hoped that a new synthetic 'blockbuster' ACT would be on the market by 2010 but according to the not-for-profit Medicines for Malaria Venture (MMV) earliest hopes are now for 2015.[150, 151]

In May 2010 Craig Venter of J. Craig Venter Institute in Rockville, Maryland announced he had created 'artificial life'. His team made a synthetic copy of a bacterial genome (of 500 genes - we have about 25,000) and inserted it into another live host bacterial cell whose own DNA had been removed. This second cell was then only being controlled by the synthetic genome, as it is the DNA in the genome that directs the cell's activities. So this combination of synthetic genome plus the (already live) host was something totally novel, and the proof that it 'worked' was that this new bacteria went on to divide in the normal way that bacterial cells do.

While this was a significant achievement which took 15 years and £30m to create, we would argue however against the Economist's claim that 'mere mortals have now made artificial life' for two main reasons. Firstly it was a copy of an existing, naturally occurring genome; (all synthetic molecules and organisms so far are copies) and secondly it wouldn't have got anywhere without the live host cell, and all the essential stuff (polymerase enzymes, ribosomes, mRNA, mitochondria, cytoplasm) that the host cell contained. Venter hadn't created new life-giving chemicals or designed a previously unknown live creature. What is hugely impressive is that after a couple of rounds of cell division, all cell components would have been coded or directed by the synthetic genome, bar the mitochondria.

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xx For example, the speed at which DNA can be synthesised increased more than 500 times between 1990 and 2000.

xxi Artemisinin, commonly known as wormwood, has found limited use because of the cost of extracting it from plant sources. At present, farmers in East Asia and some parts of Africa are growing wormwood for medicinal production. Thanks to synbio the gene responsible, amorpha-4,11-diene synthase, and the mevalonate isoprenoid pathway from Saccharomyces cerevisiae have been engineered into an Escherichia coli for mass production. Due to increasing resistance to other drugs, the synthetic artemisinin holds significant promise for malaria victims worldwide.

Although the speed of DNA synthesis and experimentation is increasing, the staggering complexities of gene expression, incompatibility of genetic 'parts' and unpredictability of the cellular 'circuits' still constitute massive hurdles to 'progress'.

Synthetic biomolecules - modified proteins

Using established genetic techniques, proteins have been modified so that they can detect brain inflammation and disease.[152] Possibly on the edge of what can be defined as synbio, a synthetic glycosylation process has been developed by Glycoform[xxii] to produce a more predictable mimic of EPO to help manage anaemia in people with chronic kidney disease.[153, 154]

BioNanoSwitch

The hope is that this device[xxiii] will allow observation of how drugs interact with genes, interfacing with artificial limbs, and improving the application of field dressings in combat.[155]

Examples of International Activity

EU

The New and Emerging Science and Technology (NEST) programme under the EC Framework Programme 6 (FP6) Funding round has provided early stage grants for 18 synbio research and policy projects. TESSY (Towards a European Strategy for Synthetic biology), a 2-year project that ended in December 2008, was funded by NEST and aimed to highlight opportunities and recommendations for different stakeholder groups with a view to advancing synbio in Europe. Also, the EU has supported 13 partner institutions under the banner 'PACE' (Programmable Artificial Cell Evolution) which has, as its mission statement, 'the goal of bringing the binary and living worlds closer together'.[156] ***SynBioSafe*** was a project under the auspices of NEST that looked at the social, security and ethical aspects of synbio. The project produced a series of publications with some final commissions due to be published in June 2009. The project's funding came to an end in December 2008 but it still seems to be active!

USA

The USA dominates this research area, based on numbers of scientific publications, scientists involved and funding, as well as by provision of post-graduate courses for students. It held its first national meeting on the subject at MIT in 2004. Funding comes mainly from the NIH and the Government Defence and Energy Agencies. It has a Governmental Office of Biotechnology Activities.[157] Other notable ventures include University of California (with Jay Keasling leading the development), MIT and J. Craig Venter Institute. Certain think tanks in the USA have taken a keen interest in the development of synbio. The Alfred P. Sloan Foundation has funded SynBioSafe projects in Europe and is funding a significant programme of work at the J. Craig Venter Institute looking at the regulatory framework around synbio. Both the Hastings Centre and Wilson Centre have hosted events or produced research considering the implications of the science. The American Association for the advancement of science published a document addressing the security risks of biological research.[158]

The USA based ***Biobricks Foundation (BBF)*** instigated the flagship series "Synthetic Biology x.0" of international conferences in 2004. 'SB 4.0' took place in Hong Kong in 2008, bringing together researchers who worked in the fields of biological parts and systems design and build or enabling technologies and leaders with an interest in the educational and policy implications of this science.

China, Japan and India have all demonstrated growing investment in this technology. The iGEM[159] competition is a handy barometer of those countries showing most interest.

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xxii *www.glycoform.co.uk*

xxiii This molecular device "... is invisible to the naked eye, and is about one-thousandth of a strand of human hair in size. The switch comprises a strand of DNA anchored in a miniscule channel of a microchip. A magnetic bead is attached to the DNA, and a biological motor powered by the naturally occurring energy source found in living cells – adenosine triphosphate (ATP) – will 'pull' the DNA and therefore the bead. These elements working together create a dynamo effect which in turn generates electricity.
The result is a device that emits electrical signals – signals that can be sent to a computer. The switch therefore links the biological world with the silicon world of electronic signals."

Strengths

Although researchers have had the basic knowledge for this science for over 35 years, only in the past few years has the technology been available to enable the knowledge to be turned into reality.

In higher education, the first Masters course in synbio started in the Autumn of 2008 at Imperial College, London. The University of Nottingham, produced a comprehensive report in May 2008 on the Social and Ethical Challenges, written by Andrew Balmer & Paul Martin of the Institute for Science and Society.

There are six Biotechnology and Biological Sciences Research Council (BBSRC) funded networks now in a number of other leading Universities and also a large Engineering and Physical Sciences Research Council (EPRSC) funded project on the Chell led by Cameron Alexander at Nottingham.

There is a growing amount of pan-European activity. UK Universities involved in UK-EU consortiums include:

- the University of Portsmouth, which is the coordinating centre and holds the patent for the BioNanoSwitch [see above];
- Oxford University, which is involved in the development of 'Nanomot', a pan-European project to "create a complete platform comprising a modular 'toolbox' of versatile sub-cellular building blocks that can be assembled into robust functional units such as chemical nanoreactors, nanoactuators and nanoengines. Proof of concept will be provided by demonstrating that the blocks can be combined into a prototype drug delivery device;"
- Southampton University, which is the coordinator for the Neonuclei project, which aims to create synthetic analogues of cell nuclei capable of self-assembly in a biological setting;
- MRC Cambridge, which is involved in the Orthosome project, aiming to create an artificial genetic system;
- Imperial College, which is taking part in the Probactys project to produce programmable bacterial catalysts.

Since 2003, the Massachusetts Institute of Technology (MIT) has coordinated an international Genetically Engineered Machines competition (iGEM) in which undergraduates learn about synbio by designing and building a 'genetically engineered machine' during their summer vacation. In 2008, 84 teams from 21 countries entered, with the UK sending six teams (2nd highest after USA) from Sheffield, Newcastle, Bristol, Cambridge, Imperial College and Edinburgh. Imperial College won two prizes and all but one team won medals. In 2009, 110 teams competed with the UK again performing well and winning prizes.

Activity in regulation and development:

- The Biotechnology and Biological Sciences Research Council (BBSRC) established in 2006 a working group involving seven universities: UCL, Birkbeck; Nottingham; Cambridge; Edinburgh; Bristol; Durham; and Sheffield.
- The Royal Society of Chemistry held a chemistry-biology interface forum conference 'chemistry to engineer new biology'[160] in September 2008.
- The Foreign and Commonwealth Office held a seminar on oversight, education, awareness raising and codes of conduct with the aim of preventing misuse of the life sciences.[161]
- The Royal Society (RS) held a discussion meeting in June 2008.[162] RS has a 'Synthetic Biology and Policy' coordination group.
- The Biomedicine and Society (BIOS) centre at the London School of Economics has projects looking at the socio-political and regulatory challenges arising from synbio.[163]
- The Academy of Medical Sciences and Royal Academy of Engineering published the 2007 report on Systems Engineering.[164]
- Brian Rappert at the University of Exeter has published extensively and runs international workshops on cross-cutting issues surrounding synbio; Malcolm Dando of Bradford University has been involved in raising awareness of the need for those involved in life sciences to consider bio-security issues.
- Jane Calvert at the University of Edinburgh has written extensively on intellectual property and commoditisation of synbio having previously researched gene patenting. She spoke at the first 'RoSBNet' synbio network meeting in September 2009 at Oxford.

Weaknesses

Translation

"It is far more problematic to translate this knowledge into real world applications outside the laboratory".[165] Yet it needs to be remembered that it is very early days for this science and the challenge of translation is both a motivating factor for researchers and a reassuring truth for the public.

Capacity
Although there is the BBSRC network, only in autumn 2008 did the first Masters course in synbio begin at Imperial College and UCL. There is only one DNA synthesis company in the UK compared with 24 in the USA and 5 in Germany.

Impact on trade and development
Where natural products have formed the basis of pharmaceuticals such as wormwood, there are associated local production economies. If synthetic *Artemisinin* becomes commercially available it would ensure that no local production in East Asia or Africa of the natural product could be maintained, but whether the impact will be significant is questionable.

Intellectual Property
Where synthetic processes and building blocks are patented even before the end-product itself is likewise protected, there is concern that the potential for development of synbio will be stifled as many patents being filed are both broad in scope and speculative. MIT has tried to overcome this through the development of its Registry of over 2000 standardized biological building blocks (BioBrick parts) based on an Open Source model. These DNA sequences can be used by any researchers with the conditions that they report any improvements, modifications or new biobricks back to the Registry. It is probably necessary that a review is taken of the intellectual property procedure both to see if standard patent criteria are really being applied but also to ascertain whether progress in health and other arenas is being hampered by unnecessary protectionism.

Governance (see also Threats: Risk to public health)
While the governance of new technologies has received a lot of attention [see opportunities], there is clearly room for improvement. The consequences of the lack of a mandatory framework were demonstrated in 2006 when a Guardian journalist was able to obtain part of the DNA sequence of the smallpox virus from a DNA synthesis company.[166] Likewise in January 2009, New Scientist ran an article on 'The rise of the garage genome hackers' in the USA, featuring home laboratories assembled by enthusiastic amateurs with reagents and parts obtained from sources ranging from specialist suppliers to e-bay. It featured the group DIYbio, which was formed in 2008 to co-ordinate the enthusiasts and their response to worries about oversight of what they do; it has appointed leading Harvard synthetic biologist George Church as its academic advisor. He reasons that the more people work in this area, the more likely we are to find answers to our healthcare and energy crises. Again there is disagreement as to the significance of this 'weakness' due to the inherent complexity and difficulties of this science. Five years ago, however, Church also said that the consequences of biohazards "loom larger than chemical and nuclear weapons, since biohazards are inexpensive, can spread rapidly world-wide and evolve on their own".[167] Obviously everything should be done to encourage open engagement without repelling 'DIY' enthusiasts with burdensome bureaucracy, but at the same time society should be reassured with statements of purpose, monitoring of supply of components and a mandatory registry of research 'trials'. A framework covering some of this was published by the J. Craig Venter Institute, "Synthetic Genomics: Options for Governance", in 2008; if it was all implemented, it would go a long way to reassuring both governments and the public of safety precautions, though it doesn't include the compulsory registration of research trials. This is not compulsory in other disciplines either but there is a welcome move among academic institutions, e.g. Oxford University, to insist on registration of all trials before they are authorized.

Opportunities

- Reduced costs and improved access: Production of chemicals or compounds which are difficult to obtain from natural sources.

- The BioBricks Foundation, based at MIT, has a registry of standard DNA parts as mentioned above which are made freely available and which produce predictable effects. As this registry is expanded and gains popularity it should help ensure faster progress and act as a bastion against protectionism.

- $42.5m was invested by Gates Foundation into synthetic biology research in 2004, and it has recently announced funding for further 'unusual' research. With Government support, now would be a good time to enable more Universities to get involved in this speciality.

- The majority of research is focused on the field of bio-energy. This might not seem controversial or relevant to health, but the crop yield needed to sustain what is being dubbed the new "sugar economy"[xxiv] would mean there would not be enough land to grow crops for food. Public health crises would spiral.

xxiv This is because industrial production will be based on biological feedstocks (agricultural crops, grasses, forest residues, plant oils, algae, etc.) whose sugars are extracted, fermented and converted into high-value chemicals, polymers or other molecular building blocks.

Chance to review Governance

The UK Scientific Advisory Committee for Genetic Modification (SACGM) Compendium of Guidance asserts that synthetic biology is covered by current Genetic Modification regulations (However the guidance that SACGM is only that, guidance for good practice).

Also in place are the recent guidelines from the OECD [168] which set out principles such as licensing of 'genetic interventions' and examples of best practice for health care inventions in the international context. They seek to foster the twin objectives of stimulating innovation, while maintaining appropriate access to health products and services. As awareness grows of synbio amongst academics, there is the ideal opportunity and time to have a review of future synthetic biology regulations, some of which is already being undertaken by the BBSRC.

Health Potential

Most of these are beyond the time frame of this report but to give an indication of the expected potential some hoped-for applications are noted:

1. Production of synthetic forms of hard to obtain, unstable or expensive drug components such as Artimisinin described at the beginning.

2. Smart drugs target or programmed to release at a particular location in the body.

3. The study of genome evolution and the expansion of ribosome function could enable the production of more efficacious protein therapeutics, for example, human growth hormone.

Threats

Public Health concerns

Broadly, public concern will revolve around risk of application; life scientists concern revolves around risk of 'GM' type rejection; security specialists concern revolves around ignorance.

'Dual Use' refers to the potential for research and development to be applied both malevolently and benevolently. Alexander Kelle of the Synbiosafe project in his 2007 Synthetic Biology & Biosecurity Awareness in Europe report quoted the biosecurity expert Malcolm Dando of Bradford University on risk awareness. *"Life scientists, according to Dando, do not share the threat perception widespread among biosecurity experts concerning bioterrorism or biological warfare. They don't think that their own work might contribute to the threat. Life scientists have practically no knowledge of debates within and concerns of the security community and they have no knowledge of legally binding international regulatory instruments, such as the Biological Weapons Convention (BWC)."*[169]

So for instance, smart drug technology could also be used to deliver toxins to particular cells of the body, rather than restorative therapies. Or new viruses and bacteria could be created that were destructive rather than therapeutic.

Environmental contamination due to the potential living, breeding nature of some of these synbio applications is another area about which the public need to be reassured, on top of the malevolent use of these technologies. This could take the controversy about GMO's to a new level: NB international Biosafety Protocol uses the term Living Modified Organisms (LMO) to highlight their potential to multiply and distinguish the organism from the product (e.g. food). The Canadian ETC organisation has undertaken an in depth critique, and their press release on their 2007 Synthetic Biology 'Extreme Genetic Engineering' report[170] stated, *"The danger is not just bio-terror, but bio-error"*, concluding, *"ETC Group's new report concludes that it is not enough to regulate synthetic biology on the national level. Decisions must be considered in a global context, with broad participation from civil society and social movements. In keeping with the Precautionary Principle, ETC Group asserts that - at a minimum - there must be an immediate ban on environmental release of de novo synthetic organisms until wide societal debate and strong governance are in place".*

There is no doubt that the synbio community needs to be part of a very public Human Genome Project (HGP) ELSI type approach (detailed in chapter 4) to building confidence if it is to be able to develop and deliver on its promises. The public needs to be reassured about strong governance of synbio, which currently is not in place. The comprehensive approach of the Human Genome Project and lessons learned from the GM crop scare need to be applied. Their concerns are not only about malevolent use of technology (deliberate), but also laboratory accidents (weakness) and unintended consequences (ignorance).

Intellectual Property

(see weaknesses)

From the Royal Society meeting on Synbio in June 2008: *"There are unresolved ownership and intellectual property issues. It was suggested that these must be addressed in the near term to avoid future difficulties. Participants relayed that there are already some tensions between scientists and universities around innovative academic research on for example biofuels."*

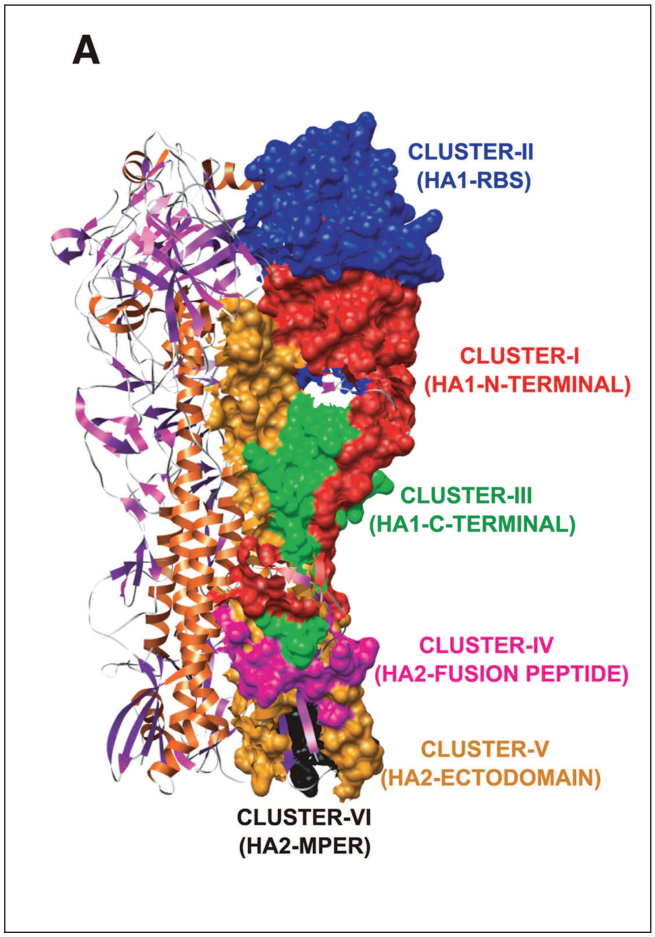
Life

Science fiction has focused on the concept of artificial intelligence and the prospect of humanoid robots. In parallel with extraordinary developments in this field lie less-noticed, but perhaps in the long term more significant efforts to create artificial life through the field of synthetic biology, which seeks to build organisms (replicating current ones or devising quite new ones) through an engineering approach to the building-blocks of life. While still at a very early stage, governments in the UK and elsewhere have begun to channel significant resources into the research. Will it fundamentally

challenge what we mean by 'life'? What are its risks if something goes wrong - or maybe if it goes right?

The Bottom Line

- Synbio is the deliberate design of biological systems and living organisms through the application of faster and refined biotechnologies and engineering principles.
- There is a lot of (seemingly fragmented) discussion within the scientific community about the application, safety and regulation of this science.
- However this is a high-risk science because of the applications of research. Most awareness of this is among those who have worked in the arena of biological and toxic weapons but there is little evidence for life scientists knowing or thinking about the risks, regulations or thinking through the repercussions of their experiments.
- The artificial replication of hard- or expensive-to-acquire substances could bring huge benefits to health care, however this science is new and we should beware of too much hype.
- We feel there should be a review of prioritisation of funding for research, overseen by a body which is guided by core values.
- This is the science, not robotics or Artificial Intelligence, that opens up the questions on "what is life?"



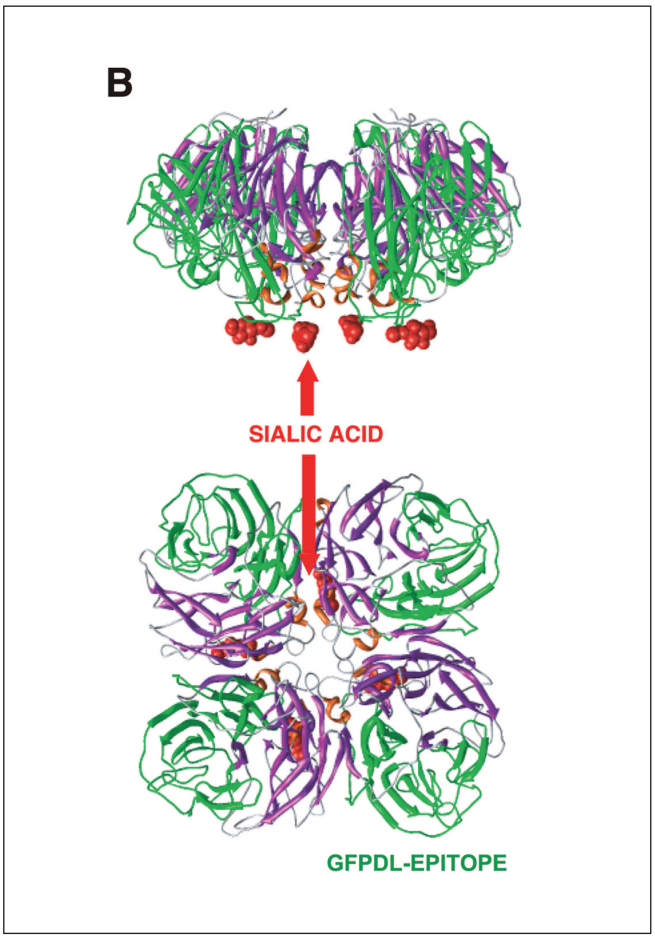


Fig 6: Main antigenic clusters in the structures of haemagglutinin and neuraminidase recognized by antibodies from H5N1 virus infected individuals (Khurana S, Suguitan AL Jr., Rivera Y, Simmons CP, Lanzavecchia A, et al. 2009 Antigenic Fingerprinting of H5N1 Avian Influenza Using Convalescent Sera and Monoclonal Antibodies Reveals Potential Vaccine and Diagnostic Targets. PLoS Med 6(4): e1000049. doi:10.1371/journal.pmed.1000049)

Part 3
New technologies under the microscope

Appendix 2
Other developing technologies

In the preceding appendix we took a more in depth look at what we considered to be the four most immediate and significant emerging technologies for policy makers. However there are many other technologies, some of which overlap with those four, which are gaining ground and which have healthcare applications. We wanted to go into a little more detail than we had in part 1 with some of these, although on the whole we have focused on direct relevance rather than progress with diagnostic or processing technologies. All are noteworthy, but only time will tell whether they will deliver what some of their proponents claim for them.

1. Nanotechnology and Nanomedicine

Nanotechnology is not new! It is a term used to describe the control of structure and behaviour of processes and particles in the natural sciences on a tiny scale, such as atoms and molecules, which scientists have known about for centuries. What's newer is the term 'nano-' which prefixes a variety of terms to indicate that the scale is miniscule i.e. 1 nanometre = 10^{-9}m,[xxv] and the fact that since the end of the 1980s the atomic force microscope allowed us to 'look' at these entities for the first time.
When the scale of particles is so small, the scope for exciting novel applications but also unintended consequences is significant.

Nanomedicine is a rapidly expanding field aimed at healthcare using molecular tools and molecular knowledge of the human body. The focus tends to be on:

- using different cellular delivery systems by nanoparticles of larger therapeutic molecules;
- improved analysis and disease detection;
- developing nanoscale support structures for human tissue engineering.[171]

Examples of Functions and Applications

Nanoshells:** Enable targeted therapy. By varying the size of the nano-core and the thickness of the metal covering, the nanoshell can convert light into heat. If the nanoshells are directly injected into the cancer tumour and radiated with the relevant wavelength of light, they destroy only the cancer cells.[172] Alternatively the nanoshells are combined with antibodies that only bind with the cancer cells. In this way they can then be irradiated, either to burn the cancer cells directly, or to release anti-cancer drugs directly into cancer cells.[173] Could replace and revolutionise oncology as chemotherapy and radiation destroy both healthy and unhealthy cells.

xxv or conversely 100,000nm = 1mm.

Nanowire sensors* are designed to detect disease including home-cancer detection kits[174] or make DNA testing much faster, cheaper and more convenient that microarray techniques used now.[175, 176]

Nanopharmaceuticals - where the reduced size of particles (e.g. liposomes,[177] nanocrystals[178]) enable greater solubility (so drugs can be taken orally) and greater reactivity (lower concentrations required). Already being applied.

Nanopores* - molecular detection and analysis – with a British company a leader in the cheaper DNA sequencing race.[179]

Known values, legal, safety and societal considerations

- The 'Nanodivide' has been postulated where the gap between developed and developing countries turns into a gulf and exacerbates already existing health inequalities.
- Safety and toxicity concerns include the side effects of nanomedicine e.g. how the body gets rid of nanoparticles is unknown. Research last year also raised concerned about the carcinogenic properties of some nanomaterials.[180]
- Dual use of this technology is where therapies designed for treatment could be used maliciously for instance in deliberate infection, and easily because the 'product' is so small and easily obtainable.
- There is a sense of a nano-race: the pressure to commercialise however must not trump safety concerns.

Economic Value

The hope is that 'nano' will mean faster, cheaper and better in medical care. The major investment by venture capital in R&D in health applications are indicative of the high expectations of rewards.

**Application hope within 5 years;*
***Application not for 10 years min*

2. Neuro-imaging

Positron Emission Tomography (PET) - building on the technologies such as CT scanning, PET provides information on metabolic activity or body function.

Functional magnetic resonance imaging (fMRI) detects changes in brain activity associated with specific cognitive functions by identifying increased blood flows in regions of the brain during a task.

Functions and Applications

Both healthy and diseased brains can be studied with regard to memory, learning patterns, emotional responses, drug effects or the impact of marketing techniques. Possible research and diagnostic future applications include:

- early pre-symptomatic diagnosis of neurological diseases e.g. dementia,[181] Alzheimer's and Huntingdon's;[182, 183]
- accuracy in neurosurgical planning;
- pain management;
- improved understanding of neurological disorders, cognition and human behaviour;[184]
- censorship? Evidence for violent media images link with reduced self-control abilities;[185]
- the assessment of patients in the vegetative state;[186]
- neuro-economics and understanding how humans make decisions;
- sophisticated pattern recognition techniques could be used to create new brain-machine interfaces to allow the disabled to control machines simply through thought.

Known values, legal, safety and societal considerations

- Artificial brain enhancement, whether in the form of drugs or implants, could raise questions about what is normal versus what is artificial brain activity.
- There are concerns over the dual-use of pattern recognition technology to predict human behaviour or read human thoughts.[187]
- Nature/nurture: advanced neuro-imaging could raise questions about individual responsibility if brain structures are shown to be 'hard wired' for certain character traits. For example, is a murderer born a murderer? This might ultimately have implications for public policy.
- 'Brainwashing' and 'Neuro-marketing' are already areas of growing interest, especially in the United States; this may ultimately require regulation to ensure that people cannot exploit knowledge of brain function to serve commercial or political ends.
- Issue of free will, many studies have shown that brain activity controlling say a motor movement precedes the conscious reporting of that movement.

Economic Value

1. Contribution to the understanding of neural disease, but only if preventative application found.

2. Worth of pain control difficult to estimate - however the cost to the economy is significant as 500m days off per year are taken across Europe due to uncontrolled pain.[188]

3. New security techniques if technologies such as 'mind-reading' are used correctly.

4. Neuro-economics and decision-making field could lead to better understanding of economics and the choices that people make.

3. RNA Interference

RNA – Ribonucleic Acid - is the messenger molecule between DNA and protein synthesis. The hope is that if the RNA molecule can be interfered with [RNAi Therapy] then we can regulate genetics and inheritance. Undesirable genes could be turned off - 'silenced'. This technique is used in Biotechnology & Gene therapy. However the latest evidence disputes this ability to 'turn off' genes.

RNAi was nominated 'Breakthrough of the year 2002' [Science] and is in the Massachusetts Institute of Technology's [MIT] top 10 emerging technologies of the future.

Functions and Applications

Research: 'Small interfering' siRNAs are widely used for assessing gene function in cultured mammalian cells or early developing vertebrate embryos.[189]

Therapy: e.g. RNAi-based antiviral therapeutics;[190, 191] *Bevasiranib* uses RNA interference (RNAi) to silence genes that promote the overgrowth of blood vessels that lead to vision loss in wet AMD[192] and in diabetes; Other indications are that specific cancers, HIV, spinobulbar muscular atrophy and even obesity could be targeted using short-interfering RNA.[193]

Benefits

It shows the potential to 'silence' disease-specific versions of genes while leaving any normal copies unharmed so could be of value in both treatment and prevention of congenital conditions such as type 1 diabetes.[194]

It is short acting, so if undesirable side-effects elicited, when the therapy stops, so should the side effects.

Known values, legal, safety and societal considerations

Risks

- Unknown macro effects of turning a gene 'off' as only part of gene function known.

- Unintended consequences e.g. published in August 2008: using RNAi to cure wet AMD might actually increase the risk for blindness from dry AMD.[195, 196]

- Non-permanency will necessitate re-administration.

- Possible induction of interferon immune response to RNAi.

Economic Value

Easy to manufacture, no virus vector (transmitter) needed.

Massive potential – yet to be realized and complexity of gene sensitivity yet to be thoroughly investigated.

4. Robot Assistive Care

Many new technological applications are being developed to assist the elderly in the home and in care. Currently these range from simple robotic devices for feeding the less able to devices for assisting mobility to robots to provide companionship, aiding memory and monitoring. There are also a range of smart sensing homes being developed that provide safety for dementia suffers in the home e.g. monitoring systems to make sure that the cooker has been turned off or feedback system to ensure that the elderly can find their way to the toilet or remember to take their medicine.[197] The major developments are currently in Japan but there are smart sensing homes, funded by the Engineering and Physical Science Research council, UK that are currently being piloted.

Functions and Applications

Japan has an aging population problem with nearly 19% of its 130 million population aged 65 and over. This is expected to rise to 40% by 2055. There response has been to aim for a technological solution – bring in the robots.

Benefits

The main benefit is to improve the quality of life of the elderly by keeping them out of care homes for longer. A second, the main motivation for the Japanese, is that with a relatively smaller number of working age people, they will not be able to spare enough of them for elder care.

Known values, legal, safety and societal considerations

The main ethical considerations are tradeoffs between keeping the elderly safely in their homes for longer and maintaining their dignity, privacy and human contact.

(i) With a shortage of care workers and increasing technological sophistication in robot care and monitoring, old people may find themselves without human contact for longer periods of time. Emergency staff will be available when monitors alert them.

(ii) Robot companions with AI can be viewed as a form of deception

(iii) There are privacy issues with the intensive types of monitoring available. Who will have access to memory devices and data on companions?

(iv) The use of robot companions can be seen as infantilizing the elderly

(v) In keeping the elderly safe from harm, robots may imprison and disempower them.

Economic Value

Service robots are the biggest growth area in robotics predicted by a recent World Robotic Report to hold a 70% share of the robot market by 2010. A recent survey has found that while there are currently 1.6 million operational industrial robots on the planet, there are already nearly 4 million service robots. There are not just for elder care but it gives an idea of the market.

5. Robots/AI and medicine

As opposed to providing 'care' or monitoring in health, there are also developments in robotics that are designed to provide alternative therapies and means of treating patients. Medical robots for surgery are already on the theatre floors of many hospitals in the UK, although some surgeons we spoke to said their main advantage so far was for hard-to-access areas such as pelvic surgery.[198] It was the subject of a BBC programme in 2008 featuring Lord Darzi as a proponent of robotics in medicine. The programme was presented by Professor Lord Winston in who was sceptical of their current use. The programme also feature robot doctors (visiting wards), enabling surgeons based elsewhere to talk to their patients in absentia.[199] This enables people to see and communicate with their own doctor after surgery even if on a robot, which they prefer to seeing a different doctor. In addition it enables doctors to see highly infectious patients or patient suffering from biochemical exposure or radiation.

Functions and Applications

1. Robot delivery - picking up patient to take them to places in the hospital.
2. Pharmacy robots – mixing drugs and finding and delivery drugs to pharmacists.
3. Robots for training – delivery babies and resuscitation.
4. Micro-robots for clearing arteries are under development in Korea,[200, 201]
5. Organ biopsies – medical robot 'Pneustep' – carries out organ biopsies during MRI scan – made of plastic and powered by light and air.[202]
6. AI systems to assist with diagnosis.
7. 2007 micro robots for carrying cameras including 'bugbots' and therapeutic capsule endoscopes[203, 204] being developed at the Carnegie Mellon University. These applications and their benefits were debated by Professor Winston and Professor Noel Sharkey on Radio 4's 'Today' programme in August 2008 and followed up by an article in the Guardian.[205]

Benefits

There are great potential benefits for robot surgeons. They can work inside an MRI machine to help neurosurgeons, as they become more portable they can be taken to the scene of an accident, e.g. a motorway pile up, to save time as the biggest problem is getting patients back to the hospital. This will also be good for serious emergencies and quarantines.

Known values, legal, safety and societal considerations

While the robots are remote controlled the main ethical consideration is the patient's right to have human contact and care. However, the contact and care does not have to come from the surgeon. Although the surgeon can operate remotely, other staff can be on hand to care for and provide the appropriate bedside attention, as well as talk to relatives.

If we reach a point where routine surgery such as removal of appendices can be carried out autonomously with little attention from medical staff, there may be some danger in treating patients as objects on a production line. But this need not happen if society and the medical profession are careful to lay down strict guidelines.

Economic Value

This could have considerable economic value. US products such as the very expensive Da Vinci system are selling very well on a worldwide basis. The UK has a solid skills base for manufacturing this equipment as has been show by the Imperial College medical surgery group. Moreover, with a shortage of skilled medical staff, robot surgery could help to reduce hospital waiting lists and thus save money.

6. Stem Cells & Regenerative Medicine

This technology continues to develop and in the case of adult stem cells, has been utilized for many years. Stem cells are 'starter' cells that can grow into any type of adult tissue e.g. nerve or muscle or act as a repair system for the body replenishing specialized cells, and can also maintain the normal turnover of regenerative organs, such as blood, skin or intestinal tissues.

Their forms can be:

1. human Embryonic Stem Cells [hESC] that were first isolated in 1998 (17 years after they had been in mice). They can theoretically differentiate into any tissue form;

2. adult or somatic stem cells are non-specialised (undifferentiated) cells found amongst specialised (differentiated) cells in a tissue or organ. Their origin is unknown.[206] It is argued that many of these should be called 'progenitor cells' as they don't have the ability to replicate indefinitely in the way that stem cells do. They act as a 'repair system' for the body;

3. induced pluripotent stemcells [iPS], a process developed in 2007 by Prof Yamanaka, enabling adult cells to be forcibly taken back to artificial, embryonic-type form. This research had been enabled by previous research on hESC.[207] There are some whispers of dispute however in some quarters with the concern that these cells are cancerous transformations.[208] Further trials and monitoring is necessary.

Once stem cells are isolated they can replicate indefinitely creating what is known as a 'stem cell line'. Regenerative Medicine is the attempt to harness the natural healing powers of the body and to design new materials to replace or aid the repair of diseased or damaged tissue using stem cells.

Functions and Applications

"Bone regenerates quite readily, so the challenge there is more of an engineering problem," says Professor Shakesheff. *"But looking at the heart and liver and using stem cells to see if we can encourage them to grow is a completely different matter. I suspect we'll still be working on those in 30 years' time."* [209]

Applications of adult stem cells[210] include leukemia, lymphoma and various blood disorders [all available on the NHS], cartilage regeneration,[211] prolonged insulin independence in type 1 diabetics[212] [piloted], Crohn's disease[213] heart disease, reconstruction of neuronal pathways in e.g. Parkinson's or Alzheimer's and 80 other applications.[214] Adult blood forming stem cells from bone marrow have been used in transplants for 30 years.

As far as embryonic stem cells go, the regeneration potential of these cells is the subject of thousands of clinical trials and although there are no treatments yet available, there has been a substantial gain in knowledge of cellular development and potential drug responses from research. One recurrent obstacle is that these cells also give rise to tumour formation[215] but it is hoped that iPS cells will overcome this problem.

For iPS, it's early days in experimentation with these cells but there are already iPS cell lines being generated for experimentation in cardiovascular disease, diabetes and neurology. Human neural cells derived from iPS cells have been used to treat spinal cord injury in mice.[216] After 7 weeks the effects were still present and further monitoring was planned for 6 months to check whether any tumours grew (results of this monitoring could not be found at time of print).

Known values, legal, safety and societal considerations

- The drive to capitalise on embryonic and iPS cells is huge; a leading proponent in the field, Professor Weissman, commented at last year's international symposium that *"The approach of different peoples to stem cell research in each country differs according to their religion, politics, and ideologies. In creating international standards, we won't achieve anything if we try to make allowance for the regulations of each country to eliminate risk."*[217]

- There remain moral concerns surrounding tissue and cell sources (embryos, umbilical cord blood, aborted foetuses etc.)

- There is also major concern over the regulatory set up in the UK which is incredibly complex and off-putting to new investors, even in the uncontroversial adult stem cell field (see appendix 3).

- This area has received much attention in the press due to the claims that have been made by some that it will lead to many cures. While there are a growing number of researchers involved in this area, some no longer think that there will be a radical breakthrough in the near future. Potential public misunderstanding could also lead to funds being directed towards the wrong projects.

"When you are desperate any offer seems attractive, but stem cells and gene tests off the web are a no-no."[xxvi]
Sir J. A. Muir Grey.

Economic Value

Regenerative medicine using adult stem cells has already transformed the treatment of many diseases, although the techniques remain costly.

If regenerative medicine can begin to deliver on the hopes it has raised of reversing effects of degenerative diseases where the neural damage is localised such as Alzheimer's and Parkinson's (but not for example Multiple Sclerosis) it will transform society and generate huge economic benefits. Research detailed elsewhere in this paper indicate that this is at least a couple of decades away.

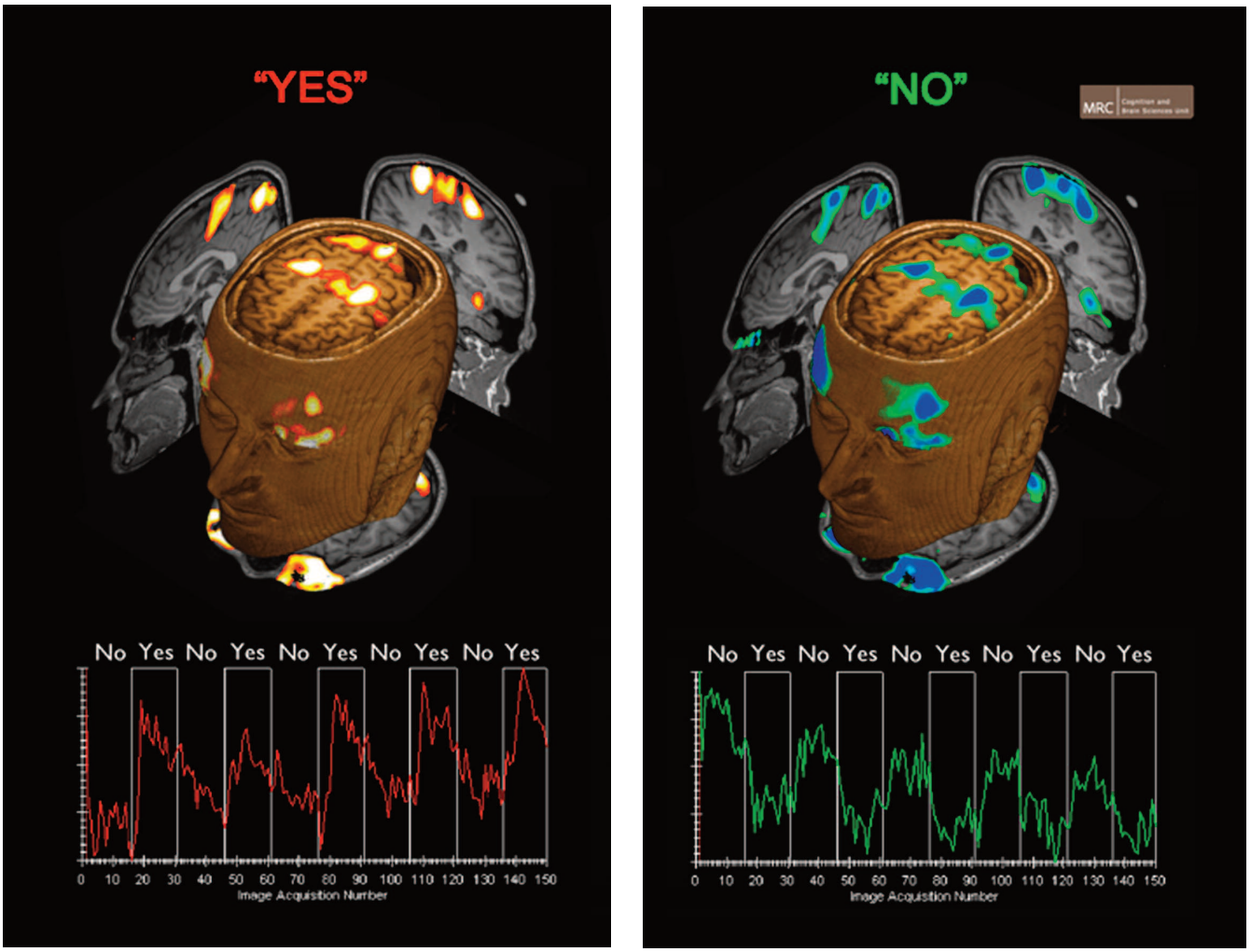


Fig 7: Neuro-imaging using fMRI was used to enable subjects to answer questions by modulation of their brain activity. This method led to one patient, formally thought to have been in a vegetative state, to be able to correctly respond to autobiographical questions. Image provided by Martin Monti, MRC Cognition and Brain Sciences Unit.

xxvi Director of the Clinical Knowledge, Process and Safety quoted on the NHS Choices website available at: http://www.nhs.uk/news/2008/12December/Pages/StemcelltherapyQA.aspx

Part 3
New technologies under the microscope

Appendix 3
EU overview of regulatory hurdles to clinical trials

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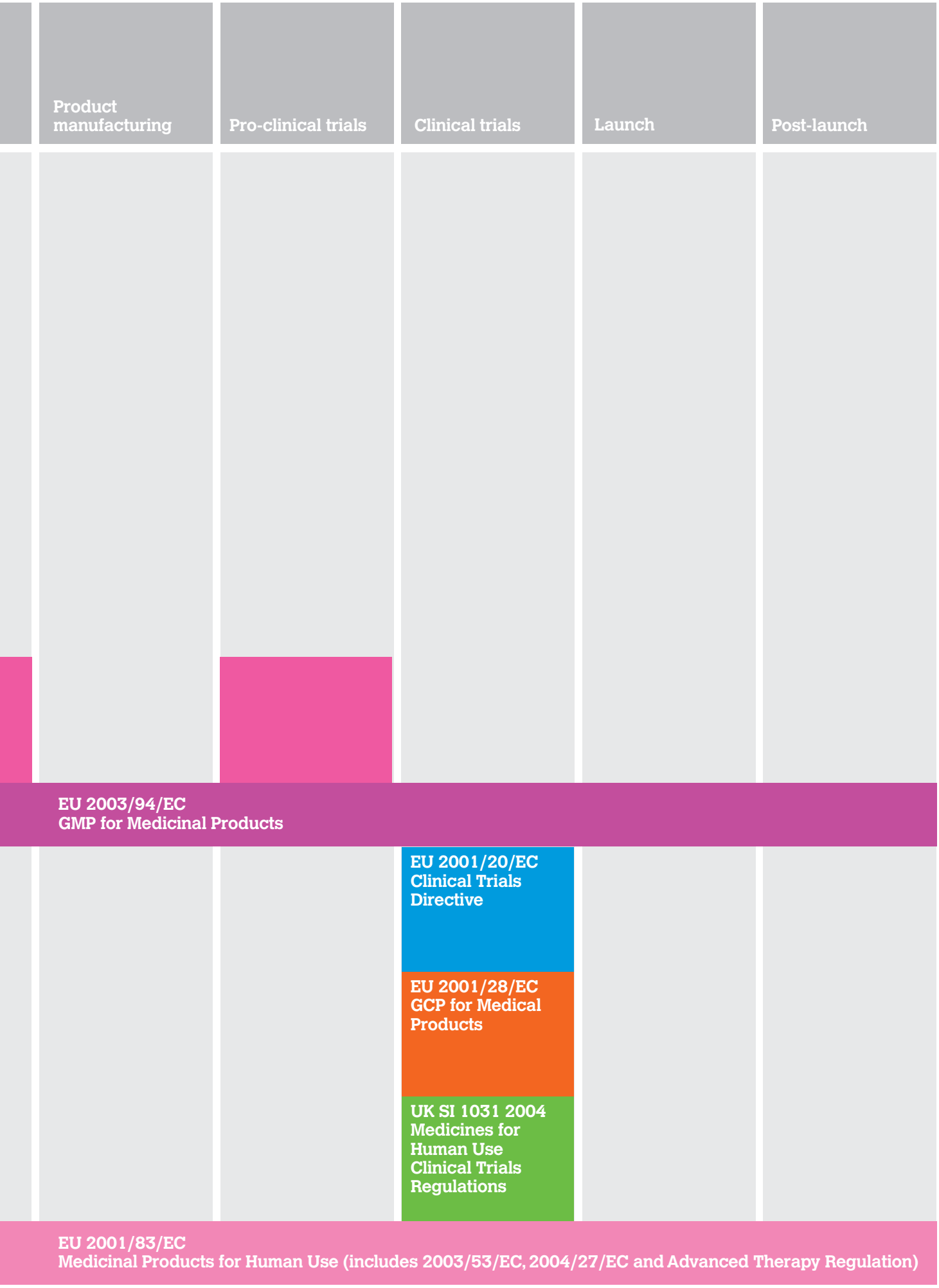
Product manufacturing
Pro-clinical trials
Clinical trials
Launch
Post-launch
EU 2003/94/EC
GMP for Medicinal Products
EU 2001/20/EC
Clinical Trials
Directive
EU 2001/28/EC
GCP for Medical
Products
UK SI 1031 2004
Medicines for
Human Use
Clinical Trials
Regulations
EU 2001/83/EC
Medicinal Products for Human Use (includes 2003/53/EC, 2004/27/EC and Advanced Therapy Regulation)

Part 3
New technologies under the microscope

Appendix 4
PGD single gene conditions

This is a list of conditions for which the Human Fertilisation and Embryology Authority (HFEA) has so far agreed are sufficiently serious that it is acceptable for medical clinics to test for them by using use pre-implantation genetic diagnosis (PGD). There is dispute around the their definition of 'serious' as many of these conditions are not life-threatening.

5 Alpha Reductase Deficiency (5ARD) insofar as that condition affects males, with simultaneous sex determination

Acute Intermittent Porphyria

Acute Recurrent Autosomal Recessive

Rhabdomyolysis (ARARRM)

Adrenoleukodystrophy (Adrenomyeloneuropathy)

Agammaglobulinaemia

Alpers Syndrome
alpha thalassaemia/mental retardation syndrome

Alports Syndrome

Alzheimers Disease - early onset

Anderson Fabry Disease

Androgen Insensitivity Syndrome

Aplastic anaemia - severe

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Barth Syndrome

Battens Disease (infantile)

Beta Hydroxyisobuyryl CoA Hydrolase Deficiency (Methacryic Aciduria)

Beta Thalassaemia

Bilateral Frontoparietal Polymicrogyria

Birt-Hogg-Dubé Syndrome

Branchio-Oto-Renal Syndrome (BOR)

BRCA 1 (increased susceptibility to breast cancer)

Breast Ovarian Cancer Familial Susceptibility (BRCA2)

Bruton Agammaglobulinemia Tyrosine Kinase (BTK)

Cardiac Valvular Dysplasia

Carney Complex

Central Core Disease of Muscle

Cerebral Cavernous Malformations (CCM)

Charcot Marie Tooth Disease

Chondrodysplasia Punctata
Choroideraemia

Chromosomal rearrangements (various)

Chronic Granulomatous Disease

Citrullinaemia type 1

Coffin-Lowry Syndrome

Congenital Adrenal Hyperplasia
(21 hydroxylase deficiency)

Congenital Fibrosis of the Extraocular Muscles

Congenital Stationary Night Blindness

Crouzon Syndrome

Cystic Fibrosis

Cystinosis

Czech dysplasia, metatarsal type also known as
Progressive pseudorheumatoid dysplasia with
hypoplastic toes

Diamond Blackfan Anaemia

Downs syndrome

Dystonia 1 Torsion Autosomal Dominant (DYT1)

Ectodermal dysplasia (Hypohidrotic)

Ectrodactyly, Ectodermal Dysplasia, Clefting

Syndrome (EEC)

Ehlers-Danlos Type IV

Epidermolysis Bullosa
(Hallopeau-Siemens & Herlitz junctional)

Facioscapulohumeral Dystrophy

Familial Adenomatous polyposis coli (FAP)

Fanconis Anaemia A

Fanconis Anaemia C

Fragile X Syndrome

Gaucher's Disease (Type II)

Gonadal mosaicism

Greig's Cephalopolysyndactyly

Haemophilia A
Haemophilia B

Harlequin Ichthyosis

Hereditary diffuse gastric cancer

Hereditary motor and sensory neuropathies

Homozygous familial hypercholesterolaemia

Hunters Syndrome

Huntingtons Disease (Huntingtons Chorea)

Hydrocephalus

Hydroxyisobuyryl CoA Hydrolase Deficiency

Hyper IgM Syndrome - Hypogammaglobulinaemia

Hypophosphatasia (Infantile/ Perinatal lethal)

Hypophosphatemic Rickets: X-linked dominant (Xlh)

Hypospadias (severe)

Ichthyosis

Incontinentia Pigmenti

Juvenile Retinoschisis

Krabbe Disease

Leber's hereditary optic neuropathy
/ Lebers Optic atrophy

Leigh's (subacute necrotising encephalopathy
of childhood)

Lenz syndrome

Lesch Nyan Syndrome

Leukocyte Adhesion Deficiency (Type I)

Li-Fraumeni Syndrome

Long Chain 3-hydroxyacyl-CoA Dehydrogenase

Deficiency (LCHAD)

Lymphoproliferative Syndrome

Lynch syndrome (MLH 1)

Lynch syndrome (MLH 2)

Macular Dystrophy (childhood onset - variant of Retinitis pigmentosa)

Marfan Syndrome

Medium-chain acyl-Co A dehydrogenase

MELAS (Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes)

Menkes Syndrome

Metachromatic Leukodystrophy

Multiple Endocrine Neoplasia (Type I)

Multiple Endocrine Neoplasia Type 2A (MEN type 2A)

Multiple Exostoses

Muscle-Eye-Brain Disease

Muscular Dystrophy (Beckers)

Muscular Dystrophy (Duchenne)

Muscular dystrophy (Occulopharangeal)

Myoclonic epilepsy and ragged red fibres (MERFF)

Myotonic Dystrophy

Myotublar myopathy

Neurofibromatosis type I

Neurofibromatosis type II

Neurogenic muscle weakness, ataxia, retinitis pigmentosa (NARP)

Niemann Pick Disease Type A

Niemann Pick Disease Type C

Oculocutaneous Albinism Type 1A

Oculocutaneous Albinism Type 1B

Ornithine carbamoyl transferase Deficiency (OTC)

Ornithine transcarbamylase deficiency (OTD)

Osteogenesis Imperfecta (Type II)

Osteogenesis Imperfecta (Type III)

Osteopetrosis, Autosomal Recessive 5 and Osteopetrosis, Infantile Malignant 3

Ostheopathia Striata with Cranial Sclerosis (OSCS)

Otopalatodigital syndrome (Type 2)
Paragangliomas 4 (plg 4)

Partial Lipodystrophy, Familial (Type 2)

Pelizaeus Merzbacher Disease

Phenylketonuria (PKU)

Plakophilin 1 (PKP1) associated ectodermal dysplasia syndrome

Polycystic kidney disease

Pompe Disease (early onset)

Popliteal Pterigum Syndrome

Prader Willi Syndrome

Propionic Acidemia

Pyrodoxine-dependent seizures

Recurrent Digynic Triploidy

Recurrent hydatitiform mole

Retinitis Pigmentosa

Retinoblastoma

Retinoschisis (Juvenile)

Sandhoff Disease

Sanfilippo or Mucopolysaccharidosis Type III A

Sensorineural deafness - autosomal recessive non-syndromic

Severe Combined Immune Deficiency (x-linked)

Sickle Cell Anaemia

Smith Lemli Opitz Syndrome

Spastic paraplegia

Spinal Muscular Atrophy (SMA1)

Spinal Muscular Atrophy and Respiratory Distress (SMARD1)

Stuve-Wiedemann Syndrome

Succinic Semialdehyde Dehydrogenase Deficiency (SSADHD)

Tay Sachs Disease (infantile onset)

Torsion Dystonia
Treacher Collins Syndrome

Tuberous Sclerosis (TSC2)

Turner's syndrome (Mosaic)

Tyrosinaemia Type 1

Ullrich Muscular Dystrophy

Von Hippel Lindau (VHL) Syndrome

Wiscott-Aldrich Syndrome

Wolman's Disease (Acid Lipase Deficiency)

Part 3
New technologies under the microscope

Appendix 5
The four most significant converging technologies - summary of 'Bottom Lines'

Genetics & Designer Babies

- There have been some exciting triumphs in genetic medicine but in most cases these constitute incremental changes rather than any transformation (acknowledged by the Wellcome Trust in the Lords' Genomic Medicine report). A number of technology experts have argued that the government has pinned too much hope on a biotechnology revolution.

- Genetic medicine seems to be taking longer than anticipated to deliver the hoped-for revolution in personalised, tailored medicine. Some feel that progress in genetics has revealed more about our complexity and our unrealistic expectations of what this field of medicine could deliver. Others feel however that the current course of clinical implementation is as expected and still have high hopes for 'personalised medicine'.

- The most progress and potential is in the domain of prediction of drug responses. Most successful applications have been in the field of cancer gene-expression testing.

- The UK is at the forefront of research, but in part this is controversial. The UK is not a signatory to the one binding international instrument in the field, the ECHRB (Oveido 1997) which, among other things, outlaws therapeutic cloning. It has also not signed or ratified the European Convention on Biomedicine and its protocols, which set ethical and clinical standards for genetic testing and research.

- Genetic screening is currently a relatively weak predictor of disease and may increase stigma, anxiety and discrimination. There is currently a dispute in the scientific literature about whether predictions will significantly improve. The public are not being adequately protected or informed about the serious limitations of 'direct to consumer' genetic tests and kits.

- The cost, the nature of the invasive procedure of IVF and the complexity of 'simple' traits such as blue eyes mean that while PGD will not result in designer babies in the near future, an increasing interest in sex selection and the principle of design raises fundamental questions for long-term policy review.

- As new treatments are found for genetic conditions, the use of PGD should be reviewed.

Neural implants and bodily IT devices

- Implants and IT developments are developing rapidly and needs to be taken seriously; these devices are no longer in the realm of science fiction but relevant to all of us.
- In our 'Age of technology' there is a huge amount of interest and enthusiasm for new IT applications.
- We are familiar with certain applications such as pacemakers without really thinking about them as 'implants'.
- Some interventions will have medicinal alternatives that are cheaper or less risky. Others, like heart pacemakers (CRT) are cheaper than a lifetime on medication.
- Many are a novel and unique way of tackling a problem (e.g. paralysis) that allows technology to undertake the task that can no longer be undertaken by the individual.
- However the development of thought and emotion control through implants or sensors raises huge issues about the loss of independence, privacy and freedom.

Neuro-therapuetics: therapy and lifestyle drugs

- There is a growing market for neuro-therapy and lifestyle drugs.
- There is no expected breakthrough in the prevention or treatment of dementia in the next 20 years, although if there is an increase in investment in R&D for dementia this may change.
- We need to plan for an increased demand for services in dementia over the next 20 years, which will have a significant impact on the cost to the country of the NHS and Social Services.
- There is a lack of investment in the development of therapeutic treatment for mental illness.
- The debate lines are being drawn between those who think that performance-enhancing drugs should become a part of everyday life and those who think they should be banned, just as they are in sport.
- There is an immediate need for Government to build on the work of Foresight Drugs Futures 2025? and the Academy of Medical Science's Brain Science, Addiction and Drugs [2008], including increased consultations on lifestyle drugs and developing a high-priority plan for public engagement.
- 'Lifestyle drugs' are being increasingly sought by the public; there is a need for a professional consultation on prescribing of psychoactive substances by health professionals.

Synthetic biology

- Synbio is the deliberate design of biological systems and living organisms through the application of faster and refined biotechnologies and engineering principles.
- There is a lot of (seemingly fragmented) discussion within the scientific community about the application, safety and regulation of this science.
- However this is a high-risk science because of the applications of research. Most awareness of this is among those who have worked in the arena of biological and toxic weapons but there is little evidence for life scientists knowing or thinking about the risks, regulations or thinking through the repercussions of their experiments.
- The artificial replication of hard- or expensive-to-acquire substances could bring huge benefits to health care, however this science is new and we should beware of too much hype.
- We feel there should be a review of prioritisation of funding for research, overseen by a body which is guided by core values.
- This is the science, not robotics or Artificial Intelligence, that opens up the questions on "what is life?"

About 2020health.org

What we are

- We are an independent, grass-roots, think tank for health and technology interested in realistic solutions.

What we do

- Identifying issues and bringing informed people together to create solutions.
- Demonstrating how to improve health and quality of life through successful commissioning, competition and technology.
- Exploring the benefits of public and private cooperation.
- Examining the consequences of healthcare decisions on society, lifestyle and culture.

Why

- Ensure policy reflects grass-roots wisdom and experience of professionals.
- Broaden involvement and debate on key concerns to give value for money.
- Build on the achievements of the present to create the vision for improved healthcare.

How

- Combining the experience of practitioners, experts and policy makers in the public and private sector through projects, research publications and debates.
- Restoring trust, confidence and responsibility to professionals and enabling people to have their say through active participation and networking.
- Publicising our work through the press, events and meetings with policy makers.

Where
We are based in the heart of Westminster.

Primary concerns
Inequalities, wise use of resources, uptake of new technologies, evidence based care.

Current Interests
Commissioning; Causes of mental health illness; Elderly care; Work and wellbeing; NHS IT; Value-based pricing; long term conditions; reconfiguration; diabetic care.

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Julia Manning

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