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## **Biotechnology and the promise of tailor-made medicine**

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My topic is about how new technologies are emerging in medicine, and how they may affect health care policy through their interactions. Usually, health care policy discussions end up with the question: who pays? How much freedom will the patients get? We often tend to forget that modern medical practice is shaped by technology. Medical technologies have changed the way in which we practice medicine, and they are going to change these even further.

We performed a study in 2005 on how Swedish health care may be perfected by using some of the emerging technologies, and certain areas indeed have the potential of causing radical changes in how medicine might be performed, and also showing that this will require political and regulatory changes in order to come to fruition.

Pharmacogenomics, or smart drugs (slide); this doesn't mean that they make you smarter, but that they act smart in your body. Once upon a time, inventing new drugs was basically a matter of trial and error: you tried things out on people and sometimes they got better. Once medicine got a bit more scientific, you would try products on many people, and if most of the got better, fine.

What is happening now is that we have a lot more information about how the body actually works, and that enables us to do rational drug design. But we are also discovering that the interaction between the drug and our genes has an important effect. This produces some interesting challenges for the pharmaceutical industry. This slide shows the development of scientific publications in pharmacogenomics. It started in the early 1960s: during the Korean War, anti-malaria drugs were given to soldiers and the side-effect was anaemia. Most of these soldiers were black, and it was discovered that this population lacked the enzyme to break down the drug. This started serious research into how drugs affect different people.

When I take a medicine, I obviously pray that it does indeed have the effect that the doctor expects. But my body may break it down very quickly, in which case I don't get much out of it; I may also break it down very slowly, which for a man of my age and weight means that the effect is far too high. This might entail side-effects and poisoning.

Or it may turn out that the drug is not absorbed in the appropriate way, or that it affects me in some other way.

In the early days, epidemiological studies could determine that a certain population genetically predisposes it for some side-effect. But in the 1990s, a wonderful synergy occurred as we simultaneously achieved better and faster computers, and better genetics. We suddenly had enormous databases which could be searched very rapidly. This produced genomics: the combination of genetics and informatics. You could combine the analysis of drug reactions with people's genetic fingerprints. This meant that we could get the right dosage of the right drug to the right person.

Now the problem is: can we use this mass of information to help people, keep the pharmaceutical industry profitable without causing cumbersome regulations?

I guess most of you understand the basics of genetics, so I'll be brief. Inside each cell are the chromosomes which are really piles of DNA. The DNA molecule encodes the proteins manufactured by the body; a regulatory structure tells the cell what substance to produce at what time in response to the environment. A gene is essentially a recipe for making a protein. The proteins act inside the cell, and their interactions can be very different. Usually, we have different versions of a gene; we have inherited one from our father and one from our mother. And in most cases, they are roughly equivalent. But sometimes the variations are quite significant. A typical example is the gene for Cytochromoxidase C. This is a very important enzyme which breaks down many molecules in the body, including many pharmaceuticals. And certain versions of it are much more efficient at breaking them down, which means that the people in this situation will automatically need a higher dosage of the medicine.

Before genomics, it was very hard to find out who these people were. The doctor would try different dosages over time, but in the case of depression for instance, the patient will suffer while the doctor is trying out what the right amount is. Conversely, the people with slow enzyme will end up with the side effects. All this because of the random differences in the DNA.

This can also be used in another way. Drug development faces the problem that some people don't react at all to a certain medicine, although large populations respond well. Breast cancer genes for instance are very vulnerable to certain chemical interventions. But only the individuals with that particular mutation causing the cancer will benefit from the drug. Similarly, HIV patients with rare variants will have to be isolated in order to develop a drug which will at least benefit the majority.

This obviously has a great impact on the issue of getting drugs through the pipeline. It's a sad fact that, although science and technology are advancing, we are not seeing an increase in the number of drugs, on the contrary. The reason is that we are demanding a lot from the drugs. Discovering new drugs is an excellent area for genomics: it's fairly easy to come up with new ideas for candidate drugs. The problem is the next step: convincing your boss that this is worth pursuing, all the way from animal testing to

human trials. At each step, the cost increases enormously. Initially, computer simulations are possible. But there are always strange and unexpected side effects. Viagra for instance was initially intended as a blood pressure drug.

Pharmacogenomics can hopefully help to make these early trials cheaper by selecting more genetically homogeneous populations which have similar reactions, in order to have a clear view of the side effects involved. Later on in the clinical trials, we might also select more promising sub-populations, so that the drug may be approved at least for these categories. But this will of course create a situation where a drug exists for a small population; but the larger group will not benefit.

Another problem is that we live in a very risk-averse society. And in the later stages of development, other groups become involved who think that the most important thing is that the future drug is not too expensive. In Sweden, we have observed that patients become more cheerful as new drugs and technologies are being developed, whereas the politicians get more worried about paying for it.

Pharmacogenomics has another benefit: it makes it easier to test for adverse reactions. This is a DNA chip (slide): the surface is covered with different DNA sequences. You dip it into a sample, and some of the DNA in the sample sticks to it. Using various optical measures, you obtain a fluorescent light showing a fingerprint of the genes of the individual. This provides for cheap genetic testing, and in the future it might be used against bacteria and viruses. If I see my doctor with the flu, he can check which version it is and give me the right medicine. Also, I can discover that I am particularly susceptible to a certain disease, which may hit me in my 80s.

This will of course create interesting dilemmas for the insurance companies which are generally not allowed to screen for this kind of information. In Sweden, regulations determine that only a particular medical agency may decide if I should get genetic testing; but I can also get it on the internet! Before, breast cancer was considered one single disease. Today, we know that it is caused by several different potential mutations. Some are easy to define and to treat, others are ill defined, and others yet are purely environmental. Suddenly breast cancer has dissolved into a number of different diseases. And we may find great drugs for some of them, but it may also turn out to be for a fairly small patient group. We might end up with orphan drugs which are not economically viable.

But the common diseases actually have different origins. There is a strong suspicion in the neuro-science community that schizophrenia is not a single disease, but might in fact have ten different core causes.

I'm a computer scientist, and my profession always tends to bring up Moore's law to illustrate how computing power multiplies over time. This graphic is Moore's law for genomics: (slide) the length of DNA which can be sequenced at a certain time and a certain cost. And we can see the extremely rapid increase. Regulations might say otherwise, but we are going to see basement gene hackers very soon. Also, thanks to

nanotechnology, we will see laboratories on a chip. This is essentially a small lab, sending liquids between different sensors. In the future, hospital labs might actually be replaced by laptops in the doctors' offices, or perhaps in the patient's home.

The problem is that, although this chip is technically feasible, it is going to be rather tricky to fit it into our current health care organizations. The hospital labs will fight very hard to show that they are necessary, and it might even be true.

The future has this annoying tendency of arriving in the wrong order and at the wrong speed. We are getting wonderful diagnostics tools at present, which enable us to diagnose diseases which we cannot do anything about! This is rather depressing, until you realize that many of these diseases will not strike you before old age, and that quite a few things will happen in the next 20-30 years. People suffering from cystic fibrosis have experienced increasing life expectancy: initially, it was very low and patients died very young. Treatments have improved faster than the rate at which people are ageing. The point is that we may be surprised by the diseases which don't increase; but we cannot know that and this makes it harder to make predictions.

We are collecting ridiculous amounts of information in genomics these days, and it's even worse when it comes to neuroscience. We don't really know how to deal with all the data. One important aspect is the chemical reactions on the different parts of the brain and the consequences. As we start to manipulate the different areas, we may actually be able to intervene in some complex cognitive functions.

This is what a cat's brain looks like (slide). You won't be able to make much out of this from your seats, I can't either even if I look at a high-resolution picture: everything is connected to everything else in a horrible mess. Humans have essentially the same system, but with four times as many boxes. But there is a kind of logic to this and we are beginning to understand it. Emotional neuroscience ten years ago was truly embarrassing: if you were not doing research on depression, you were not doing serious research on emotions. These days, things are much more interesting: what does a happy brain look like? If you do brain scans on people in love, a mother seeing her child or somebody listening to beautiful music, we can identify the commonalities of pleasure and enjoyment. And some of these emotions have fairly simple chemical systems. It turns out for instance that some people are born with a lower set point for happiness than others; very unfair! This of course keeps all the ethicists at Oxford very busy, wondering if these people should be treated. Come to think of it, maybe we should treat everybody to make them happier!

The interesting thing is that we can go all the way today, from a single molecule or receptor and build a case for how this affects memory and personality. We are still far from doing this efficiently, for instance memory disorders, but we are getting there. The problem is that it will take a lot of time to discover how we may shape the brain through the drug pipeline. And of course, ethicists and social commentators agree that it's better for people to suffer a bit ...

This is a memory-enhanced mouse (slide). It was genetically modified to make it learn better. At the same time, it is also more sensitive to pain, because the modified receptor is also used for pain reception. This could probably also work in humans, although both technically and ethically, we are still far from trying it out. There are already drugs which affect the memory, and of course doping in sports has existed for a long time. But in a few years, we will see that the athletes competing are not going to be as strong and fast as the elderly people watching them on television. If gene therapy is prohibited in professional sports, it is still possible for a patient who has broken a bone (but then, he won't be allowed to participate in the Olympics afterwards!).

Doping also exists in the Fine Arts. Concert musicians quite often use beta blockers to calm their nerves before a performance. But that does mean that classical music is suffering from a doping epidemic? Does this affect the music itself?

A friend of mine once made the distinction between “drugs” (narcotics etc) and healthy food, like bread. But I recently ate bread containing ginseng and other ingredients which are supposed to make me brighter and smarter. You may compare this to the difference between heroin and ritalin; the latter is chemically very similar to amphetamine. But if I take ritalin to get high, it's a narcotic. If I take it because I have attention problems, it's a medicine. But if I'm normal and take it just to enhance my attention (which in some cases it does) this is an area which is going to expand and we need to think about this, instead of refusing to “treat healthy people”. In fact, once we have all the diagnostics tools, it turns out that nobody is entirely healthy! We could all be better.

These potatoes (slide) are normal potatoes, even if they look exotic. On the other hand, there are genetically modified bananas which are used as vaccines. This can be very useful in tropical developing countries where it is difficult to transport medicines. Maybe bananas are a bad example, since you won't be able to tell the medical banana from the ordinary one; but you could use another fruit to produce a vaccine for cholera, for instance. This may be applied to the immune system to create vaccines for cancer, or diabetes. And of course some researchers are experimenting vaccines against cocaine and nicotine. We can easily imagine politicians in the future wanting to vaccinate people against drug taking, and by the way, let's find a way to prevent children from eating too many sweets as well!

Technology are posing a number of challenges, although some of them look more daunting in a slide presentation than in a lab or a clinical trial. But many of them will become very relevant for health care policy. The problem in a risk-averse society is that the answer is more policy which in turn produces more risk-averse policies.

**Robby Berloznik**  
**(Flemish Parliament Technology Assessment Center)**

Technology assessment really started in the United States, and effectively ended in 1995 when the US Congress deprived its Office of Technology Assessment of its funding. In Europe, the situation is quite different: there are 12 or 13 national parliaments with this capacity to advise them on technology.

A couple of years ago, Belgian parliamentarians said that science and technology developments required independent information which is not carried by a particular group with objectives of its own. We look at the consequences of introducing new technologies, wanted or unwanted. We do research and organize public debates; it is a multidisciplinary practice at the service of Parliament, not government or any particular ministry. There is a European network, but the members work in different ways and with different approaches.

To get the discussion going, I'd like to present a study to give you an idea of what we do and how. We just finished a report for the European Commission on the ethical and social aspects of genetic testing and another one on brain science a couple of weeks ago. We also work on human enhancement and reinforcing the knowledge society; elite sports and genetic doping; functional foods; and pharmacogenomics.

We review the literature and we invite stakeholders, including members of the public to form interdisciplinary focus groups. There are issues and controversies in society. If you discuss pharmacogenomics, you are dealing with informatics and statistics and also the possible misuse of information.

Pharmacogenomics may also alter the relationship between doctors and patients. I read somewhere that about 50% of all factors involved in a disease are not genetic or physical. Another point is the genetic divide: who can afford this kind of medicine? Anders Sandberg mentioned genetic minorities and orphan drugs. There is a societal risk that small groups will not benefit from drug development.

The study done by our Swiss colleagues concluded that we should be careful with so-called smart drugs, or "personal pills" because they may create false expectations. Also, biobanks are indispensable but need to be regulated regarding patient privacy.

Will pharmacogenomics develop into a profitable business? The market is unpredictable first of all. Second, what will the consequences be if the market is split between patient groups for which the industry will be developing products? How will the market react, and how will the industry react?

It is generally assumed that pharmacogenomics will reduce health care costs. On the other hand, it is probable that widely available genetic tests, predictive treatments will be

used more extensively. Patients with no symptoms will demand a cure, and this can put pressure on the health care system.

The danger of a genetic divide should not be underestimated, but neither should it be overstated. The moral issue could be that there is no obligation to provide everybody with the best possible treatment. On the other hand, there is a moral duty to encourage development of drugs for genetic minorities. Therefore, government should encourage drug companies to commit themselves to ventures which are less profitable.

The general conclusion is that there should be more public debate, whereas currently it involves specialists, split up between different areas. A good debate on pharmacogenomics is possible and would be enlightening, considering the amount of information, and this could avoid the problem of public acceptance of this kind of new products. The public perception of biotechnology is different from that of food for instance, and the idea of genetically manipulated medicine could raise problems for the marketing of these products which are very interesting.

The right to health insurance must be guaranteed, but we have to make the distinction between mandatory and voluntary insurance. For reasons of fairness and solidarity, premiums should be determined independently of the individual seeking insurance. But in the case of voluntary insurance, both parties should have access to the same risk-relevant information.

In summary, we try to add to the discussion and the decision-making process by providing information which gives all perspectives. Our normative objective is not to get less regulation, nor is it to seek profits from industry.

## **Discussion:**

### **Fred Smith (Competitive Enterprise Institute, Washington DC):**

The insurance issue is very important but it is misunderstood in the United States. A number of states have already precluded the use of genetic information, assuming that this would lead to a fairer system. Insurance is of course trying as much knowledge as possible to divide the population into homogeneous risk pools, and then charge a premium.

We are coming, in the US and Europe, to a breakdown of the hierarchy control system for technological change. The US arguably created this process with the FDA and Europe then exacerbated the situation by introducing the precautionary principle. But essentially, hierarchy priests will decide what is good for us and therefore protect us from our own lack of knowledge, etc. But this breaks down when the “us” becomes a “me”. We are seeing now the potential of designer drugs in a world which is increasingly wealthy and driven by internet knowledge. Governments, for financial reasons or for reasons of fear, are trying to block this development, but in a global world people can go elsewhere. You can get plastic surgery in Thailand, or cancer surgery in Mexico. People go elsewhere and come back much more pleased. Harmonization, that evil idea, is to stop this competition from happening. I don’t think it’s going to succeed, but we then run the risk that Europe and the United States will drive out science and technology because of regulation. Given a choice between protecting my health and protecting the bureaucrats, I know what I would do.

### **Lena Johansen (Eudoxa):**

One important thing is to combine innovation with business models; innovation is needed to create sound products. Genetics is used now to pool orphan diseases to raise money for research which may then be put into the public domain and possibly be picked up by pharmaceutical companies. A friend of mine has been working on orphan diseases and his company has patented their own disease, using it as an incentive for industry.

Have the panelists any thoughts on business models like this in connection with pharmacogenomics?

### **Anders Sandberg:**

Pharmacogenomics is often presented as a real challenge to the pharmaceutical business model, since this is very much based on blockbuster drugs, because of the length of the pipeline. That’s the reason why we are seeing so few new drugs, and of course getting small drugs to market is a regulatory and economic nightmare. This may be why we are

not seeing a stampede of pharma companies rushing out to embrace pharmacogenomics, because they don't really want to change their business model.

But it is possible to change things from the outside. I think patient groups so far have been overlooked, but they might actually become the funders of research. Thanks to information technology, it's a lot easier today for a private person with no economic or academic background to pool resources and network to achieve things which previously would have required huge organizations and central planning.

Insurance can probably be used in another way, namely by having a genetic insurance. When I debate human enhancement with people in Oxford, the question is often "what happens if something goes wrong?" The American solution would be "let's sue my parents for giving me those bad genes". And my parents who would like to give me good genes, might also feel the need to make sure that the Alzheimer gene is absent and that they don't get sued. But you can extend this to a less extreme situation: why not take out an insurance against getting a very bad genetic hand which would raise your premium.

**Peter Van Osta (Real Software Group):**

I work in technology development for the pharmaceutical industry, and I'd like to comment on regulation. In the 1990s, the patient groups working in the AIDS movement in the USA were very successful in changing the way in which antiretrovirals were developed. It gave the AIDS community better access to drugs under development, and many people concerned about orphan drugs can learn from this. In the near future, I think we will see more of this, where patient groups will put pressure on governments to make less stringent regulations for development of drugs benefiting smaller groups in high need of innovative drugs.

**Robby Berloznik:**

This is certainly a lesson for the future, but I would like to broaden this beyond patient groups: general societal and political pressure on the pharmaceutical industry is certainly increasing, at least in Belgium. We have had over the past two years a public debate on rising health care costs and the role of the pharmaceutical industry. There is an assumed causality between the rise in drug costs and the general lack of resources for health care. On the other hand, in Flanders the pharmaceutical industry is highly regarded: one of the most important Flemish personalities in the last century was Dr. Paul Janssen (Janssen Pharmaceutica).

**Fred Smith:**

The Competitive Enterprise Institute was very active in the AIDS campaign, working with gay groups on the issue. The problem was that once the gays won and gained

priority, they lost interest in a neutral system. Once, the National Institutes of Health were interested in health; now, there are 15 or 20 disease subgroups and the goal of every group is to get a new institute and its disease on top of the heap. This is bad in general, but especially bad when the disease involved is not initially fatal. At a recent conference in Washington, the point was made that the FDA model is particularly sensitive to side effects. When you are dealing with quality of life disease, neurological diseases such as Parkinson which kills you at a very slow pace, you end up with a tremendous reluctance to allow dangerous drugs which might radically improve the quality of life. In fact, the participants said, “if only Parkinson were cancer, we would have a much faster process”.

Patient groups are currently just pushing for priority and more money, which puts us all into a zero-sum game within a declining health budget. The real challenge is to find ways to liberate patient groups to make them take responsibility for their own research. One analogy: in the US, we have rules for investment. Most people are allowed to invest in safe assets, but high-risk investments like hedge funds require certain standards and tests. We might think of a “qualified patient role” where patients are asked to go through a process of review and then be allowed to take medicine without government approval.

**Annette Dumas (European Patients’ Forum):**

We should be careful not to put too much responsibility on the patient groups. Most of them find it hard to survive financially, and adding the burden of research may not lead very far. It needs to be a coordinated approach between patient groups, industry and government as well.

Nor should we only talk about the price of medicines, but about the costs which may be saved by prevention in terms of workdays lost etc.

**Anders Sandberg:**

I didn’t mean of course that patient groups should fund all future research, but they can do much more. We need to split up the current centralized research funding, because it really turns everything into a zero sum game.

Preventative medicine is the real promise, and it is something which could fit into many current business models: if a drug can prevent Alzheimer’s, most people will want it, and it will be profitable. Pharmacogenomics will also help to show what medicine can be used preventively. The problem is of course that, if I take preventative medicine against heart disease, we need to be very careful about side effects, since I will possibly be taking the medication for decades. Therefore, we also need to accept that it is sometimes necessary to take risks in order to remain healthy.

**Fred Smith:**

Celebrities are helping in this: Michael J. Fox got Parkinson, others cancer etc, and these people can become a nameplate to attract attention, funding, organizing festivals and so on. At the moment, a lot of this money has in my view been diverted into lobbying for a larger share of a fixed pie, which in the longer term is self-destructive.

Rather than going through the control trial experiments involving 5,000 people, you might have tens or hundreds of thousand people providing information on a website directly. This will be noisier data, but it will be more accurate because people won't lie and they won't be pre-selected because they are healthy instead of having the disease. The internet makes it possible to assemble small sums to make large sums.

**Lene Johansen:**

There was a drug taken out of testing in the US because it wasn't producing good enough data; but at a second glance, there were tremendous results among the African-American patients and testing then resumed for this population only, asking for FDA approval. Now, skin colour is genetics at a very crude level, but we have seen in focus groups that perception of biotechnology is race-based to some extent. African Americans tend to be very suspicious to medication which is not for whites. Do you have any comments on this?

**Robby Berloznik:**

I never heard of this, which shows that we need better communication. This is another type of genetic divide, based on perception. But there is another one which is economic: if you don't have the money, you won't buy it, as this kind of genetic testing won't be cheap. This should also interest policy makers.

**Anders Sandberg:**

I somewhat disagree: the reason that this drug was accepted for blacks is that although skin color is crude genetics, it has at least some correlation. In general, this is not going to work since Africans are a lot more genetically diverse than other populations. What really should exist are genetic races which are determined by the composition of the genes, but that doesn't correspond to what we see in culture. I don't think anybody will become racist because of genetic descent (but given human stupidity, this is a possibility).

The problem is that once we find a way of separating two groups of people, this will become an issue; and more information is enabling us to make those distinctions. In the long run, these will be so numerous that they won't really matter. Meanwhile, the tension

will come from having genes X, race Y and socio-economic group Z and this is where trust becomes most important. Building trust for a drug is important both for the industry and for patient groups, but we also need it in society.

I often hear people say “this new technology is great, but let’s make sure that nobody profits from it”. We laugh at this since we know that profits are necessary for development, but many people think profits are bad, and especially making a profit on selling medical treatment. Ideally, drugs would be developed altruistically. Emotionally, we live in a culture where this is not accepted. Stem cells are seen as a wonderful thing, but nobody should have to pay for them; and this will maybe ensure that stem cell research does not occur, simply because of a misguided altruistic reason.

**Fred Smith:**

In the United States, there was a massive attempt to cut the links between the market and the marketplace of ideas. It was argued that any research having any commercial funding should be stigmatized, and any advisory role for people having been involved in business should be disallowed in government. Only “objective” people (government officials, NGOs) should be allowed to participate in policy making. If that continues, it will be very hard for the market to play a positive role in this area.

At the other hand, the rich are the only ones to afford innovations in the early stages in any case. The rich are the white mice used to test high-priced low quality products; and if it works out it enables the rest of us to benefit from high-quality products at a low price. If you disallow the rich to try out experimental products, the rest of us will never have them. If the egalitarian solution is to deny anyone access to anything before everyone can afford it, then none of us will ever have anything.

**Waldemar Ingdahl (Eudoxa):**

We have discussed biotechnology and bioethics, but there has been a debate for the past decades about when we are going to see biopolitics, where political parties make stances on these issues. After all, they have a lot of information on this, but can we begin to see any trace of this in political programs in Europe?

**Robby Berloznik:**

My experience is quite the opposite. When I look at research trends, biomedical and bioethical issues are becoming increasingly prominent; this is not an isolated development, but because policy makers are demanding it. If you look at the programs in the EU Commission, these questions are very visible. The only problem is that the information gets valorized in different compartments of policy making: research, health care, industrial research, innovation, etc.

**Anders Sandberg:**

I think biopolitics will emerge, because there is a huge demand for values; voters expect politicians to express some kind of values. But right now, no political party will campaign saying “we have this conception of human nature”. The huge demand for bioethics is a bit hampered right now by a false consensus, since nobody is willing to stand up and say “this is right, this is wrong”.

But people are getting tired of this and we may well see some sort of biopopulism emerging eventually. And once the “bio-conservatives” get moving, the “bio-liberals” will have to come out of the woodwork.