03 PERSONALIZED MEDICINE

A la Carte Health Care

INNOVATION FOUNDATION BANKINTER

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Many thanks.
Fundación de la Innovación Bankinter.

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Executive Summary

The Medicine of the Near Future

In June 2000, Tony Blair and Bill Clinton held a joint press conference at which they announced the completion of the Human Genome projects— the availability of a first draft of the genome or genetic code of the human being. This milestone, one of the greatest scientific achievements in human history, means that today our generation may well be facing a quiet revolution which will change our current understanding of medicine, ushering in what is generally known among the scientific community as *personalized medicine*.

This new situation will allow the progressive application of treatments —preventative and curative— based primarily on individuals' genetic information. This contrasts with the situation to date where it has been based on symptoms, in a system where the doctor's opinion and experience were of vital importance. The promise that personalized medicine holds out is for an improvement in the effectiveness of treatments and a reduction in side effects, since they will, a priori, be targeted at those individuals, and will have a better response.

For the time being, in a ten-year timescale (the period for which the forecasts in this study are based), we will not see individualised treatments for each person, but mainly segmented treatments, targeted at groups of individuals with similar genetic features. This marks, nonetheless, a substantial change over the prevailing concept at present of "one-size-fits-all" treatments and drugs, under which all research has centred on finding pharmaceuticals for a wide majority of the population suffering from specific ailments.

These changes have been made possible by the enormous advances achieved in both molecular treatment and in information technology[1], enabling the Human Genome Project to be completed several years ahead of schedule. These factors have also brought the cost of sequencing each of the basic components of the genome down from $2 to almost 1 cent in the last eight years. Scientists are even talking of the possibility of obtaining a person's complete genetic code at a cost of less than €1,000 in coming years, possibly months, as a result of the application of technologies such as biocomputing, sequencers and biochips.

1. The human genome is composed of around three billion basic elements, making up about 25,000 genes.
These astronomical figures mean that processing the genome consists mainly of a problem of massive data processing.

This change will undoubtedly have a major economic and social impact and has aroused the interest of the Fundación de la Innovación Bankinter, in its desire to detect and monitor emerging trends, as part of the regular meetings of its "Future Trends" forum.

The context of the coming of personalized medicine

This process is taking place at a time of some commotion in our existing health models, especially in the pharmaceutical industry and in public healthcare systems.

Over recent years, spending on health care has increased steadily. It now accounts for nearly 15% of America's GDP and 8.5% of GDP in countries in the Euro zone, as compared to 11.9% and 7.4%, respectively in 1990. As a result of these increases, public health systems are experiencing major funding problems, given that, for example, countries in mainland Europe meet 75% of all healthcare expenditure.

Costs are rising in all areas of healthcare, but the fastest increase is in the pharmaceutical sector. The backdrop to this increase is a situation in which the world's pharmaceutical industry has seen a systematic reduction in the number of approved drugs, despite a threefold in the industry's R&D spending over recent years. It takes over $800 million and almost 15 years to develop a new drug.

To make matters worse, the public healthcare systems, driven by their own precarious situation, are putting pressure on the pharmaceutical industry. This pressure directly affects the profitability and even the viability of this important industrial sector.

My Notes

This situation has resulted in a wave of mergers and take-overs in the pharmaceutical industry, leading to a doubling of the market share of the ten largest pharmaceutical companies to over 50% in 2002. This is a defensive concentration which has not, however, managed to substantially improve the performance of the industry, which in recent years performed notably below the average on stock markets.

In the midst of all this commotion in the healthcare system, society continues to bring pressure to bear for an improvement in healthcare quality, given that at present, many treatments are only 70% effective and secondary effects cause over two million hospitalisations every year, at an approximate cost of $100 billion, or around 1% of GDP. In addition, we are witnessing a rise in a many diseases for which there is no effective treatment, such as cancer, Alzheimer's disease and Parkinson's disease.

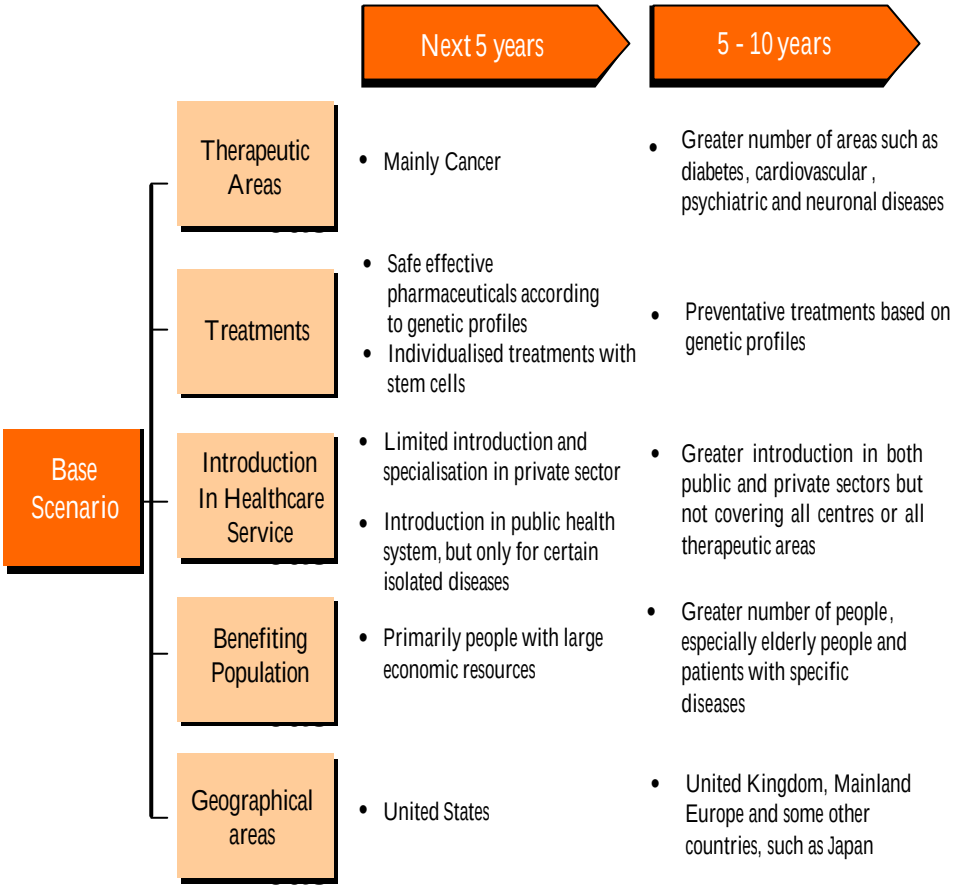
By its very nature, personalized medicine is going to substantially affect the different elements making up the healthcare system. It will modify these components both through the promise it holds out of bringing new more effective treatments with fewer side effects, and also through the additional investment and expenditure required for its introduction and maintenance. At the same time, the process of developing drugs is also going to change, making it possible to lower costs and favouring the marketing of new pharmaceuticals in areas already covered by other "traditional" ones. This will have a serious impact on the revenue of large pharmaceutical companies. Finally, it will affect individual people's life expectation and quality of life, with a corresponding impact at all levels, social and business-related.

The FTF's View of the Development of Personalized Medicine

FTF members believe that the development of personalized medicine is an inescapable reality; a new scenario which is being introduced steadily and quietly, but which in 10 to 15 years' time will be seen as a major revolution in the field of medical treatment and, thus in the health and quality of life of the wider population.

As a result of the FTF's deliberations, we have taken a base scenario of development of personalized medicine for the next ten years, whose key features are shown in the figure below. In this scenario, shared by the majority of the FTF members, the first practical advances would be made in under five years, although we forecast that it will take ten years before we see wider introduction in terms of the number of diseases and the people benefiting. Here it is important to stress that practically none of the experts is predicting a scenario of slower development, although a small group considers that change will come more quickly, mainly in terms of the number of diseases affected over the next five years.

Most Likely Scenario for Personalized Medicine according to FTF Members

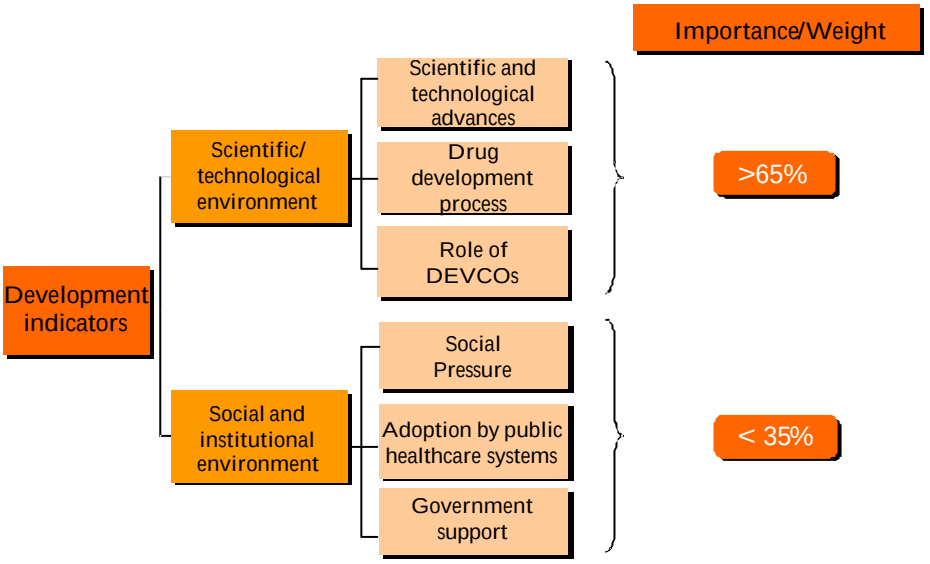


As a result of this new situation, FTF members feel, major changes are in the pipeline: greater number of diseases with effective treatments; improvement in life expectancy and, above all in quality of life for individuals; increase in all items making up healthcare spending (related to GDP); reduction in the public sector's relative share in healthcare spending, and consequent increase in the role played by the private sector; emergence of new players and new business models in the pharmaceutical industry; and moderate increase in the number of drugs approved and greater profitability of these.

These changes will have a major social and economic impact, not only because of their substantial effect on countries' GDP, but also because their possible influence on the health and conduct of individuals will mean that all sectors of the economy will be affected to a greater or lesser extent. In view of this situation, each industry will have to assess the possible impact and the strategy it needs to follow depending on the scenario for the development of personalized medicine.

In order to facilitate this process of strategic deliberation, in a climate of great uncertainty regarding the speed at which these changes will be introduced, the forum has tried to identify indicators that will provide information and will be useful in monitoring the environment and consequent adaptation of business strategies (a summary of these indicators is given in the figure below).

Main indicators influencing the development of personalized medicine according to FTF members



FTF members consider that technological factors will undoubtedly have the greatest influence on the speed of the process. Social and institutional aspects, however, will also be important and will therefore have to be taken into account as elements that could facilitate or hinder the introduction of the technological advances in the health-care system.

In conclusion, the advances in genome science and its basic application—known as personalized medicine—have already arrived and will bring about major changes that will affect not only the gigantic global pharmaceutical industry and models of public health care, but also the lifestyle and quality of life of society in general and, as a result, all business sectors.

Fundación de la Innovación Bankinter.

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CHAPTER 1

Prologue

1 Prologue

It is an honour and a pleasure for me to be asked to write a few lines about the theme of this book. I was lucky enough to take part in the meetings held on 1-3 December 2004 under the heading "Third Future Trends Forum Meeting", and to hear the excellent papers and discussions which, as you can appreciate yourself from this book, were of such great importance and significance. I would go so far as to say that the Fundación de la Innovación Bankinter has taken a bold and pioneering step in holding a meeting on a theme whose social and economic repercussions will only be seen in the future—albeit the immediate future—such as personalized medicine.

It is well known that a pharmaceutical product may often be highly beneficial for most users, but sometimes prove not to be of utility for a certain number of consumers. This apparent riddle has now been solved by the giant steps that have been taken in genetics, particularly the Human Genome Project, which has clearly established the great similarity between all the inhabitants of this planet while at the same time showing that no two people are exactly the same. For this reason, pharmacogenomics —the study of the individual response to pharmaceuticals—is of key interest.

It costs approximately one billion dollars to develop a new pharmaceutical product, since it requires intensive study of the pharmacokinetics, pharmacodynamics and multiple interactions, and calls for participation by as large as possible a number of subjects. None of this, however, can prevent the possible appearance of problems when the drug is administered to a specific patient, with resulting economic losses. As a result, we are in increasing need of a system of personalized medicine. The idea might seem like the stuff of science-fiction, but happily this is not the case: technology advances in leaps and bounds and it is expected that it will soon be possible to determine the genome sequence of any individual for less than €1000. Perhaps by the time this book is published, that will already be the case.

Naturally this type of technology, and for example the possibility pointed to recently in the work of three different American universities, of quickly identifying the "SNPs" (single nucleotide polymorphisms) in a genome simply and effectively, will be of great help to us in understanding individual responses to treatments with pharmaceuticals. Naturally, personalized medicine will also create many social problems which we must address, related to insurance and more importantly, to the ethical problems raised by genetic knowledge at an individual level. Nonetheless, the benefits will be greater than these problems and they will ultimately be solved.

Dr. SANTIAGO GRISOLIA
Winner of the Prince of Asturias Prize for Scientific and Technical Research, 1990.

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CHAPTER 2

Introduction

2 Introduction

A la Carte Health Care Arrives

Making a commitment to the future does not only involve keeping our eyes open to the new accessible technological situation that seduces and invades us and is so markedly altering the way we communicate, work and interact socially. Our lives may now be facing another crucial revolution by which they will not simply be changed, but improved, tended to and even extended in unforeseeable ways. Following the announcement in 2000 of the conclusion of the first draft of the human genome, *personalized medicine* is now standing at the door, visiting card in hand, and we are beginning to see to what extent the scientific and pharmacological advances resulting from a knowledge and understanding of the genetic structure of a specific individual will affect us.

We will certainly be faced by new techniques in customised medicine, geared towards more precise diagnoses, more reliable estimate of the risk of suffering certain pathologies and treatments which more closely match individualised— or segmented — genetic profiles. We are coming close to a scenario of medical prescription based on genotype[1] or genetic characteristics rather than on on phenotype or observed features, and a new context in which traditional medicine, which primarily uses an analysis of symptoms and the experience of physicians, will be relegated to a second place.

As a result, the gigantic pharmaceutical industry is now facing its greatest revolution, now that it seems clear that the costly and complex method currently used for developing drugs, based on pharmaceuticals that are effective and safe for a broad majority of the population, is likely to be supplanted by the latest advances of new sciences such as *pharmacogenomics* and *pharmacoproteomics*. These sciences will make it possible to target pharmaceuticals at the right person or, rather at the right segment of population, and this will to a large extent help eliminate secondary effects, optimise response to treatment and, probably have a direct influence on the costs resulting from ineffective treatment.

However, this new horizon also presents a new diffuse and multifaceted scenario, in which current models of drug research, production and distribution will be changed; in which the future of public health systems, strongly dependent on the price, effectiveness and secondary effects of treatment, hangs in the balance; in which society faces potential changes in quality of life and life expectancy and the possible emergence of new ethical and moral conflicts; in which the business models of many industries will be affected to some extent or another.

1. There a glossary at the end of this document giving a description of some technical terms that appear in the text.

A definition for personalized medicine

Personalized medicine (in the sense in which the term is used in this text) is a generic description of all the advances in disease diagnoses and treatments resulting from a knowledge and understanding of the genetic structure of a specific individual. In the specific literature, this concept is sometimes called *genomic medicine*, insofar as its development is based on discoveries relating to the sequencing of the human genome.

In general, we are not talking about individual preventative and/or curative treatments for each patient, but rather more segmented treatments applied to groups of people with common genetic characteristics. One exception to this rule are treatments with stem cells, which, for the purposes of this report, we have decided to include among the technologies making up personalized medicine, given their possible impact in a very near future.

Nonetheless, we have deliberately decided to exclude any research related to genetics which is currently the subject of great legal and moral controversy, and which is still at an embryonic stage, far from any reasonable practical application on human subjects. This includes cloning and genetic manipulation of organisms.

Before going on, I would like to stress that this chapter, like other parts of the document, includes certain scientific terms and assumes a very basic understanding of certain notions in the field of genetics. If you have any doubts, we recommend that you first read the appendix at the end of the document which explains what the genome is and what the project of genome sequencing has involved in rather more detail. We have also included a brief glossary of terms which you can turn to while reading this document.

But, is personalized medicine something new?

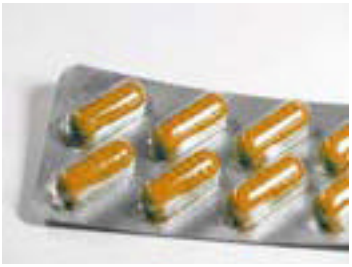
The idea of personalising medicine is nothing new; to date it has existed in traditional medicine in the form of, for example, tailor-made master formulas created by pharmacists, transplants, individualised treatments, etc. The main difference with this new concept is that the personalisation of the treatment is based on the patient's genome rather than on symptoms, trial-and-error methods, and other systems.

Consequently, the challenge consists in using the genotype instead of the phenotype when treating a patient; of going from an analysis of symptoms, in which the doctor's opinion and experience were of basic importance, to an analysis based on people's genetic information.

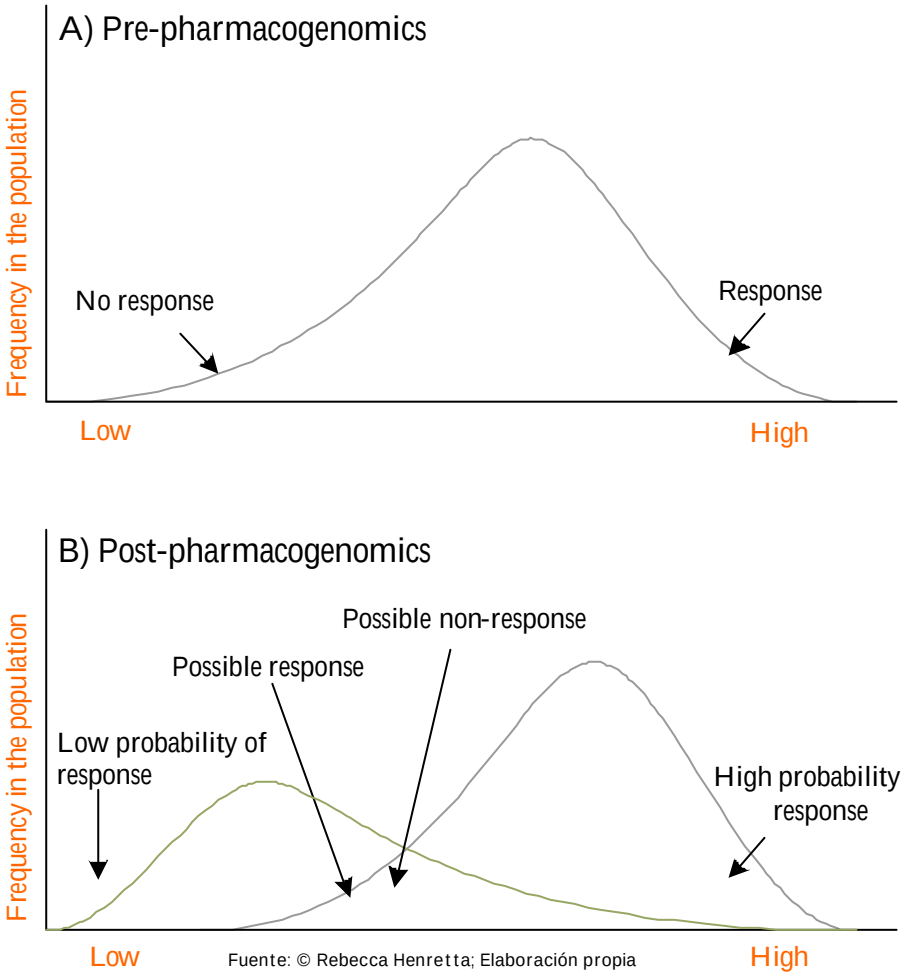
To date, most drugs have been developed using a "one drug for all" paradigm; in other words, they had to be safe and effective for a broad majority of the population. This has always led to a series of problems, mainly related to the high variability of response to treatment depending on each individual's genome:

- Reduced effectiveness of some drugs, resulting in effectiveness rates of less than 70% for such common conditions as epilepsy, high blood pressure and diabetes.
- High rate of secondary effects, with an estimated two million hospitalizations per year in the United States as a result.
- Difficulty of launching new drugs on the market as a result of the high variability of response among the general population.

In this context, as we have already said, the latest advances are leading to the emergence of new sciences that will decisively influence the process of developing and applying new drugs. We are referring to pharmacogenomics, which studies the way in which a person's genetic inheritance affects the organism's response to a pharmaceutical product, and pharmacoproteomics, which goes one step further and studies how pharmaceuticals influence the transformation of the genome into proteins. Understanding genetic functioning will therefore be the key to creating personalized drugs with greater levels of effectiveness and safety and will solve many of the problems associated with traditional medicine.



Response to the drug before and after pharmacogenomics



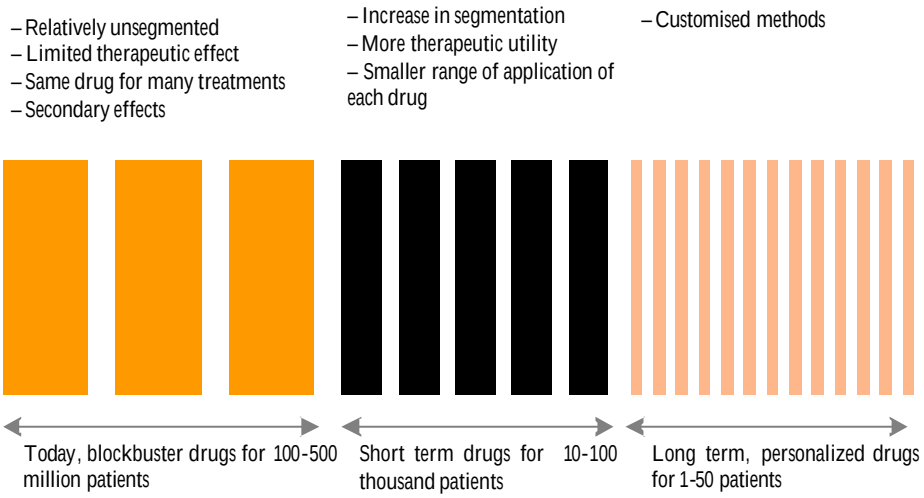
Fuente: © Rebecca Henretta; Elaboración propia

Specifically, as we can see from the illustration above, when faced with a medicine in our present pre-pharmacogenomics era (a), individuals are divided in two groups: those who do not respond to it and those who do, the latter being the majority. Pharmacogenomics (b) will enable us to break patients down into segments depending on their genetic profile. Thus, in the group of patients who respond to a drug, we will have individuals with a high probability of response to the drug and others with a low probability. Similarly, among patients who do not respond, there will be

some with greater a possibility of response and others with a more reduced probability of response.

Pharmacoproteomics will go even further and make it possible to establish segmentations based on the process of manufacturing proteins by the genome. As we can see in the figure below, this segmentation would lead to the appearance of numerous drugs targeted at ever smaller segments of the population, for whom it will improve the effectiveness and reduce the side effects as compared to drugs with a wider application.

Progressive segmentation in the application of personalized drugs to the general population



Fuente Roland Berger Strategy Consultants; Elaboración propia

In many cases, this segmentation would lead to the categorisation of new diseases, given that it will be possible to expand on the present symptom-based one once we have a greater knowledge of the way those diseases develop depending on variations in the genome of the patients. As a result, for example, we might move to a position of having three different types of diseases where we now only diagnose lung cancer.

All of these concepts also open new areas of work and applications in the field of preventative treatments, which could be designed according to the genetic code of the person and their propensity to suffer certain diseases.

In order to take advantages of the segmentation of treatments it will be vital to develop biomarkers, that is to say, any system based on genetic knowledge that makes it possible to obtain preliminary information on the most suitable treatment for a certain patient and disease.

And why personalized medicine?

Obviously, in view of the Fundación de la Innovación Bankinter's commitment to detect and monitor emerging trends from a position of neutrality and independence, we could not ignore this situation and, thus the "Future Trends Forum" (FTF) project, seeks to offer, in this third meeting, its vision and conclusions of the economic and social impact of the imminent commencement of personalized medicine.

The FTF members freely propose, vote and, finally, decide on a theme which will then be debated in depth, with participation from leading specialists, at a meeting held every six months. At this fourth meeting it was decided to address the possible application of the sequencing of the human genome in the area of medicine and pharmacology, given that it is becoming increasingly clear that this is a scientific breakthrough with the potential for an even deeper and, above all, inevitable impact.

A series of factors has recently come together to create an ideal environment for personalized medicine to become a reality, rather than the stuff of science fiction. These aspects area:

- *Molecular knowledge and understanding of the genome*, as a result of the completion of the project of sequencing the human genome in 2000, which represented one of the greatest milestones in the history of science.
- *Continued technological advances and greater data processing capacity,* with a clear fall in the cost of processing the basic components of the genetic code (falling from 2 dollars to 1 cent in the last eight years), making it possible to consider the possibility of performing economically affordable tests to find the genome of specific individuals within a period of 1 to 2 years. As we shall see, the obtention of the genome with its more than three billion components has now become a problem of number crunching and it will continue to evolve apace with advances in computing.
- *Greater knowledge of the way many diseases develop and their relationship with the genetic code for individuals.*

My Notes

Other views of the development of personalized medicine

Finally, it is important to state that although the opinions set out in this document reflect the majority opinion on this subject, there are other views on the development of personalized medicine and its possible repercussions. These arguments and points of view are also reflected in this section, with a view to enriching the reader's background and placing him or her in a better position to take decisions in this regard.

The key aspect about which some people differ in their general perspective is the importance of the genome in the development of diseases. According to these other opinions, the person's circumstances (environmental conditions, lifestyles and social structures) is much more important than the genetic code when it comes to explaining the development of diseases, given that the surroundings interact with the genes and alter them continuously.

In their opinion, personalized medicine — as defined in this report— will not have a significant impact in improving the effectiveness of medical treatments and reducing their side effects. In contrast, it will have a significant impact on the cost of healthcare in the new paradigm.

The main conclusion that has been drawn is that, despite the fact that it is very necessary to improve our knowledge of diseases, where a knowledge of the genome will clearly make a positive contribution, it is also necessary to spend some of those resources on prevention and on campaigns to encourage people to change their lifestyles. These actions (such as, for example, campaigns in favour of a healthy diet, prevention of traffic accidents, etc.) might possibly have a greater effect than the benefits obtained from all the investment devoted to personalized medicine.

My notes

FTF: A watchtower for changing trends

The "Future Trends Forum" has become the real showcase of Bankinter's "genetic code"—innovation and a commitment to the cutting edge developments. It is a forum in which opinion leaders, experts from different areas of knowledge and leading international scientists and intellectuals seek to anticipate advances in the near future, detecting social and economic trends and technological movements, analysing their possible effect on different areas and deciding which conclusions merit publication. This all uses a methodology whose central pillars are a multidisciplinary approach,

neutrality and globality, so that the public can be sure that the conclusions and the diversity of opinions deriving from these meetings on personalized medicine —and any other new development— are built on solid foundations of rigour, reliability and absolute credibility.

The pages below set out the analyses that FTF, together with ESADE Business School (which acted as a methodological consultant) has made of the possible impact of personalized medicine in areas such as the public healthcare system, the pharmaceutical and biotechnology industry, our own society and other sectors of influence. As well as the executive summary and this introduction, the document consists of a chapter establishing the right context for an understanding of personalized medicine from a technological, economic and business perspective, and a final chapter of conclusions setting out the FTF's vision of possible scenarios for the future and the most likely areas of impact.

This is another example of the Fundación de la Innovación Bankinter's commitment to increase social awareness of technology and research, and stimulate the creation of business opportunities based on the emerging trends that have been thus detected.

This project consolidates Bankinter's proactive attitude and its leading edge stance to society at large.

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CHAPTER 3

Present Situation and Context of Personalized Medicine

3 Present Situation and Context of Personalized Medicine

The purpose of this chapter is to establish the context required for a proper understanding of some of the most interesting aspects of the advances of genome research, particularly the medical applications in what is often called personalized medicine or genomic medicine, and the main associated technologies that are available.

We also need to examine more closely the context of development and the possible implications for the main players in this scenario, such as the pharmaceutical and biotechnology industry, public health systems, and other sectors, such as the insurance industry and even society itself.

3.1. Development of personalized medicine

Past

Medicine has always been personalized: from time immemorial the physician, the shaman, the witch-doctor and others have directly observed the patient, trying to find a remedy for his or her ills. On occasions they prepared pharmacological treatments by mixing up substances they had to hand, seeing that they were beneficial for the patient.

However, as humankind accumulated knowledge and systematised the relationship between medicines and their beneficial effects, recipes for preparing these substances became more widespread. Specifically, it was in Hypocrites' Greece (4th century BCE) that medicine began to take on a certain scientific nature and the first recipes —or prescriptions— were written.

In the sixteenth century, the Swiss doctor Theophrastus Phillippus Aureolus Bombastus von Hohenheim (more commonly known simply as Paracelsus), began to correlate chemical processes observed in nature with vital internal processes of the human being; he introduced more complex chemical components into pharmacology, such as mercury and antimony. The idea of organic processes as chemical processes was beginning to take hold.

However, even with the development of the pharmacy in subsequent centuries, up to the beginning of the nineteenth century, physicians, apothecaries and chemists continued to prepare their ointments, syrups and pills locally, using simple material they had to hand, customised to the needs of each patient. needed and store them up for future patients. The age of the drug industry had dawned.

In this industrial era, with the emergence of giant pharmaceutical companies manufacturing large amounts of the same pharmaceutical which they applied to major segments of the population, medicine began to focus on more general treatments. At the end of the day, we humans were sufficiently like one another to react similarly to the same chemicals. Since then, the pharmaceutical industry has grown and grown down to our own times, when the industry moves about 350 billion dollars a year worldwide, a similar figure to that of the automobile industry.

Present

To a certain extent, though, everything was to change in 1953, when scientists Watson and Crick built their model of the double helix of the deoxyribonucleic acid molecule. This was DNA, the material which comprises our genes and is found in the chromosomes of every cell of every living organism. As Watson and Crick said themselves, it contained the secret to life itself[1].

Between this essential discovery in the 1950s and our own times, there have been major breakthroughs in our understanding and in the development of techniques that allow us to untangle better the chemical structure on which genetics is founded and understand how it works.

My Notes

Ever better techniques have been developed for identifying the existing bases and the order they occupy in a specific sequence of DNA and we have identified which ones belong to genes. In this way, we are identifying an ever greater number of genes, isolating them and understanding their function using techniques such as introduction in other organisms or cell cultures, correlating malfunctions with certain disorders in the organism and thus creating new strategies for understanding and curing disease.

Human Genome Project

In 1990, the scientific community, in conjunction with certain economic interests from private corporations devoted to sequencing of DNA bases, and with the establishment of a multinational public consortium including the United States, the United Kingdom, France, Japan, China and Germany[2], begin to work together on a monumental project (not entirely free from competition), which involved sequencing the billions of A, C, T and G bases to be found in the human genome and furthermore, to identify the position of the approximately 25,000 genes it contained.

This project would also make it possible to find new, faster and cheaper methods for sequencing bases, alongside new computer developments that would simplify the task of processing the vast quantities of data which were swamping the scientists.

1. At this point we recommend that you read Appendix A, which gives a simple description of what the human genome is and what it means.

2. Other countries joined later

With a budget of over three billion dollars and an initial period of 15 years, the project has become one of the most important in human history, placing genetics among the great scientific feats alongside the project to put a man on the moon and the development of nuclear energy.

The first draft of the genome was obtained in June 2000, five years ahead of schedule, due to the emergence of new advances which made it possible to speed up the project and reduce costs.

Future

What have we achieved by sequencing a person's complete genome? Firstly, the development and refinement of techniques that allow the costs of sequencing to be reduced to the point where it has now become a viable possibility to completely sequence the DNA of any given person and not just a human type.

It is now being said that within a few years it will be possible to sequence a given person's genome for about $1,000. This is an amount that seems reasonable enough to allow such an analysis among to be included common diagnostic tests. This would lead to an exponential improvement in our understanding of diseases (what modifications in the genes may be involved in them, what they do or don't do), and thus an escalation in the possibilities of improvement and cure for many patients through treatments that are better suited to their genetic profiles.

And what comes after the genome? The sequences of amino acid bases specified in the genome define how to manufacture the proteins that make up the tissues of living beings. The incredible diversity of life is built out of little over twenty basic amino acids.

It is now time, therefore, to tackle the task of analysing proteins: how they are formed, what their structure is, what properties they have, how they come together, what effect is caused on our health by their failure, absence, excess, etc. This undoubtedly represents another immense challenge for the scientific community: it will no longer be tackling just four nitrogenous bases aligned in a one-dimensional structure along the DNA molecule, but more than twenty amino acids, forming complex molecules with three-dimensional structures, uniting to form the tissues and other substances of living beings. Nonetheless, these gigantic challenges have given rise to great expectations in the field of the development of new pharmaceuticals, such as:

- Analysis of specific parts of a person's genome, including that of an unborn child, will make it possible to improve significantly the diagnosis of the risk of suffering diseases in the future, both in terms of precision and the number of different diseases covered.

- The identification, by means of a genetic analysis, of the utility of a drug for a specific individual, and the level of secondary effects will in principle make it possible to save money and reduce negative effects by not supplying drugs to people to whom they are not suited.

- The development of drugs at molecular level, specially adapted to the genetic design of a specific individual, would enable advances in what we might call customised or tailor-made medicine.

- And finally, it would be possible to correct diseases by repairing tissues manufactured through the differentiation of the patient's own stem cells.

3.2. Current position of the science

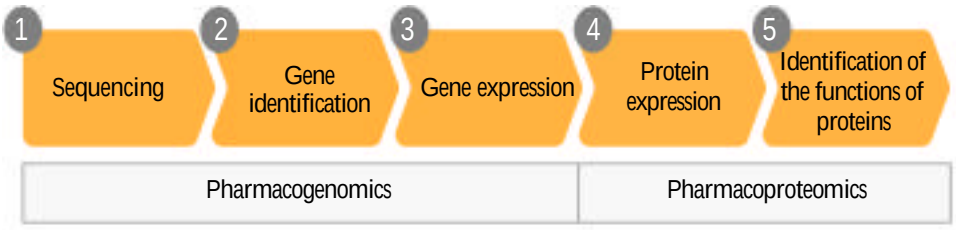
The sequencing of the genome unquestionably marks a major breakthrough and in coming years it will lead to a true revolution in diagnosis techniques using DNA analysis, and in the design and development of new safer and more effective pharmaceuticals.

Nonetheless we should be cautious: much work still remains to be done, both in terms of understanding the functions of the genes and their relations to diseases and in our understanding of the mechanisms used to generate proteins and the way proteins operate. Essentially, there are many questions which should make us wary of the extent to which it will be possible to satisfy all the expectations created, at what price and how soon the innovations will come. This section seeks to give a brief description of the current situation of research and development in the field of personalized medicine.

Many discoveries and advances have been made in the last few—centuries most particularly in the twentieth century—which have been useful in developing personalized medicine. Well known milestones include classic genetics, spearheaded by Mendel, Darwin's theory of the evolution of species and Watson and Crick's discovery of the double-helix structure of the DNA molecule.

Nonetheless there have been many other advances, especially in recent years, oriented to a great extent towards developing technologies that have enabled us to industrialise, scale, automate and reduce the cost of sequencing procedures. Initially carried out in a somewhat makeshift manner by scientists, such procedures have dramatically increased both the pace of this type of medicine and the expectations vested in it. These include computerised systems for simulating gene and protein structure, which have enabled theoretical models to be developed which can then be looked for in nature and the mechanisms of nanotechnology, which make it possible to work at molecular levels which would have been unimaginable a few years ago.

Traditionally people have worked in many different ways: gradually discovering genes and proteins and their function in the organism, identifying fragments of DNA chains that they subsequently worked out how to fit together or finding physical and chemical phenomena that have acted as markers for the various structures which need to be worked on in this field. These are aspects which in one way or another have been gradually systemised and even industrialised, to the point where today we can be said to be working on five fundamental aspects or well-differentiated tasks in the research, development and valorisation of genome-related medicine: *sequencing, gene identification, gene expression, protein expression* and finally, *identification of the functions of proteins* (see figure).



The first three aspects belong to the domain of *pharmacogenomics*, that is to say the pharmaceutical science that uses discoveries and research made with genes, whereas the last two use *pharmacoproteomics* science, related to the proteins specified by the genes.

Although there are companies and laboratories involved in work and research that relates to all five of these stages and traditionally many isolated discoveries have been made which could be classified in any of these five stages, general science might now be said to stand essentially between the second and third phase, i.e., the analysis of the genes contained in chains of DNA.

We will not need to advance as far as the end of the fifth stage for personalized medicine to become a reality; it will be possible to obtain results once we have made significant advances in the third phase. Advances in the other phases will allow us to increase even further the effectiveness of the treatments and develop treatments targeted at more specific population profiles.

Sequencing

The first step to be taken with the genome consists of sequencing it— in other words, identifying the specific order that the A, G, C, and T nitrogenous bases occupy in the type DNA of a species. This is a bit like identifying the sequence in which the letters of a book are written, an indispensable step before we can try to work out how to read the paragraphs and chapters, let alone the stories themselves.

The Human Genome Project (or HGP) took on the monumental task of identifying the order of the 3 billion bases that exist in human DNA.

Companies like Celera Genomics and the international consortium of the human genome project have developed techniques for sequencing bases and for storing and processing all this information.

The advances will depend on the possibility of sequencing the genome of a specific organism (for example a particular patient), instead of the typical genome for a generically representative individual. This will be made possible thanks to the development of ultra-fast sequencing technologies, which, among others improvements, will allow for a continuous reduction in the price of sequencing the bases.

The continuous fall in the cost of sequencing is of central importance in the practical applications of the project human genome.
Source: Ren Ee Chee; Own preparation.

Gene identification

The next task consists of identifying the genes (some 25,000 of them) in the human genome, which are contained in the DNA chain.

In essence, the genes are groupings of nitrogenous bases of the genome which encode a specific function in the organism. It is important to state that not all the bases found in the sequence of a chain of DNA belong to genes; indeed, only 3% do; the rest of the DNA does not perform any known function (it is known as selfish DNA).

There are now many techniques and technologies for identifying genes, ranging from simple techniques based on observation of an individual's phenotype, such as eye colour or the presence of a hereditary disease, to complex mechanisms of analysis at molecular level. Describing these mechanisms lies outside the scope of this report.

My Notes

Differentiation of gene expression

Gene expression is the process whereby the information coded in a gene is converted into present and operating structures in a cell

An understanding of gene expression — that is to say knowing how genes work and express themselves — is the next great challenge in the analysis of personalized medicine. It is an important advance on the previous point, since it seeks not only to find out where a gene is located and what sequence of bases forms it, but also to begin to

understand its function, how and where is activated, what causes it to malfunction, what types of mutations can be caused, etc.

This is the domain of pharmacogenomics, with the emergence of the first useful molecular principles for manufacturing drugs targeted at certain genetic profiles. Here, companies such as Millenium Pharmaceuticals, Curagen, Sangamo, Gene Logic, Quark, and others are heading major work on the development and marketing of practical applications for these technologies.

Differentiation of protein expression

Finally, the basic function of the gene is to encode a protein. The next step is therefore to understand what proteins are manufactured and what they are for. This is a complex challenge both at molecular level and in terms of data processing, given that in this case more than twenty amino acids combine to form millions of molecular structures known as proteins, with complex properties: difference from one to another, three-dimensional, folding, special adjacency and attachment properties, proteins whose excess, defect or malformation are responsible for all sorts of diseases.

The search for pharmacological solutions derived from this research constitutes the beginning of pharmacoproteomics, an area in which the leading players are companies like Vertex, Praecis, Abgenix and Medarax.

Identification of the functions of proteins

This is the most advanced phase, at which our understanding of the function of the protein is complete and it is possible to activate and deactivate genes, differentiate cells from stem cells, facilitate or impede the production of proteins, create tissues, design genetic therapy, etc.

3.3. Current position of the technology

The complete sequencing project of the human genome, together with the many applications that have already been found in the field of genetics, has allowed an entire industry of suppliers of technological solutions, techniques and procedures to spring up, offering an essential platform for the pharmaceutical and biotechnology industries, who will be in charge of developing pharmaceuticals and treatments tailored to people's genetic profile.
This section is intended to give the reader a closer view of the main groups of technologies currently involved in developments related to genome research, without even

attempting to cover all the different types of techniques that are currently available.

Biocomputing

The human genome comprises three billion bases and there 25,000 genes that encode proteins from the genome. This gives some idea of the vast quantity of information that needs to be stored and analysed. This volume has resulted in many problems of computational calculation, such as identifying certain sequences, repetitions or other structures within a chain of DNA that might allow us to rebuild the huge jigsaw puzzle that arises out of the identification of thousands of fragments of DNA in different experiments or predict the three-dimensional structure and properties of the molecule of a specific protein, specified by a gene or group of genes.

It has therefore been necessary to develop a whole new branch of computer science, known as *biocomputing*, covering a host of techniques and solutions often developed ad hoc to address very specific problems. They include software tools for viewing, simulating and predicting molecular structures, linking up bits of DNA, systems for storing and recovering genetic data, etc. Over recent years, there has also been an explosion in the genetic information that is available to the public, especially over the Internet, leading to the development of a new set of tools for recovering and analysing the available data.

Sequencers

The discovery in 1983 of the chain reaction of polymerase or PCR3 represented a major advance in sequencing the bases of nucleic acids which aligned to form the structure of DNA, i.e., identifying the order occupied by the well-known A, C, T and G bases in the genome, and understanding this structure

This is a chemical process whereby multiple copies of a DNA molecule or specific portion thereof are made, causing, in a way, an amplification of the sample to macroscopic levels where it could be observed and measured using instruments available in the laboratory.
Another important advance in this regard came between 1985 and 1991 with the invention of the automated fluorescence-based DNA sequencer, from which other more advanced techniques have subsequently been developed such as slab gel and sequencers based on capillarity. These technologies use mechanisms that allow fluorescences to be created in the DNA molecules which can be detected by a chip that is sensitive to this type of luminous radiation and automatically identifies the sequence of bases found.

3. Del inglés Polymerase Chain Reaction

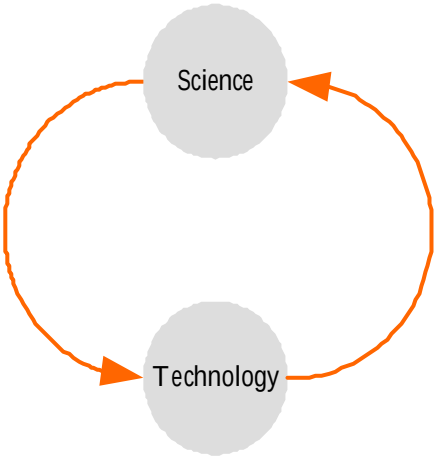
Biochips

A *biochip* is a device that performs a series of miniaturised laboratory tests which are repeated in a micro-array. It is capable of performing thousands of analyses at the same time on a small portion of DNA and of detecting, for example, the presence of different genes simultaneously.

Companies such as Affymetrix, Orchid Bioscience and even Motorola are harnessing the possibilities offered by the production and application of *biochips*.

Technologies for the future

Any scientific discovery of a marker, physical, chemical or biological phenomenon that allows us to know more about the biological structure of genes and proteins is normally followed by automation, industrialisation and cost reduction of the procedure through technological advance. This in turn leads to new advances in science allowing new discoveries.



There have been many recent advances in different fields which are useful for developing medical and pharmacological solutions based on discoveries in the way the genome operates. These include the application of mass spectroscopy to speed up the processes of data separation, analysis and acquisition from DNA sequences. Likewise, the development of integrated analyses in chips, as described in the previous point, is a branch of the technology which is set to mushroom over the next few years.

The reduction in the size of the samples needed for an analysis and the increase in the speed of analysis—to such an extent that that they will become useful advances for diagnosing disease—will be other important aspects of the future development of all these technologies and discoveries.

In order to transfer these technologies from the laboratory to the hospital it will be necessary to simplify the procedures involved, as well automating, industrialising and reducing costs with automatic, easy-to-maintain machines.

3.4. Practical examples

The Mayo Clinic

The prestigious Mayo Clinic, in the US, with its characteristic comprehensive approach to patient care, has been one of the pioneers in the use of genome information in patient analysis. Traditionally, the clinic has made complex correlations between patients, diagnosis and results from clinical laboratories, to which it is adding genetic information from the analysed individual.

Above all, the Mayo's purpose in this regard is to enable the doctor to determine virtually how a patient is going to respond to a specific treatment based on their genetic profile, and to exclude drugs that might have adverse side effects before beginning the treatment properly.

In 2002, the Mayo signed an agreement with IBM to develop a large genetic database that would give researchers at the centre faster access both to information from the genome and to clinical and laboratory tests. The main goal is to improve diagnosis, identify the best processes and design the most effective treatments.

A genome drug: Herceptin

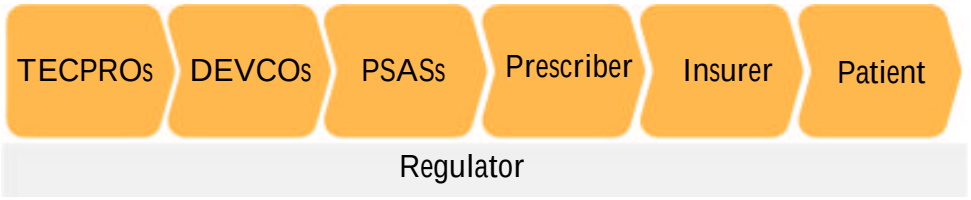
Roche was the first company to bring out a drug developed for a specific genetic profile, Herceptin. This drug is targeted at approximately 30% of women with metastatic breast cancer, which is developed by overproduction of the proteins necessary for cellular growth and division, in this case through over-expression of the protein HER2. Herceptin is a monoclonal antibody which is specifically designed to recognise and bind with the HER2 protein, preventing it from causing excessive growth of cancer cells and helping the immune system to fight the cancer.

3.5. Context of development of personalized medicine

Having shown the current extent of development of personalized medicine and the technologies that are making it possible, let us now look at the context in which this is happening and the possible implications for the main agents involved. We will leave FTF's specific evaluation of the main scenarios and implications for the future till the next chapter, together with the most immediate consequences of current developments in this field.

Value chain in the healthcare industry

In order to be able to assess and understand in greater detail the development and impact of personalized medicine, it is important to place it within the framework of its environment and specifically within the value chain of the healthcare industry. As the figure below shows, this comprises the following activities/participants:



- *Regulator*. The regulator is the leading player in the value chain of the health industry, establishing the rules of the game under which all other activities in the chain function. We feel it is worth examining this figure separately in view of the great importance of regulation to the industry. This category includes governments and international public organisa tions such as the regulatory agencies in charge of approving new drugs (for example, the FDA in the US and the EMEA in Europe).

- *Technology Platform Providers*. These are the companies that provide the technology needed for developing drugs and performing the other activities in the value chain. The great importance of technology in developing personalized medicine, including new fields such as bio-computing, means that the importance of this groups is set to rise in coming years.

My Notes

- *The pharmaceutical and biotechnology industry (drug development companies or DEVCOs).* These are the companies that develop and supply the pharmaceuticals and similar items that allow the other agents in the chain to provide patients with suitable treatments. These pharmaceuticals have to meet the necessary requirements established by the regulatory agencies before they can be marketed.

- *Health care service providers (HCSPs).* These are the groups responsible for providing, in clinics and hospitals, the diagnostic tests and preventive or curative treatments needed by people who suffer or are likely to suffer some ailment or disease. Generally speaking, the health care services have focused more on cure than prevention, although a change in this trend is now being seen, particularly in countries such as the United States.

- *Prescriber.* Although the role of the prescriber of the appropriate medical treatments to a patient might be included in the previous link in the chain, we think it should be separated, since it represents one of the groups that may be most affected by the development of personalized medicine. To date, this role has mostly been performed by doctors.

- *Insurance companies*. These are the institutions that provide their customers with sickness risk insurance coverage. It is a role which is played by both the public and the private sector. In the case of the public sector, this is the most important role it plays, given that, the taxpaying public can have access to health services, the extent of which varies from country to country. The fact that some countries, such as Spain and elsewhere in Europe, also offer health care services represents an additional vertical integration which is not necessary for the provision of a universal health service, since the system could reimburse patients the medical expenses charged to them by private clinics (establishing a maximum reimbursement according to the type of health care).

- *Patient.* The end user of the entire chain and also an active participant in it. HE or she sometimes also plays the role of other links in the chain, as in the relatively widespread phenomenon of self-medication.

Let us now analyse in greater detail the context of the development of personalized medicine in the four areas covered by FTF's deliberations:

(1) Pharmaceutical and biotechnology industry.

(2) Public health systems

(3) Social aspects.

(4) Other sectors affected.

In addition, in order to analyse the context we have added a specific section on the legal environment, given its particular relevance to this subject.

The pharmaceutical and biotechnology industry

Among the many aspects affecting this industry, the report centres on the areas considered to be most relevant from the perspective of the FTF and personalized medicine; specifically, in the recent development of the industry, possible changes in the profitability of the drugs and the possible business models that emerge in response to the new circumstances.

Recent development of the industry[4]

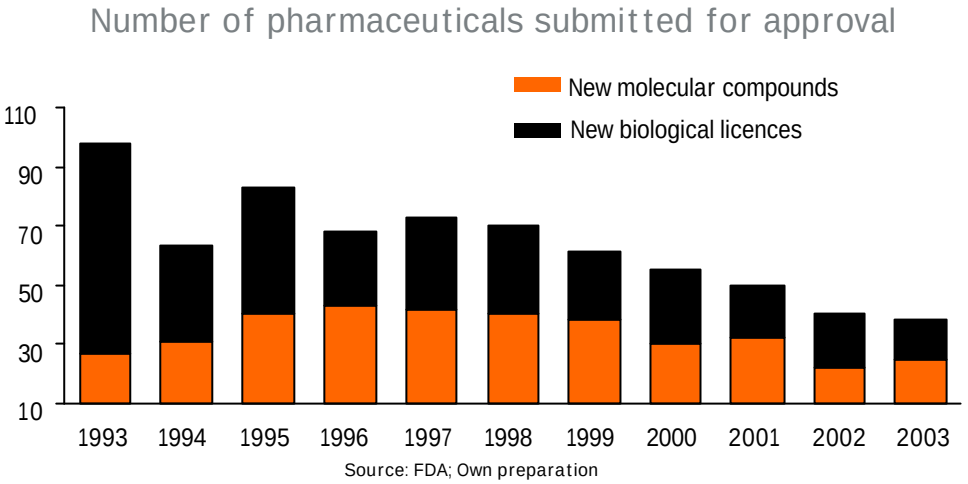
The pharmaceutical industry saw vast development during the second half of the last century, with spending on pharmaceutical products soaring from approximately sixty billion dollars (0.8% of GDP in the case of OECD countries) at the beginning of the 1980s to over $350bn (1.4% of GDP in the case of OECD countries) in 2002. In Spain alone, the pharmaceutical industry —according to figures from Farmaindustria— employed almost 40,000 people in 2002.

This development has been based largely on the development of *blockbuster* drugs, in other words, drugs with sales of over one billion dollars a year. These drugs have been developed under the paradigm of the search for effective drugs with few side effects for the majority of the population suffering a given disease ("one drug for all").

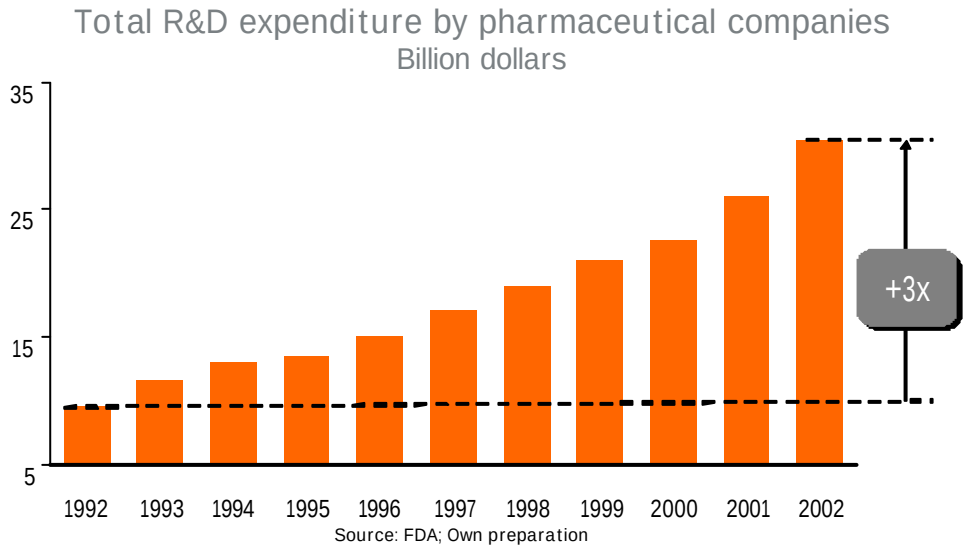
Over recent years this model has lost validity, and this has been reflected in the following factors:

- *A significant and ongoing fall in the number of drugs being developed.* The following illustration shows the number of new compounds submitted for FDA approval in recent years. The downward trend is obvious. Various factors have influenced this fall, one of the main ones being the growing difficulty of finding new pharmaceutical products that are effective and safe for a very broad majority of the population. Combined with this fall, there are the cases of withdrawal from the market of recently approved drugs (with subsequent re-introduction subject to restrictions), as is the case of the COX-2 inhibitors (Bextra, Celebrex and Vioxx), withdrawn because of the serious side effects caused amongst some patients.

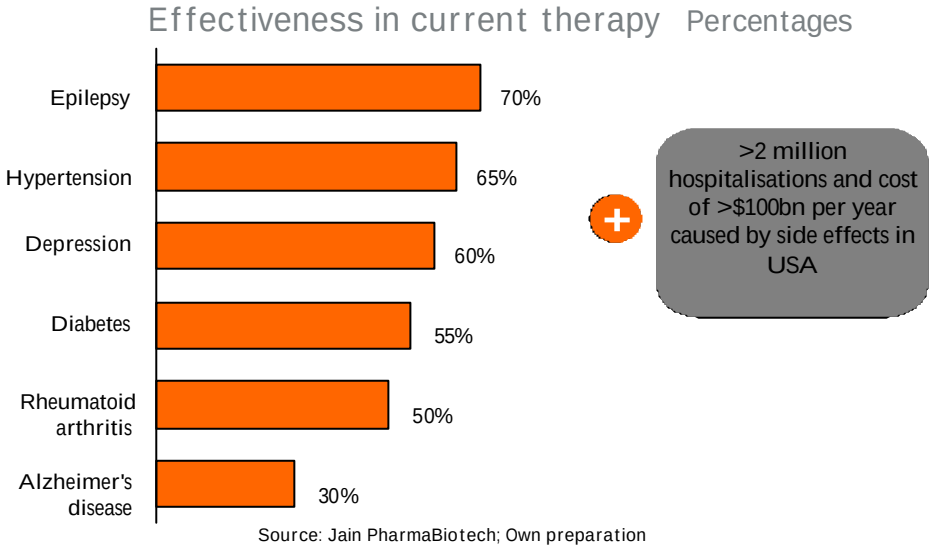
4. This section is intended to provide the context of the industry from the point of view of the areas in which personalized medicine may have the greatest impact. A complete strategic and competitive diagnosis of the industry would require a separate report specifically devoted to this area.



- *A marked increase in the cost of developing new drugs.* In contrast to the fall in the number of pharmaceutical products developed, the graph below shows that total expenditure on R&D amongst pharmaceutical companies multiplied more than threefold in recent years, to around thirty billion dollars in 2002, representing an average annual growth of over 10% and an average development cost per pharmaceutical of over $800m. Another relevant figure is that it now takes an average of close to 15 years to develop a new pharmaceutical.



- *Limited effectiveness of drugs and high impact of secondary effects.* The highest effectiveness rates for most diseases do not reach 100%, and as we can see in the illustration below, the effectiveness of the drugs used to treat some relatively frequent diseases is only 60-70%. These levels do not appear to improve with new generation drugs, as we see in the case of newly developed statins (overall effectiveness of between 30 and 70%[5]), and antipsychotics and antihypertensives which, despite the fact that they do not offer clear improvements in effectiveness, are among the fifteen most expensive drugs in the Spanish national health system. Combined with these factors, there is also the high human and economic impact of secondary effects, resulting in an estimated two million hospitalisations per year in the United States and a cost of over $100 billion (around 1% of that country's GDP).



Source: Jain PharmaBiotech; Own preparation

My Notes

The response of the pharmaceutical industry

The primary response of the traditional pharmaceutical industry to these circumstances has been a process of consolidation, with a great number of large-scale mergers and take-overs (many to values in excess of fifty billion dollars). As a result, the market share of the ten largest companies in the industry rose from 36% in 1996 to 53% in 2002. Leading examples include the mergers of Astra and Zeneca in 1999 (an operation valued at $36bn), Pfizer's acquisition of Warner-Lambert in 2000 for ninety billion dollars and the merger of the resulting group with Pharmacia in 2002, the merger of Glaxo Wellcome with Smithkline in 2000 (valued at $74bn) and the more recent take over of Aventis by Sanofi for around $70bn.

5. "Gasto en medicamentos e innovación terapéutica". Butlletí Groc, volumen número 17.

Leading companies in the pharmaceutical industry

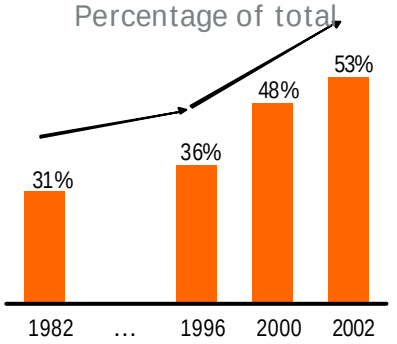
percentage of total sales in the industry

1996		2002	
Company	Turnover Billion dollars	Company	Turnover Billion dollars
1. Glaxo Wellcome	13.026	1. Pfizer / Pharmacia	42.281
2. Merck & Co	11.617	2. GlaxoSmithKline	26.979
3. Novartis	9.858	3. Merck & Co	21.631
4. Bristol-Myers Squibb	8.702	4. AstraZeneca	17.481
5. Hoechst Marion Roussel	8.652	5. Johnson & Johnson	17.151
6. Roche	8.462	6. Aventis	15.705
7. Pfizer	8.188	7. Bristol – Myers Squibb	14.705
8. American Home Products	7.924	8. Novartis	13.497
9. SmithKline Beecham	7.431	9. F. Hoffman - La Roche	12.630
10. Johnson & Johnson	7.188	10. Wyeth	12.387

Source: Script's Pharmaceutical Company League Table; Own preparation

Market share of the ten largest companies in the pharmaceutical industry.

Percentage of total

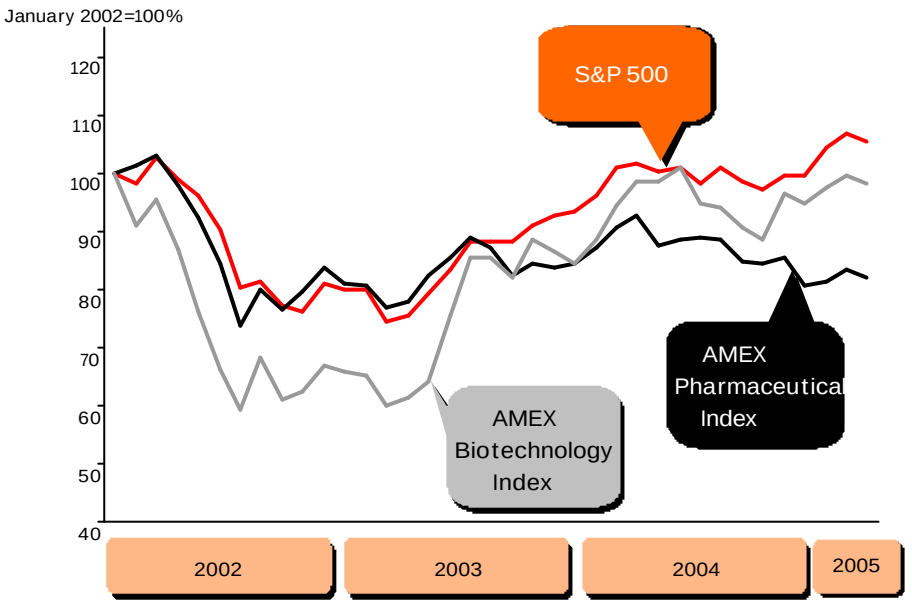


Source: Script's Pharmaceutical Company League Table; Own preparation

This process of consolidation has enabled pharmaceutical companies to increase their R&D budgets significantly but, nonetheless, they have been unable to significantly increase profits. As a result, share prices in the industry have fallen behind market average in the last three years, as the illustration below shows. During this period, whereas the market rose by nearly 6%, the pharmaceutical industry saw a fall in value of almost 20%. In contrast, while biotechnology companies (the new players on the market) have not exceeded market averages either, they have had a better ride on the stock market than traditional pharmaceutical companies, which seems to suggest that

they enjoy greater confidence in the capital market. This is especially true for the last year and a half, when they stood well ahead of the pharmaceutical companies.

Share prices of pharmaceutical companies



Source: Yahoo Finance; Own preparation

Changes in profitability of drugs

Within the aforementioned context, personalized medicine is going to have a clear impact on the profitability of drugs, affect as it will market size, price levels and development costs. Future profitability will influence these companies' balance sheets and share prices, and also have an impact on the development of new drugs and the extent to which new competitors emerge.

Market size

The basic principle behind personalized medicine consists of adapting pharmaceuticals and treatments to genetic profiles and even managing to individualise them, as in the case of stem cell treatment.

As a result, the market size of new pharmaceutical compounds will be smaller than at present—for example, 25% of present figures if there are 4 drugs for the same disease, targeted at 4 different genetic profiles[6]. At the same time, existing drugs will see a reduction in their market as new pharmacogenomic drugs are developed that improve effectiveness in certain segments of the population. In addition, we need to take into account the possible impact on the overall market for each disease; on the one hand, the market might grow if the number of people for whom the drugs are safe and effective increases, but on the other the greater effectiveness of the drugs might also reduce the amounts required to treat them.

All of these factors represent new opportunities and threats for the industry: opportunities, in that they will make it possible to capture a segment of the market through the launch of new pharmaceuticals and to develop new markets for those for whom no effective drugs existed in the present scenario; and threats because the present drugs produced by many laboratories will lose their market, which will have a negative impact on the earnings of the company that produces and markets them at present.

Prices

There can be no doubt that the new drugs will offer patients (and public health systems) better value, because of their improved effectiveness and reduced side effects.

What is not so clear is whether this value will translate into higher prices. On the one hand, because they affect health, especially chronic or difficult-to-cure diseases, the demand may be extremely insensitive to the price and this will facilitate higher prices. On the other hand, the huge pressure exercised by the public health systems on prices might make possible increases more difficult.

Development costs

In order better to understand the influence of the new paradigm on development costs, the illustration shows in simple terms the process prior to the launch of a new pharmaceutical. As can be seen, the stage that takes up most time and resources is the third stage, since it requires a large number of tests to be run to ensure effectiveness and a lack of side effects for the majority of the population. The fact that new developments will be targeted at specific genetic profiles will significantly reduce the number of tests required, thus reducing the duration and cost of this phase.

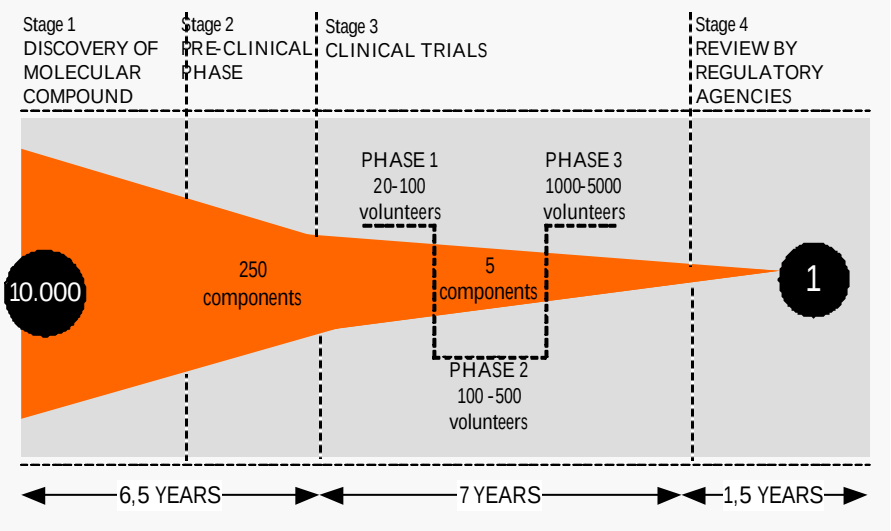
For example, an increase from 20% to 25% in the response rate in experimental phases as a result of better patient segmentation could reduce the necessary sampling by

6. As we have already explained, it could also be explained by the discovery of four differentiated diseases.
In any case, the effect is the same; where previously one pharmaceutical covered the entire population, there are now four pharmaceuticals to do the job.

nearly 50%, leading to a reduction in costs of over $100m. Similarly, the capacity to improve the failure prediction rate by 10% before mass clinical testing begins would also result in a cost reduction of around $100m.

PROCESS OF DEVELOPING NEW DRUGS

The illustration below shows the principal stages in the research and development of a new pharmaceutical, to the point where it is approved for marketing. For a molecule to be turned into a marketable drug, it must meet the following requirements: it must be effective, it must be safe and it must be industrializable (in FDA terminology this is known as "*the critical path*").



Source: FDA; Own preparation

As we can see, the process consists of 4 main stages, lasts an average of nearly 15 years and has a success rate of one marketed drug for every 10,000 molecules analysed. The stages are as follows:

- *Stage 1.* Synthesis of compounds with potential biological activity.
- *Stage 2.* Pre-clinical studies. Study of the real behaviour of the compound in enzyme systems, in cell cultures and animal models of the disease to check whether it acts as predicted. This stage also includes toxicological tests on animals. This phase concludes with an application to the regulatory body for the necessary licence for clinical trials to begin on human beings.
- *Stage 3.* Clinical trials. Consists of controlled exposure of human beings to the drug, to determine its effectiveness and safety. It is performed in phases (from 1 to 3) in which a progressively larger number of subjects is exposed to the product as the technician's knowled ge of its safety and potential activity increases. In Phase 3 the new treatment is compared with the best available treatment for that disease. This is the longest and most costly stage (nearly 60% of the total) in the entire process, since it requires tests to be run on a large number of patients in order to ensure that the drug will be effective and safe for the entire population. Of the drugs that reach this stage, only 20% achieve final approval for marketing.
- Stage 4. Review by the regulatory agencies, who assess the available pre-clinical and clinical information on the product. Essentially, these assessments focus on aspects of effectiveness and safety, although they also examine methodological aspects of the research to confirm that the results observed are real and are not a result of statistical manipulation. Following approval, the product can be marketed in that regulatory agency's area (the FDA for the United States, the EMEA in the EU).

My Notes

The regulatory agencies have two processes for reviewing the products submitted, depending on whether or not they address insufficiently covered medical needs. If they do, the review process is faster and conditional approval may even be given with preliminary clinical data. The golden rule of the regulatory agencies is proper evaluation of the profit/risk balance. This process, which awards approval as an "orphan" drug, is applied in the case of drugs for diseases with a high mortality rate, which affect a small group of the population and for which there is no effective treatment.

In general, apart from those mentioned above, the main factors comprising the final impact on development costs are as follows:

- *Regulation of drug approval and its impact on new developments.* The approval process will be very important; if the present system is not changed, it will be difficult to reduce the time and costs required in developing new pharmaceuticals. The regulatory agencies are currently studying ways of making the process more flexible, stressing the critical path, which, as mentioned above consists of safety assessment, evaluation of medical utility, and product industrialization [7]. This is a sign of the FDA's concern about the fall in the number of products being submitted for assessment, reflecting a certain stagnation in innovation which could in the long run have harmful consequences for public health. Similarly, people are beginning to assess the impact of genomics on the innovation and development of pharmaceutical products [8]. One possible short-term way of speeding up the approval process is to consider the new pharmaceuticals as orphan drugs, although, as shown in the process of developing pharmaceuticals, this is only valid for a small number of diseases and patients.

- *"Origin" of the new pharmaceutical products.* Depending on whether the new drugs have come from new research, previously rejected molecules or modifications to drugs already on the market, the development cost varies significantly, as do the opportunities for new entries. Drugs based on new research have higher development costs and open doors to new competitors whereas launches based on previously rejected drugs involve lower costs and have a greater competitive advantage for established players.

7. http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

8. http://www.fda.gov/cder/guidance/5900dft.pdf

- *Ease in finding biomarkers.* Biomarkers will be the key to associating treatments with genetic profiles, and will therefore be necessary both for the development (where they will be included at the clinical trial stage) and for the launching and correct administration of new drugs. Depending on the availability of valid biomarkers and the difficulty of finding new ones, development costs of new pharmaceuticals can vary greatly. Once again, regulation of the process of development, validation and use of biomarkers will be of key importance in this aspect.

New business models

As we have seen already, the emergence of personalized medicine will cause something of a shake-up in the business models and profit and loss accounts of pharmaceutical companies. Like any shake-up, there will be changes in business strategies and there will be winners and losers, and this will partly change the structure of the industry and its main players.

The following are some of the business models that companies in the industry might introduce:

- *Continuance of the traditional model.* Some companies may decide not to alter their existing business model, preferring to sit tight and watch trends in the development and application of personalized medicine develop. If things move quickly, these companies will possibly be forced to buy out other companies which have committed to the new medicine.

- *Focusing of resources on research into genomic pharmaceuticals.* Companies that commit themselves to this model will centre most of their resources on the research and development of pharmaceutical products and treatments targeted at genetic profiles.

  The main risk they will face is the possibility that personalized medicine may take longer than expected to become a reality. This model will clearly be the one that will be followed,—indeed is already being followed—by new players, mostly biotechnology firms, who see an opportunity in this change of circumstance.

- *Adaptive business models.* Given the uncertainty regarding the way the new circumstances will develop, many companies may develop strategies that adapt closely to these changes, thus allowing them to keep their options open depending on the scenario that ultimately prevails. Companies that opt for this model will assure their survival provided they know how to read this development properly, although it is possible that they will not be the ones with the best economic results in the short and medium term.

- *Manufacturers of generic drugs.* The trend in recent years has been for a number of laboratories to specialise in the production of generic drugs as their patents ran out. Even many of the larger laboratories have developed generic lines to offset the higher R&D expenses involved in developing new drugs. It is possible that this model will continue to operate in the future, although a variant may emerge based on the development of genomic drugs that are minor variations of other existing ones and which are therefore more effective for sub-segments of the population at whom the first pharmaceutical was targeted.

- *Comprehensive health service providers.* In view of the possible loss of income due to the reduction in markets for some blockbuster drugs, some pharmaceutical companies may decide to move up a step in the industry's value chain, offering new products and services which will turn them into comprehensive health service providers.

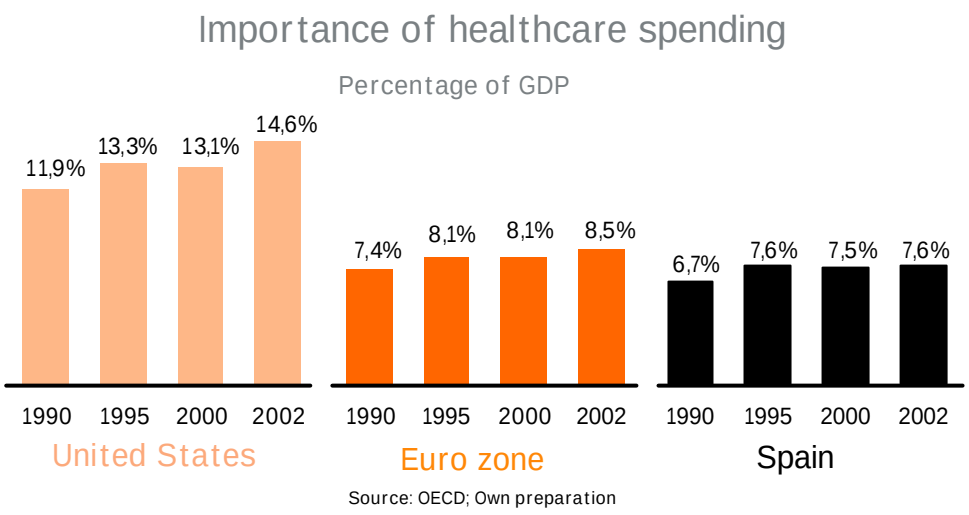
- *Collaborative models.* Given the range of possible strategies and the complexity of the new circumstances, many companies may decide to pool their key capacities. For example, new biotechnology firms may specialise in the development of new genomic pharmaceuticals, while traditional pharmaceutical companies could use their broad sales networks for distributing and marketing them.

Public health systems

Spending on healthcare[9] has seen strong growth over the last 10 to 15 years, during this period the percentage of GDP it accounts for has increased by one or more percentage points in the various OECD Countries. This trend has accelerated in the last 2 to 3 years, leading to health spending reaching levels of nearly 15% of GDP in the United States in 2002, 8.5% in Euro Zone countries and 7.6% in Spain. In per capita

9. All figures for spending on healthcare contained in this section have been obtained from statistics published by the OECD, using linear averages of countries when group data are given.
The figures for comparative expenditure have been adjusted to purchasing power parity.

terms, this represents spending of about $1,700 per person per year in Spain, nearly $3,000 in countries such as France and Germany and over $5,000 in the United States.



Source: OECD; Own preparation

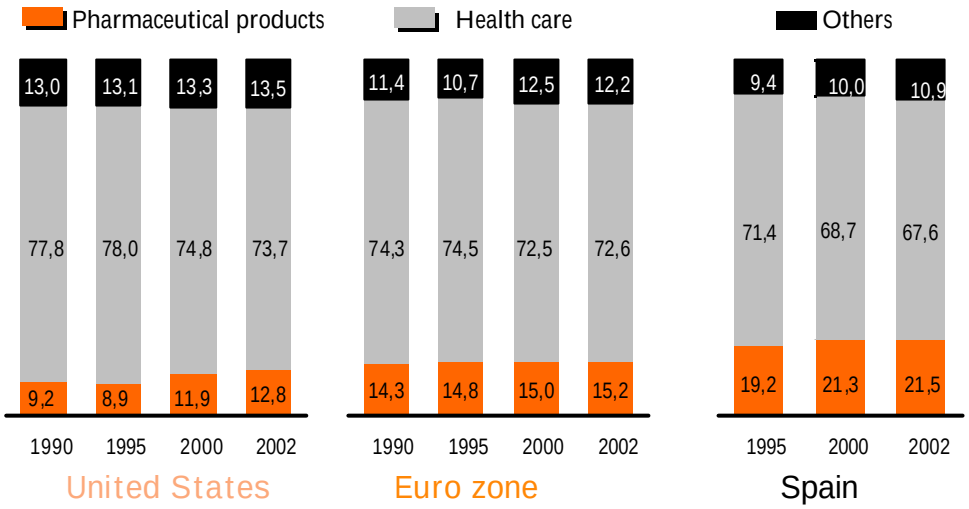
If we look at trends in spending by categories, we can see that pharmaceutical spending has grown above the average, gaining as a proportion of total expenditure. Nonetheless, we can see a certain disparity between the weight of this component in Spain (more than 20%), in other European countries (15%) and in the United States (nearly 13%). Spending on health care, on the other hand, represents somewhat over 70% of the total (slightly less in Spain), and has dropped back as a proportion of total spending, although continuing to grow in absolute terms and—except in Spain—as a percentage of GDP.

Within the area of health care, we can observe a slight rise in spending on outpatient and home healthcare, offset by a fall in relative terms in spending on hospital care. The fall in hospital spending is a result both of a reduction in the causes of hospitalisation[10] and a decrease in average hospitalisation periods, which in OECD countries have fallen from 15 to 10 days over the last 10 years. This has led to a reduction in the number of hospital beds per thousand inhabitants in OECD countries (excluding those given over to long term care) from 4.8 in 1990 to 4 in 2000.

There has also been a slight increase in the weight of all the other items, which together account for between 10% and 15% of spending on health.

Structure of healthcare spending

Percentage of total expenditure



Source: OECD; Own preparation

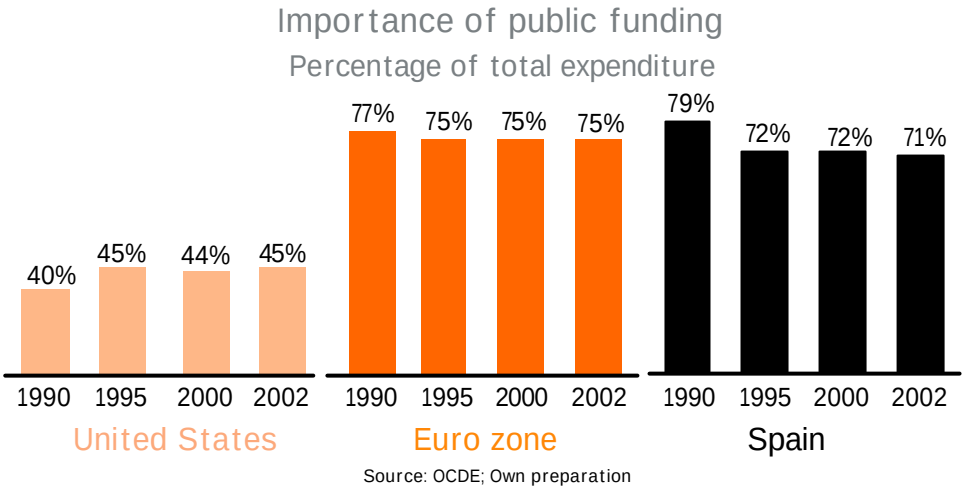
My Notes

In the area of financing of the healthcare systems, in mainland Europe approximately 75% of the cost is absorbed by the public sector, whereas in the United States the proportion is smaller—close to 50%. The following illustration also shows a slight downward trend in the participation of the public sector in Europe, and a slight upward trend in the US. As a result of major increases in spending and a high level of participation by the public sector, public health systems have experienced major financing problems which have not yet been fully resolved. This is the case of Spain, where some regions recently began to use a new tax on fuel to finance the deficit in the public healthcare system.

In the United States, this negative trend is framed within the context of a reform in the public healthcare system (known as MMA or Medicare Modernization Act), whose aim is to improve the system's performance, particularly towards elderly people, while at the same time trying to halt the rise in national healthcare spending. In the area of performance, improvements will be made to drugs coverage for the elderly segment, putting greater pressure on prices for pharmaceutical companies that want their products to be included on the list of certified products. A number of measures will be taken to cut costs: the public system will remunerate the healthcare system on the basis of the quality of the results and not just the number of treatments;

10. Hospitalization is not necessary for minor operations, except on rare occasions.

people will be encouraged to create and use Health Saving Accounts (HSAs, described below) and collective negotiation of insurance health premiums for small companies (to cover employees) will be promoted.



Source: OCDE; Own preparation

In this context, the development of personalized medicine may have a substantial impact on the development of health spending, as well as on short, medium and long-term financing requirements. Specifically, it may lead to the following repercussions:

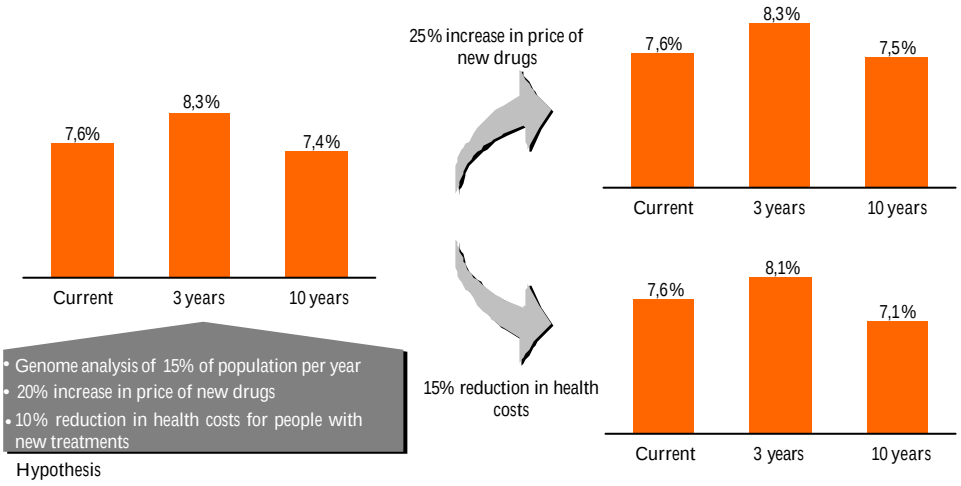
- *Pharmaceutical expense*. As mentioned in the previous section, it is possible that the price of pharmaceutical products may rise, causing pharmaceutical spending to increase as a relative proportion of GDP.

- *Spending on health care*. The introduction of personalized medicine will, in principle, contribute to a reduction in these costs, which, as we have already seen, are the largest item of spending. Thus, greater effectiveness and fewer side effects can reduce hospitalisation costs, as well as cutting, for example, the number of surgical operations, thanks to better preventative and curative treatments. Nonetheless, the aging of the populatio and possible changes in lifestyle could totally or partially offset these effects.

- Other expenses. This item may include the impact of new analyses in finding a person's genome. As an illustration, given a cost of €1,000 per person, the cost of analysing the genome of 15% of the Spanish population every year would come to over €6 bn or approximately 0.8% of Spanish GDP.

If we use take a hypothetical situation in which the genome of 15% of the population will be analysed every year; treatment costs are reduced by 10% for the population receiving personalized medical treatment and prices of new pharmacogenomic drugs rise 20%, Spanish spending on health would rise from 7.6% to 8.2% in the first 3 years and then fall to 7.3% over 10 years (see illustration below). In contrast, if the reduction in the cost of treatment were to be 15% (rather than 10%), total health spending would fall as compared to the Base Scenario to 8.1% and 7.1% of GDP in 3 and 10 years respectively, whereas if there was an increase in the price of the new drugs from 25% (instead of 20%) total expenditure would rise to 8.3% and 7.5% of GDP respectively.

Possible scenarios for trends in spending on health in Spain.
Percentage of GDP



Source: OECD; Own preparation

If we use the above scenarios, what we do appear to see is that there is a possibility that total health spending might increase in the short term, and we must ask whether the public health systems would absorb that increase in expenditure, or whether on the other hand it would be the private sector which would profit from the increase. Although the public sector has a clear incentive to reduce health costs in the medium term, possible budgetary strains might prevent short term investment, especially when the possible returns (economic and social) require a period which is longer than a single term of office.

An understanding of the development and structure of future healthcare spending is therefore a key factor both in order to understand the possible strain on financing in the public systems and to identify possible business opportunities for the private sec-

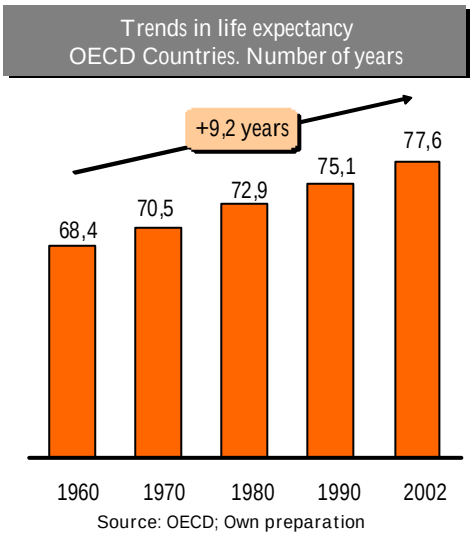
tor, especially for healthcare service providers and the insurance industry.

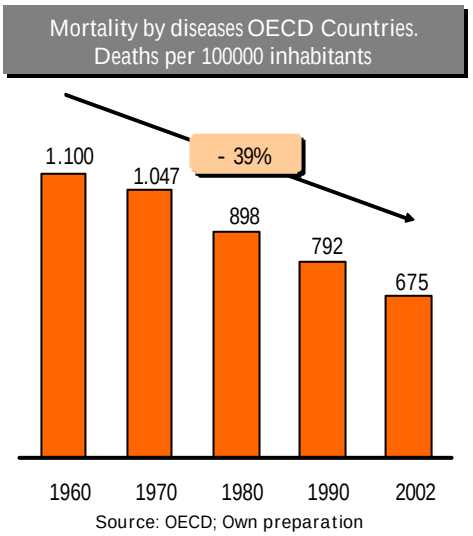
Social aspects

Among the social aspects related to personalized medicine there are two outstanding themes: health and quality of life on the one hand and ethical and moral aspects on the other.

Health and Quality of Life

The last few decades have seen the eradication of many diseases and (as we can see in the graph below), a clear advance in life expectancy, mainly among the inhabitants of developed countries where the figure has risen from 68 to nearly 78 years over the last four decades. There have been many contributing factors but, as we see in the graph, medicine and medical breakthroughs have played a leading role. As a result, the improvement in life expectancy has been caused more by a reduction in mortality among children and middle-aged people than by an increase in "maximum longevity", given that the life expectancy of people of 80 has increased by less than two years during that period.

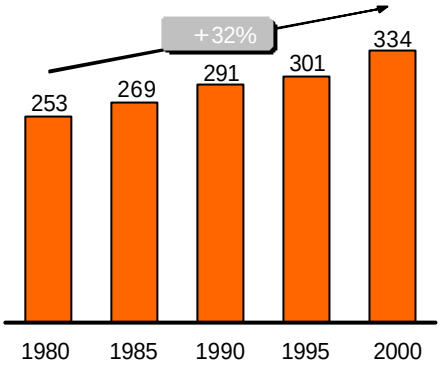




However, in many cases this advance has not led to a clear improvement in quality of life, while at the same time the aging of the population has led to the development and emergence of diseases which had previously been either non-existent or played only a secondary role, such as Alzheimer's disease. Combined with the two previous factors, this means that we are experiencing a growing impact of diseases for which there is still no effective cure, as is the case with cancer and AIDS.

Impact of cancer

OECD Countries. Incidents per 100,000 inhabitants



Source: OECD; Own preparation

All of these factors are causing greater social pressure for improvements in health, both with regard to an improvement in the effectiveness of treatments—especially in the diseases mentioned above— and in a reduction in the side effects of existing treatments. This social pressure may be an important spur to the development of personalized medicine.

In this context, there is no clear consensus regarding the implications of personalized medicine for health. On the one hand, it seems clear that an increase in effectiveness and a reduction in side effects could increase life expectancy and therefore accelerate the rate of aging of the population. On the other hand, it is not as clear what the intensity of this increase will be and the effect it will have on the quality of life of the population, and in this area factors like the following will be influential:

My Notes

- *Type of diseases for which results are achieved.* The impact on quality of life will be very different if the diseases for which drug effectiveness is improved are chronic— such as diabetes— or they are more limited in time, such as cancer. However, initial development of personalized edicine in the latter cases may have a greater impact on life expectancy.

- *Appearance of new diseases*, until now practically inexistent, which will develop as a result of the curing of other preceding ones.

- *Changes in people's living habits.* There may be positive changes in people's living habits: if they know that they are more susceptible to certain diseases, they will avoid habits or diets that might aggravate this propensity. Paralleling this, however, there may be negative changes in habits due to the possibility of curing diseases: for example, some people might take up smoking or be less inclined to give it up if a very effective cure for lung cancer existed.

- *Benefiting Population.* Depending on who assumes the leadership of the adoption of personalized medicine and, above all, the role of the public health systems, the segments of population accessing the new treatments may be confined to those with the greatest purchasing power or those suffering from very specific diseases.

Consequently, depending on the above factors, the impact on life expectation and quality of life, as well on health spending, will vary greatly. For example, high rates of effectiveness in chronic diseases, non-emergence of new diseases, some positive changes in habits and the breadth of benefiting population segments could significantly improve quality of life and life expectancy, and have a greater impact on reducing health costs. However, greater effectiveness in specific diseases, the appearance of new diseases and the development of negative habits could have a limited impact on quality of life and life expectancy, and even increase health spending in the medium term.

Ethical and moral aspects

Arising out of the possible impacts analysed in the previous point, there are a number of issues which may become relevant in the future development of personalized medicine.

Firstly, the application of treatments based on the knowledge of a person's individual genome might come into conflict with currently prevailing values in society, such as:

- *Confidentiality of personal data,* especially related to health, a category which includes a person's individual genetic information.

- *Non discrimination,* both in general social terms and in access to work and certain services (such as medical insurance). Here it is necessary to stress that there is no "normal" genetic profile and there are therefore no abnormal or inferior genetic profiles. Indeed, some profiles which are more resistant to one disease may be—and very often are—less resis tant to another one.

- *Equality of access to basic services,* since it is possible that at the beginning of the development of personalized medicine some segments of the population (e.g., those with greatest purchasing power) might benefit more than others.

- *Right to not know,* in the sense that individuals should not be obliged to know information on their predisposition to possible diseases in the future, especially to incurable diseases. We need to bear in mind that this knowledge can sometimes be more devastating than the disease itself. We also need to bear in mind that these predictions will be based on the probability, not the certainty, of suffering a disease.

In turn, the development of genetic engineering may meet considerable resistance among society in general and from certain segments in particular, with regard to aspects involving genetic manipulation, cloning and stem cell research. The first two of these aspects lie outside the scope of this report, according to the definition of personalized medicine which has been used. The third aspect would affect to a greater extent the development and application of individualised treatments based on stem cells.

Educating the public about genetics and its applications will therefore be a key factor in facilitating the introduction of personalized medicine and the acceptance of the ethical aspects mentioned above.

Other sectors affected

As we have already seen, the health industry encompasses and influences many other industries as well as those analysed above. In addition, advances in medicine cause changes in the population structure (increased aging, for example) and habits, which may have a significant impact on other unrelated sectors.

We will now analyse the context and possible implications of personalized medicine for the most relevant sectors, bearing in mind —as we have already said— that this list could be much longer and be the subject of a specific study in itself.

Prescribers

Although prescribers now essentially synonymous with doctors are an important part of health care services, they have been separated because of the specific consequences of personalized medicine for this group.

As already explained, until now medicine and, especially the role of the doctor, has been a field in which both diagnosis and treatment have been largely based on symptomology and on the physician's experience (the phenotype). With the development of personalized medicine, there is going to be a shift towards diagnoses and treatments marked in a more deterministic way by the genetic profile of the patient (genotype) and, thus, the importance of experience will diminish, especially when it comes to treatment.

These changes will have important consequences for this group. Firstly it will lead to the need for additional training in genetics as required by the new circumstances, since this is a field which is not widely addressed in medical syllabuses, and this might hinder the development of personalized medicine. Secondly, they may have to face a redefinition in their role, with clear reinforcement in some cases and replacement in others by new or existing players in the value chain. One possibility is that their role will evolve towards that of a *genetic advisor*, which will not only require greater genetic knowledge, but also extensive training in psychology.

If these changes happen, they might affect the marketing and communication strategy of the pharmaceutical industry, which currently centres on doctors.

Medical insurers

This is a sector that will be greatly affected by the development of personalized medicine, because of the impact it will have on the different areas of health spending, as we have seen already. The role played by public health systems under these new circumstances may also open, to a greater or lesser extent, new business opportunities for firms in this sector.

In terms of the possible impact on running the business and establishing services, it is important to note that there is a strategic trend towards greater individualization of risk management and thus of premiums, which can be observed in various branches of the insurance industry. A good example in the health industry is the American initiative for the creation of Health Savings Accounts which will allow people to save part of the premiums paid and not used for future occasions and even to recover it for given uses at a certain age. The purpose of the initiative is for the insured person to be more responsible for health spending and thus to contribute to reducing the rise in American insurance prices.

Within this context of greater individualization of risks, the new genome-based medicine will allow the risks of each client to be analysed on the basis of their genetic profile and different policies and products to be adopted accordingly. Special conditions might even be offered to people from certain risk profiles if they undertake preventative behaviour. However, these possible commercial strategies will have to be adjusted to legal circumstances and to two very specific areas in particular:

- *Confidentiality.* Regulation, as analysed in the following section, protects and guarantees the confidentiality of a person's medical —and by extension, genetic information and their right not to reveal it.

- *Discrimination.* As we have seen in previous points, there is concern that the knowledge of certain risk profiles might make it impossible for certain segments to take out insurance at an affordable cost.
  It is highly possible that there will be protection against this type of discrimination, which would limit the policies set out above.

Pharmacies

In most developed countries, pharmacies have to date played a role as a specialist —and in many cases exclusive—point of sale for pharmaceutical products. With the emergence of personalized medicine, pharmacies might start to play a more important role, possibly becoming the place where genetic analyses are performed, suitable doses are prepared. They might even assume the role of prescribers, on the basis of the results of the genetic tests.

Computer industry

As already mentioned at the beginning of this chapter, analysis of the human genome involves a great deal of data processing and storage. This means that as well as the large amount of information obtained from a single person, there are huge complexities of calculation when it comes to establishing relations between genetic profiles, diseases and possible treatments, in which hundreds of genetic profiles may be analysed at the same time. For example, Celera Genomics stores more than 80 terabytes of information[11].

All aspects of IT (calculation capacity, storage, data processing software, etc.) will therefore be of key importance in the development of personalized medicine. This could facilitate —as it is already doing— new business opportunities as well as the emergence of new business models, including suppliers of genetic databases.

New business

Like any change, as well as the advances listed in previous sections, the emergence of personalized medicine will create new opportunities and new types of business at every link in the value chain. For example, it is possible that in these new circumstances, we may see new businesses such as comprehensive health managers, knowledge suppliers reporting on the latest genomic treatments to appear and manufacturers of devices that allow continued health monitoring.

Legal aspects

To conclude this analysis of the context of development of personalized medicine, we have decided to include a section on legal aspects, in view of their relevance and future influence. This section centres mainly on current legislation and future trends which are beginning to emerge in this area. However, in conjunction with the development of this area, new legislation will have to be developed in which the agents involved and the regulators will play a very active role. Agents who are more proactive and quicker to submit their proposals to the regulatory body will be able to gain regulatory advantages for the development and configuration of their business..

As is the case with any legislation, there will be differences between countries and geographical areas, and this may accelerate or hinder the development of personalized medicine in some countries more than others. It is possible that "legal havens" will be created in a bid to attract research and even patients for more advanced treatments.

The three legal areas which are most closely related to personalized medicine are listed below.

11. To give an idea, a terabyte is equivalent to the amount of information contained in approximately one million average-sized books.

Drug development

As mentioned above, the launch of new drugs requires approval from the drug agencies in each geographical area, based on a very tightly-regulated process. Pharmaceutical products adapted to genetic profiles will be subject to the same restrictions, although it will probably be possible to simplify the processes, given that new drugs will be targeted at specific segments and not at the entire population. The development of specific legislation for the approval of these pharmaceuticals will be of key importance in making personalized medicine a reality.

The criteria on clinical trials at development phases will continue to apply. In the case of Spain, it will be necessary to gain authorisation from the Spanish drug agency (*Agencia Española del Medicamento*) agreement from the centres where they are to be carried out, a favourable ruling from the Clinical Research Ethics Committee and the written consent of the patient. In addition to these requirements, the companies performing the trials will have to have taken out insurance against any civil liability that might be caused by harm to patients.

Finally, the approval of a drug does not exonerate the manufacturer from any civil liability it might incur for damages resulting from the use of the product.

Genetic research

Spanish legislation permits the use of embryos for stem cell research provided they come from surplus material from processes of assisted reproduction and the parents have given their informed consent.
Development of this legislation on a national and international scale—in both permissive and restrictive terms—will greatly influence scientific advances in this area and thus the pace at which the advantages of personalized medicine can be passed on to the general public.

My Notes

Genetic manipulation is punishable by prison sentences under Spain's Criminal Code, unless it is used for correcting or eliminating serious defects or diseases in the subject of the manipulation.

Obtaining and managing the information

The possible (mis)use of genetic information make this issue even more relevant in the field of personalized medicine.

In principle, Spanish law classes information on the health of individuals as specially protected data pursuant to the Personal Information Act. There are exceptions to this

rule, mainly in cases of serious risk to health for the general populace. Consequently, in order to obtain the patient's information (such as genetic information) and except in the case mentioned above, the patient must have given their informed consent.

Furthermore, the main conclusions of task forces on genetic testing in various countries tend to reinforce the point made above. They also recommend that it should be necessary to obtain the patient's informed consent before the genetic tests are carried out and, in particular there should be a ban on discriminating on genetic grounds against people entering the labour market or taking out insurance. This is further backed by the clause on non discrimination contained in the Spanish Constitution (Art. 14), and by the future European Constitution, which is even more explicit in its prescription against discrimination on genetic grounds. In any case, this principle must be articulated against that of adverse selection, which allows insurance companies to discriminate in the prices of their premiums depending on the risk, as happens, for example, with motor insurance.

The same occurs with the articulation between the principle of non-discrimination and the possibility of not hiring workers if their health might represent a risk for themselves or those around them. Proper articulation of these two principles, both in the working area and in insurance, will have a definitive influence on the successful development of personalized medicine and also in preventing people seeing themselves as first or second-class citizens depending on their genetic characteristics.

Finally, the law gives patients the autonomy to accept or reject treatment, except in cases of clear risk for their physical or mental wellbeing.

4

CHAPTER 4

The FTF's expectations in regard to personalized medicine

4 The FTF's expectations in regard to personalized medicine

Here we take a look at the opinions expressed at the Forum regarding how personalized medicine, as defined in earlier chapters, may develop and the impact it may have. Two approaches were taken:

- First, two work sessions were held at which all Forum members were present. Several papers were read by internationally recognized experts. Each individual had the opportunity to express his/her view, either individually or in groups. Prior to these sessions, diverse information was gathered and distributed as a basis on which to work.

- Second, questionnaires were administered in accordance with the Delphi method. The aim was to determine the overall opinion of the Forum members as to the likely development and impact of personalized medicine.

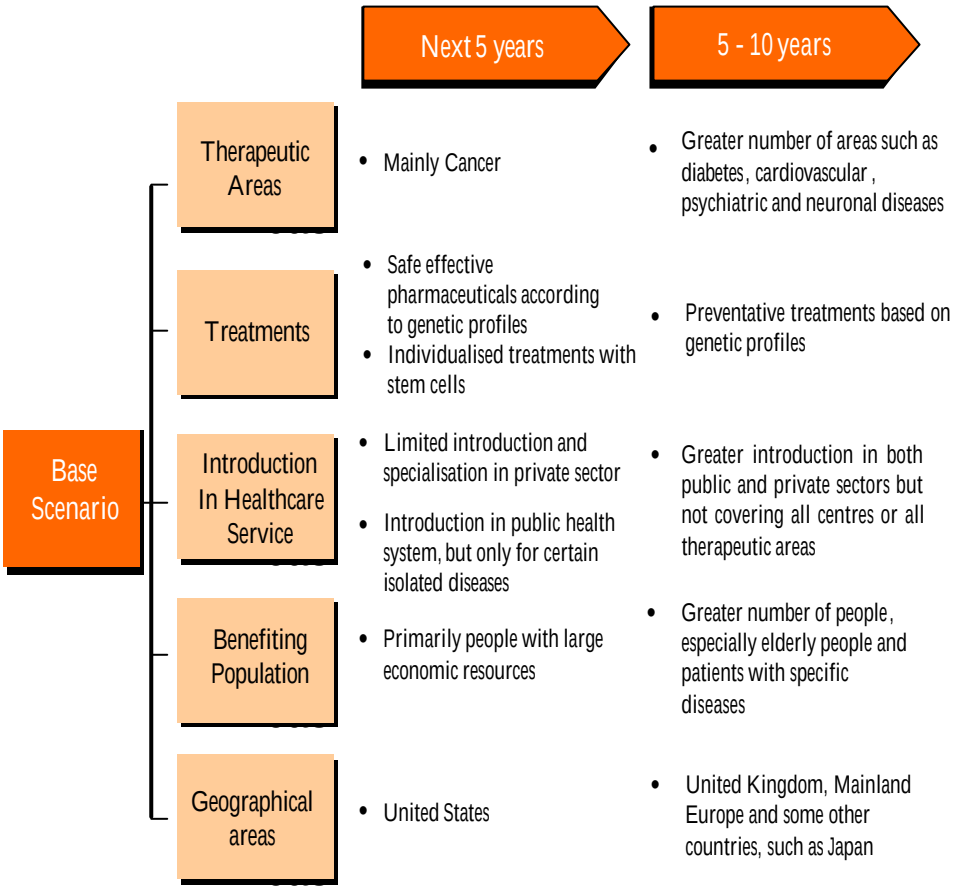
The results are here summarized in three sections. The first section deals with the most likely developments over periods of five and ten years, the second with the factors that will speed up or inhibit the advent of personalized medicine, and the third with the main effects in the four areas here under study.

4.1. What will happen?

The members are in general quite optimistic regarding the development and introduction of personalized medicine, though slightly less so with respect to the rate of the process. The broad majority believe that the question will be one of evolution rather than revolution, since advances will occur in staggered manner and be prolonged in time. All believe that when we look back fifteen years from now, it will seem like a revolution owing to the great change that will have taken place in treatments and in the understanding of illness.

The predominant feeling is that the first advances, constituting what has been called the *base scenario*, will be seen within five years, although it will be necessary to wait nearly ten years for the broader results in terms of illnesses and population affected (see illustration).

Most Likely Scenario for Personalized Medicine according to FTF Members



My Notes

Specifically, this base scenario will take shape as follows:

- *Therapeutic areas affected.* Probably the only illness significantly affected by personalized medicine within five years will be cancer. Within ten years, however, advances will also be seen in a broad range of other areas, including diabetes, cardiovascular disease (e.g. hypertension), psychiatric illness (e.g. schizophrenia and depression), and neurological illnesses (e.g. Alzheimer's and Parkinson's).

- *Types of treatment.* Within five years we will see the first medicines aimed at genomic profiles, which will be more effective and will have fewer side effects. At the same time more individualized treatments based on mother cells will begin to have positive effects. On the other hand it will be necessary to wait a few more years, though fewer than ten, for the development of preventive treatments based on genetic profiles.

- *Introduction into the health system.* Within five years the new treatments will have been adopted by a small part of the private sector, with very limited impact in the public sector. In ten years' time these same treatments will be more general in both sectors, although they still do not cover the entire health system or the full range of illnesses.

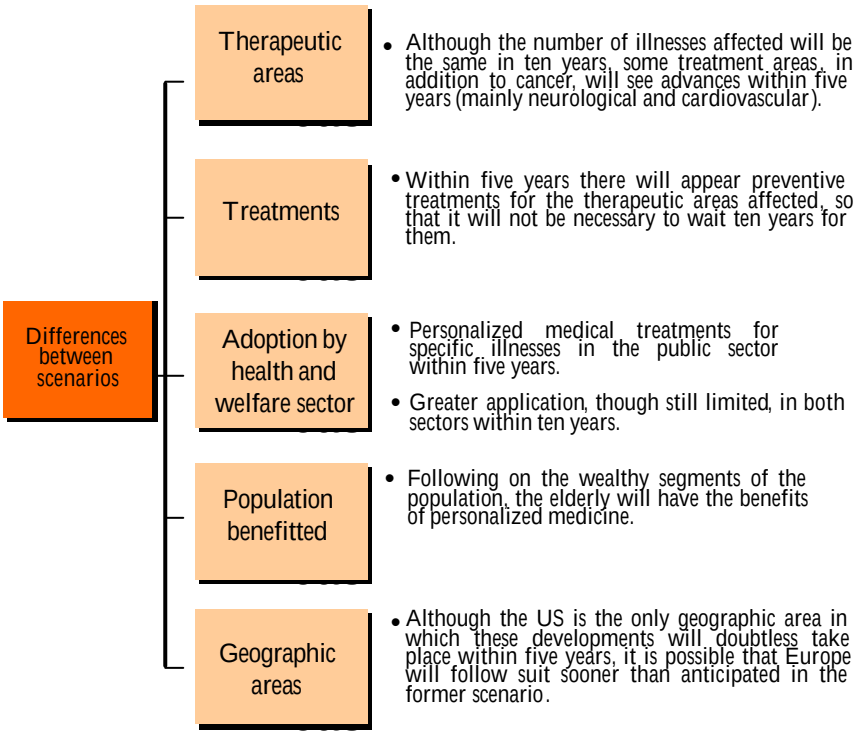
- *Population benefitting.* Within five years, most of the persons benefitting will be in a high income bracket, while within ten years the benefits will extend to a larger part of the population. In the main the people here referred to will be elderly or will suffer specific illnesses, basically those given more priority, and dealt with on a mass basis, by the public sector.

- *Geographic areas.* It is generally agreed that the first advances in personalized medicine will occur almost exclusively in the US, followed almost simultaneously by the UK, Continental Europe, and a few others countries such as Japan. In general the Forum members believe that developments in Spain will coincide with those in the rest of Continental Europe. In the case of underdeveloped countries it will take longer for these advances to become available to larger population groups.

Not of the majority opinion, a small group of Forum members believe that the base scenario defined above may develop more rapidly than that set forth earlier (see the following chart).

This *accelerated scenario* is one in which, even if the therapeutic areas affected in ten years should fail to vary significantly, in many of them (principally neurological and cardiovascular) there will be advances seen within five years. In addition, preventive treatments will begin to appear for those illnesses before the foregoing scenario, some of them in less than five years. Although only for very specific illnesses, the public health systems will begin sooner to adopt the new treatments, possibly with their limited extension to other therapeutic areas within ten years. Finally, with respect to the people who benefit and to the geographic areas affected, this accelerated scenario is similar to the base scenario, although benefits come a little sooner for the elderly, along with personalized medical techniques in Europe.

Differences between scenarios.



4.2. What will accelerate or impede the process?

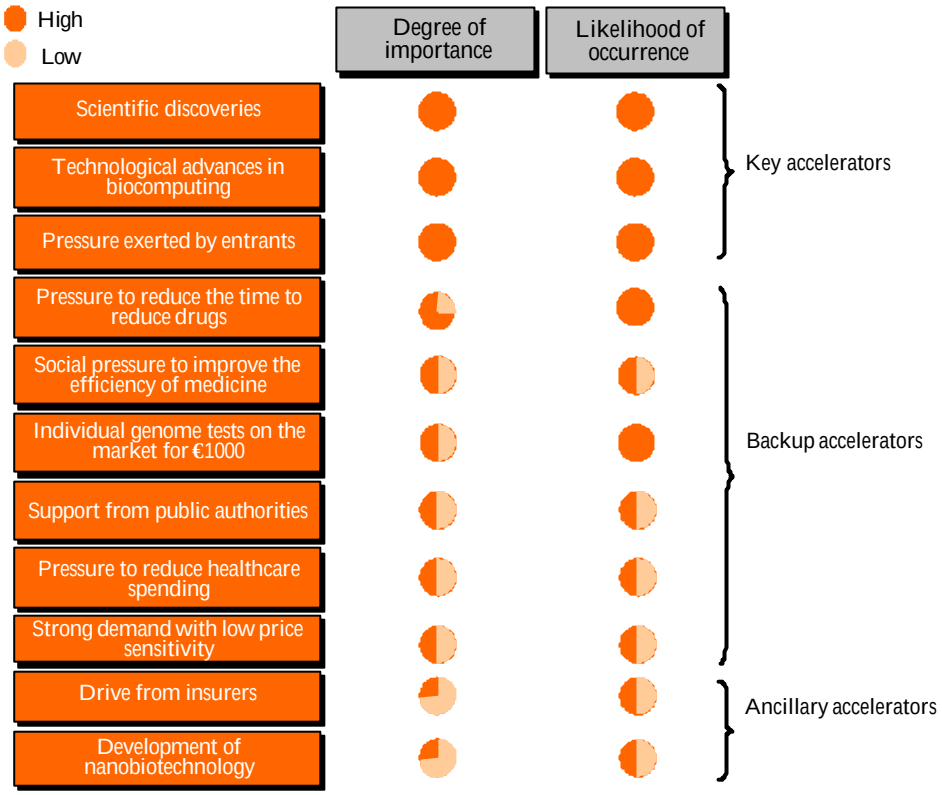
From the point of view of business it is very important to be able to know at any moment what stage a process has reached, as well as to know its rate, so that strategies can be accordingly modified. Premature investments and initiatives left too late may thus be avoided. This is especially the case in situations such as that of personalized medicine, owing to the considerable uncertainty regarding its future.

The aim in this section is to provide firms with a set of indicators, specifically accelerators, or factors that will propitiate the development of personalized medicine, and brakes, or factors that could impede such development. These indicators will make it possible to keep an eye on progress with respect to the base scenario referred to in the foregoing section.

Accelerators

In the illustration below there is a list of the main accelerators considered by the FTF. They are categorized according to their importance in the development of personalized medicine and to the probability of their attaining to reality within the period here contemplated.

As may be seen, the general opinion is that scientific and technological advances (especially in biocomputing), along with the pressure exerted by the new entrants, will be the *key accelerators* behind personalized medicine. These will be followed in importance by *backup accelerators*, i.e. social pressure and the desire on the part of institutions to enhance treatments and reduce health costs. Next will come the pressure of market demand and of other components in the value chain. As regards the probability of their attaining to reality, the outlook is quite positive insofar as concerns each of the accelerators here mentioned, especially those regarded as most important.



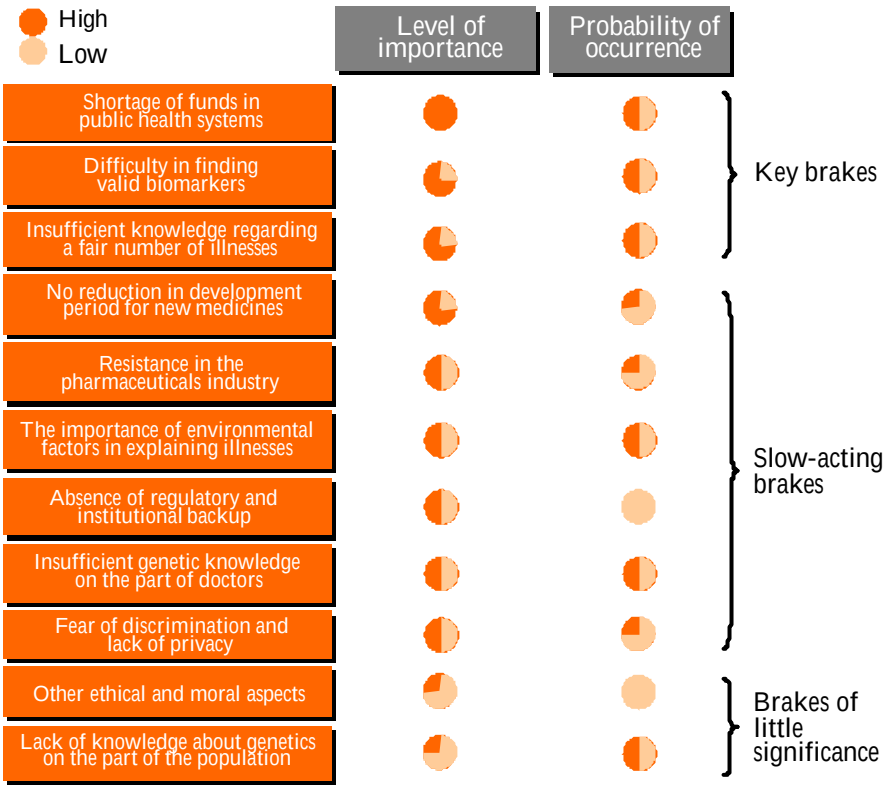
Hence what we're looking at is a push market, one that is pushed mainly by technological advances but also by demand on the part of individuals, along with institutions, for higher quality and lower costs where health is concerned. The principal indicators in question will be the key accelerators, followed by the backup accelerators. In other words advances in technology and research, the financial health of the new biotechnological firms, and the continuation of society's demand for the quick application of scientific discoveries.

My Notes

Those members of the FTF who defend the accelerated scenario for the development of personalized medicine take a basically similar view in regard to accelerators in general, but they ascribe even more importance to technological advances. Among key accelerators they include achievements in nanobiotechnology, which they regard as highly probable.

Brakes

Similarly the FTF has undertaken to pinpoint and assess those factors, as well as their probability, that might hold back advances in personalized medicine. In the diagram below one can see how such brakes as might occur are regarded as less important than the accelerators, while the greatest difference arises in the probability of their occurence. The majority opinion is that their occurrence is very unlikely.



The *key brakes*, those that will most impede the process, are on the one hand scientific, relating mainly to knowledge regarding illness and to the finding of biomarkers that will connect genetic profiles with the appropriate treatments. And on the other, it may happen that shortage of funds in the public health systems greatly impedes the widespread application of medical advances.

Less important, and less likely to arise, are the *slow-acting brakes*. Among these we find resistance to change on the part of the traditional pharmaceuticals industry, but such resistance is now less feared than it was earlier. Also considered less important and less probable than in the past are the ethical and social factors. While it is conceded that debates may arise in these areas, most members feel that the regulatory measures needed for their undertaking will be established.

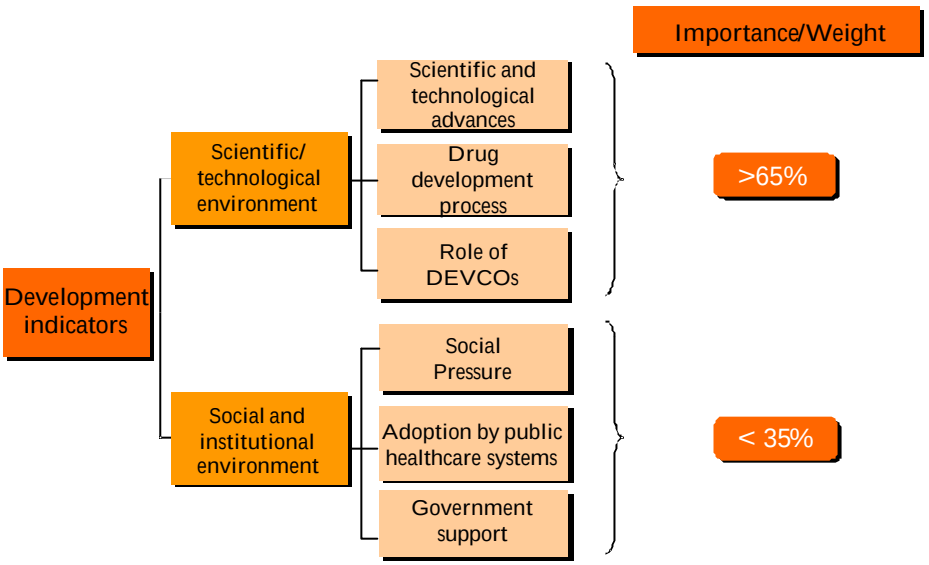
It is in the importance and future development of these factors that we find the greatest disagreement within the FTF, i.e. between the majority, which foresees the base scenario, and those who foresee the accelerated scenario. In general these latter ascribe less importance and less probability to the brakes menioned above. The principal disagreements regarding probability arise in relation to science, such as the difficulty in finding biomarkers, the failure to speed up the development of new medicines, the insufficiency of knowledge regarding numerous illnesses, and the fact that environmental factors may bear on the development of a given illness. At the same time they believe that the traditional pharmaceuticals industry is less likely to be a brake than to be an accelerator.

Indicators to be monitored

Following replies in the above areas, a framework of indicators is proposed that will make it possible to assess in a more continuous way the development and most probable scenario where personalized medicine is concerned. As shown in the figure below, the indicators are divided into (1) scientific-technological environment and (2) social and institutional environment.

These two groups contain the major factors for the future of personalized medicine. The first will be the most important, although the second may in large measure compensate for differences of performance in the first. To take an example, negative developments in the scientific-technological environment with respect to that predicted will entail delays in introduction in relation to the base scenario, even if the social and institutional environment should develop more favourably than expected by the FTF. If it were desired to assign weights to each group in order to have a tool for prediction

of the development of the base scenario, the suggestion would be to assign to the first group a weight greater than 65%.
The indicators are as follows:



Scientific-Technological Environment

This group contains three categories of variables:

- *Scientific and technological advances.* All advances in scientific research, mainly biological and medical, as well as relating to storage technologies and mass data calculation. In the case of these variables, follow-up is related to the failure so far to achieve such advances, since the majority opinion at the FTF is that they will be made. Should they not, there would be a delay in the introduction of personalized medicine.

- *In relation to the development of new medicines.* Brakes on the finding of biomarkers, insufficient knowledge where many illnesses are concer ned, and failure to reduce development time for new medicines. These can work either way, since it is expected that they will not have a great hindering effect. Should that effect be more significant, so that not so many new medicines are developed as desired, the base scenario would be held back. If on the other hand, consistently with the majority opi- nion, their impact should be limited, personalized medicine will develop more swiftly, taking on the tones of the accelerated scenario referred to above.

- *Role of the DEVCOs.* Depending on the role of the new biotechnological companies (which is expected to be salutary) and of the traditional pharmaceutical companies (judged to be neutral), the scenario could go either way. The number of new entrants and their access to the capital market, as well as the strategy of the phammaceutical firms where genomic research is concerned, will be the factors to watch.

Social and institutional environment

There will be social and institutional factors affecting the adoption of scientific and technological advances. This group includes the following areas:

- *Social pressure.* The public's attitude to personalized medicine will be a key factor where its adoption is concerned. On the one hand we have the demand of society for better healthcare, while on the other there are ethical and moral questions, especially in relation to discrimination and confidentiality. The opinion of the FTF is that the former will indeed take place, while the impact of ethical themes will be limited. If social pressure is focused more on ethical questions, the development of personalized medicine may be delayed.

- *Adoption by the public health systems.* Within the public health systems, the key variables are the pressure to reduce costs and the lack of funds for the adoption of new treatments. In general the members believe that both will be important, especially the second. If the tendency is toward investment with a view to reducing costs, then personalized medicine may be taken up more swiftly by the health authorities and thus more quickly introduced. A related question is the role of the medical insurance companies, which, although not considered critical by the FTF, could accelerate adoption, especially in countries like the US, where private systems have greater weight.

- *Governmental backing.* Backing from governments, along with the development of regulations in the area, will be factors of mean importance, though members believe there will be governmental backing, in the form of grants for research and of legislation allowing application of the new treatments. Otherwise we may clearly expect that the introduction of personalized medicine will be slower than foreseen in the base scenario described in the former section.

4.3. What impact will there be on society and on firms?

Here we consider the point of view of the members regarding the most probable impact in each of the areas here in question, i.e. (1) social aspects, (2) pharmaceutical and biotechnological industries, (3) public health systems, and (4) other sectors affected.

Unless otherwise indicated, the base scenario impact is envisaged as occurring gradually over the coming ten years. In the case of acceleration or retardation with respect to that scenario, such impact will itself affect the rate of change.

Social aspects

Health and quality of life

The predominant opinion is that life expectancy will increase, though not very much. The reasoning behind the qualification is that expectancy for persons free of illness is itself limited, and advances in this area are the result mainly of a fall in mortality rates for persons of age below sixty years. To take a case in point, life expectancy at birth has increased by almost ten years, while for persons of age eighty it has increased less than two years.

Hence ageing of the population will accelerate, mainly in the developed countries, and this may aggravate problems such as the funding of public pension systems. Where quality of life is concerned, however, some members feel that against such a background it will be more common to keep working until a later age, and this could compensate for the ageing effect.

My Notes

As regards quality of life, the predominant view is that this will be enhanced in greater or lesser measure for the entire population, although the greatest advances will be in specific segments, not only where health is concerned but also in the capacity to take up different activities. Among these segments we have especially persons of advanced age, those affected by illnesses in the case of which advances first occur, and, in general, the wealthy. Enhanced quality of life will also be enjoyed by persons suffering chronic or degenerative illness. For the majority the benefits will be more moderate.

One thing that is indeed clear is that there will be a positive change in living habits, especially in persons aware of their own propensity for certain illnesses. This change will be consistent with the present trend, among at least some of the population, toward a healthier life style. One of its features will be the greater acceptance of preventive treatments, which the members expect within five to ten years. At the same

time it would appear that negative habits, such as smoking, would not increase even with the advent of a cure for lung cancer, although in this area the view is not so close to unanimity.

Spending on public health, and such savings as personalized medicine may bring, will in large measure depend on the habits adopted. Here education will be very important, as will incentives or restrictions (e.g. in the case of insurance premiums).

Finally, and in the long term, it is probable that patients will tend toward habits typical of consumer markets. There could be strong implications for marketing strategies insofar as concerns the various elements making up the value chain in the health system.

Legal, ethical, and moral aspects

As we have seen above in connection with accelerators and brakes, it is highly possible that ethical questions will become weightier, especially those involving discrimination and privacy of information, although legislators will endeavour to deal with them appropriately and to diminish their impact. Even so, most of the members feel that inevitably there will be subtle cases of discrimination, both labour-related and in connection with health insurance, for genetic reasons.

Again with respect to regulation, in particular where personalized medicine is applied and entails business opportunities, it is anticipated that some countries will become "legal countries" from the point of view of personalized medicine. The majority opinion is that this will indeed happen, for it is already happening, to take an example, in research with stem cells. However, some of the members feel that this will not happen because, while the topic is not very controversial (especially the part less related to stem cells), legislation will not be very strict and will tend to favour extension to a large number of countries.

In any case scientific advances will very probably continue to be ahead of legislation. There may arise problems and controversies while legislation is produced accordingly, with an effect on all the aspects mentioned in this point. Thus again we see how important it is that agents interested in the application of personalized medicine, public but in the main private, play an active role in regulation so that legislation will conduce to the smooth introduction of personalized medicine, while problems that could hinder its general adoption will be avoided.

Pharmaceutical and Biotechnological Industries

Where the pharmaceutical industry is concerned, personalized medicine will very probably mean major changes in the development and profitability of new medicines. Also there may be heightening of competition, owing to advances in science and technology, between traditional companies and newer ones.

Development of new medicines

As mentioned in the previous chapter, there are steadily fewer new medicines approved by health authorities. The main reason is the growing difficulty in finding safe and effective medicines for a broad majority of the population under the present paradigm of medicine for everyone.

What the FTF expects is that, with the development of medicines based on knowledge of a person's genome, this trend will change and there will be an increase in the number of medicines approved annually. However, it will take ten years or more before we see levels of approval similar to those of the 1990s. This moderate growth will be influenced by the difficulty in finding valid biomarkers in the short term, as well as in the reduced number of genomic medicines involved in the development of new ones. In these circumstances it is possible that growth will continue in the number of medicines approved within timespans greater than the one envisioned in this report.

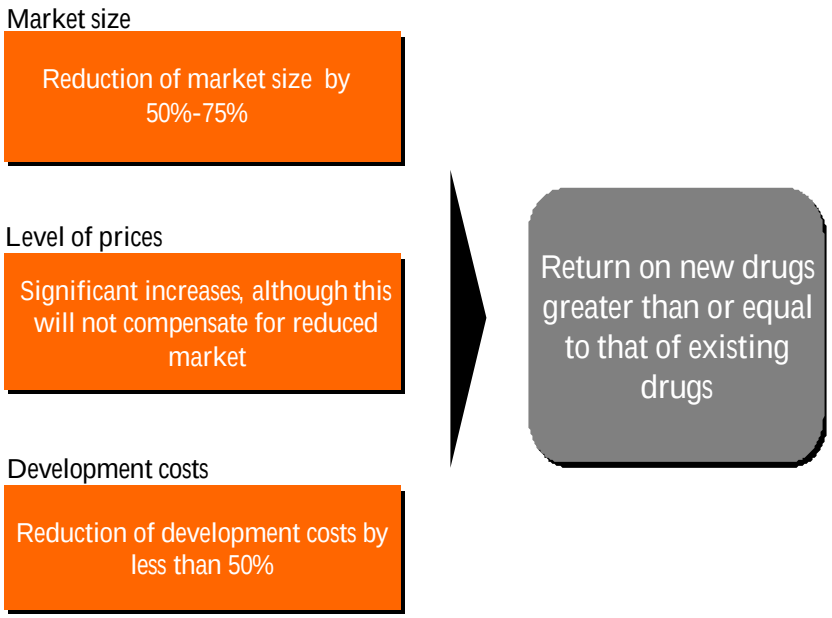
As regards the origin of the new medicines, members of the FTF say that most of them will come from the discovery of new substances. However, it is much less probable that fresh knowledge in genetics should make it possible to recover old molecular entities, discarded earlier, owing to the absence of complete analyses. Such recoveries will be easier in the case of medicines that had problems with efficacy than in the case of those abandoned because of toxicity problems. The fact that the new developments should come from new discoveries will facilitate the appearance of new starters, although in addition it will slow down, and add to the cost of, these new developments in comparison with the retrieval of medicines that failed to pass approval criteria.

Accordingly it is reasonable to expect that development costs may fall significantly, although not dramatically. These reductions will occur gradually as barriers to new development are reduced.

As regards drugs now on the market, most members are sure that the new drugs will have an impact on some of the current blockbusters, main feature of which is that they are designed for the immense majority of the population, for a broad spectrum of illnesses, and with few or none side effects. Another opinion is that the development of new medicines will be aimed at areas in which there are no blockbusters established. Each of these opinions would seem to be coherent, since everything points to a process in which new developments will in the short term be directed toward areas for which there do not exist effective treatments, and later on will extend to others in which the number of treatments already established is greater. Thus it will be necessary to wait a few years in order to see effects on the profit-and-loss accounts of the traditional pharmaceutical firms. Such effects may become significant within ten years.

Profitability of the new medicines

The profitability of the new medicines for the pharmaceutical and biotechnological industry is one of the most discussed questions in the sector. As shown in the illustration below, the FTF predicts that such profitability will be equal to, or even greater than that of current medicines, the reason being the performance of the key variables in question. These variables are as follows:



- *Market size.* The orientation of new medicines toward particular population segments may mean that their market shrinks appreciably. The opinion of the members is that between two and four medicines will be developed per illness[1], which will mean a market reduction of 50%-75%. This effect may be compensated for with increases in the overall market, these in consequence of greater efficacy and few side effects.

- *Prices.* Prices could increase significantly, although most members expect that increases will not compensate for smaller market size. A minority believe that enormous pressure from public health systems will deter price rises. Others object that the cost of medicines will be less in relation to overall health costs, which will be much below savings in health costs (nearly 70% of the overall amount as opposed to 15-20% accounted for by medicines).

- *Development costs*. As pointed out earlier, the expectation is for a reduction in development costs, although it is highly improbable that this reduction should be as much as 50%.

The members who anticipate a fall in profitability are in general more pessimistic in regard to the three variables, especially where prices of the new medicines are concerned.

Business models

The development of new technologies entails the appearance of new players on stage: firms working in genomic medicines, technology firms for the processing of information, insurance companies, medical associations, and public health systems.

The immense majority of the members believe that personalized medicine will represent an opportunity for the emerging biotechnology firms, which have methods for the development of genomic products.

With respect to the strategy adopted by the great pharmaceutical industry, many members believe that this industry will invest heavily in R&D for genomic medicines. Others are more cautious, and feel that the industry must set costs and recover from the consolidation of recent years before investing large sums.

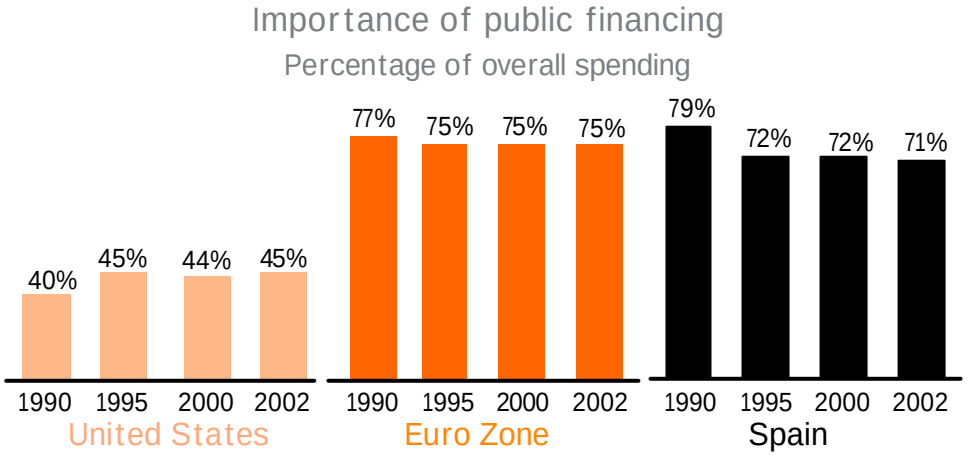
1. According to the scientific criteria, there will be identified between 2 and 4 variables which were previously considerer one illness.

Some members believe that the market share held by emerging firms over the next ten years will range between 3% and 10%. The main reason is that these firms do not have all the resources necessary for the development of medicines. They will need backing from the big pharmaceutical companies, which have the funds, the commercial networks, and the legal knowledge.

Over that same period the expectation is for collaboration between pharmaceutical companies and biotechnology firms, although some members refer to the possibility that these latter will be taken over by the big pharmaceutical companies.

Public health systems

We now look at the opinion of the members as to the impact that the development of personalized medicine could have on current public health systems. The focus is on Continental Europe, where its relative importance within the overall health system of each country is enormous:



Source: OECD data

My Notes

First we look at health spending and each of its components, then at the role of the public systems within this new framework, the aim being to assess such opportunities as may arise for the private health sector.

Increase in health costs

Over the next five years

Where the short term is concerned, most members believe that the national health bill as percentage of GNP will in general increase by at least 10^2, i.e. 5000 million 2002 euros in the Spanish case.

As for the various headings, the members make different predictions. Where spending on pharmaceuticals is concerned, few believe that these will remain stable. Most believe that they will increase, in general by at least 10%. An even greater number believe there will be an increase, slightly below 10%, in the costs of hospitalization and of treatment at clinics.

Over the coming ten years

As regards the long term, the members agree that overall health spending in most countries will continue to increase, although there is some disagreement as to whether the amount will be less than or more than 10%.

Where components are concerned, quite a number of members believe that pharmaceutical and hospital costs, as well as costs for treatment in clinics, will increase, though in all cases below 10%.

		Over next five years	From five to ten years
Health spending in relation to GNP	Spending on pharmaceuticals	• More than 10%	• About 10%
	Spending on hospitalization	• Less than 10%	• Less than 10%
	Spending on clinics	• Less than 10%	• Less than 10%
	Overall spending	• More than 10%	• About 10%

2. If the annual cost is an 8% of the GDP, a 10% increase will place it at a 8.8% of the GDP.

Another factor that will push up health spending is the increase in life expectancy that medicine of this sort may produce, although the members agree this impact will be moderate.

Along with the two foregoing factors we have tests being carried out that make it possible to obtain a fairly complete description of the genome. In the Spanish case this could have an impact up to 0.8% of the GNP, assuming such tests were carried out annually on 15% of the population.

However, enhanced efficacy and, in greater measure, reduction of side effects will help to reduce the growth of health spending, mainly in the mid term. This saving will occur in hospitalization costs more than in those relating to treatment in clinics.

Insofar as concerns the orientation of medicine towards the prevention and changes in life habits among the users of public health systems, there is little consensus regarding the impact on health costs, at least for the period here under consideration. The same thing happens with the need to train doctors in the new technologies, and there is little agreement over the impact of this, although here one does observe a slight tendency toward an increase in spending.

The role of the public health systems

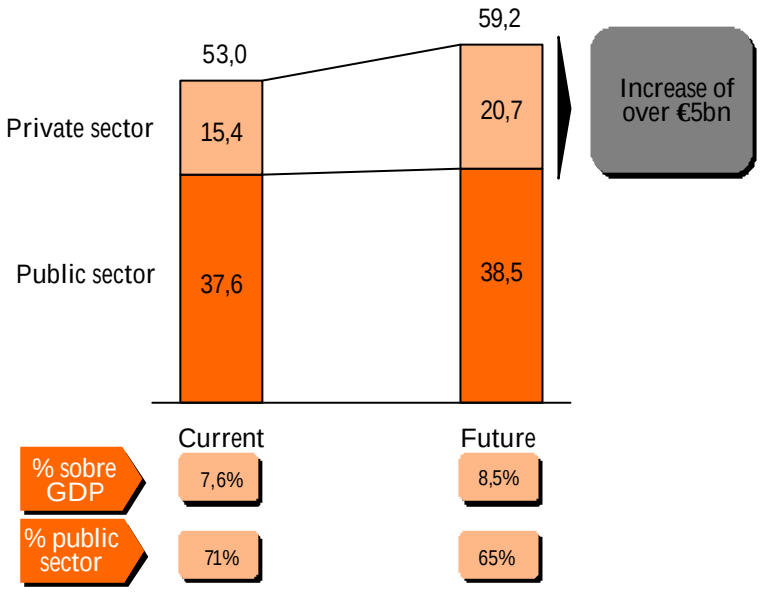
Once we have looked at how health costs will likely continue to rise in the coming years, in spite of personalized medicine, the next step is to understand predictions regarding the role that the public systems will play in the development of personalized medicine.

The members of the Bankinter Foundation agree that these public systems will not assume leadership in the development of personalized medicine, but that they will have a much more reactive role. It will be public demand that induces the public health systems to take up the new treatments. Probably the first treatments they provide will be for chronic illnesses, such as diabetes, since that is where the new treatments could most quickly result in savings.

Accepting the prediction of the FTF regarding the role of the public health systems, the experts believe that these will reduce their holdings from the current 75% to 70-65% of overall health spending.

Hence the fact that overall health spending will continue to rise (as a percentage of GNP), along with a fall in the weight of the public sector in this area, means new markets and opportunities for the private sector. In the case of Spain, as may be seen in the following illustration, additional revenue for the private sector could exceed 5000 million 2002 euros, which figure would represent an increase of 35%[3]. This increase, as pointed out above, will occur in all the major components of public health spending, so that there will be opportunities for various participants in the value chain of the health system.

Healthcare spending in Spain
(in €bn at constant 2002 rates)



Source: OECD: Own preparation

3. Assuming an increase in healthcare spending to 8.5% of GDP and a public sector share falling to 65% of total spending.

Other sectors affected

As mentioned above, the development and introduction of personalized medicine will have an impact on many sectors owing to the changes it will bring about in life expectancy, population pyramid, quality of life, and habits.

The FTF has sought to assess business opportunity for the various sectors most directly connected with personalized medicine.

Within these, and, since the great technological challenge of personalized medicine will be the processing of information, the members agree that the sectors with the most business opportunity will be the genetic databases and the suppliers of technology for laboratories. Since the general view is that new firms will be set up in these environments, these opportunities will extend to capital risk companies, which will be among the principal suppliers of capital for the new companies.

Some members point out that even without the development of personalized medicine there would be a considerable expansion in sectors connected with data processing owing to the great quantity of information to be managed in different areas of medicine, as is the case with the development of electronic files, which will gradually go further in American and European markets.

We now summarize the sectors here looked at. They fall into three groups depending on the opportunity for business that, in the opinion of the FTF, they afford:

Sectors that afford great business opportunity:

My Notes

- Suppliers of technology for laboratories
- Genetic databases
- Capital risk firms
- Consultants specializing in biotechnological markets

Sectors that afford a medium-high level of business opportunity

Clinical laboratories
Suppliers of computer technology for processing and massive data storage
Private clinics
Health consultancy

Sectors that afford a more modest level of business opportunity

Insurance companies
Legal firms
Pharmacies

In view of their special position within the value chain of the health system, we now take a closer look at the impact that these three industries might have on business, i.e. insurance companies, legal firms, and pharmacies.

Health insurance companies

Many experts believe that the insurance companies will not play a key and proactive role in personalized medicine. On the other hand, how the insurance business will incorporate and process the data is one of the areas in which opinions diverge.

It is more widely agreed that incentives will be offered to those insurance companies that are prepared to carry out genomic tests. However, there is strong disagreement as to whether the industry will go further and use genetic data on a mass basis in calculating premiums, and whether it will perhaps oblige all insurance companies to make such tests obligatory, the source of this controversy being expectations in regard to legislation. The majority opinion is that the insurance companies will not use genetic data on a mass basis because of regulations protecting confidentiality and discrimination based thereon, although they will be permitted to promote the furnishing of such information by policyholders.

It is not clearly agreed how personalized medicine will affect the profitability of these companies in the long term. Some members believe that in the short term profits may increase, but that in the long term they will fall back to current levels. Some feel that better profits will result from better health among the population, not from the exclusion of high-risk patients.

Pharmacies

Most members believe that the principal activity of the pharmacies will not change radically and that they will continue to sell standard medicines.

A minority believe that the pharmacies will broaden their operation to include personalized medicine. Nearly all members of this minority believe that they will play an important role in measuring out and distributing medicines, but not in genomic testing or on prescribing medicines based on such tests.

Doctors

As regards the doctor, the FTF believes that personalized medicine will add to the importance of his/her role. The relation between doctor and patient will continue to be the main pillar of the system, since technological discoveries cannot replace the medic. The decision whether to prescribe, as well as the corresponding responsibility, will lie with him/her.

The FTF laid stress on the importance of training and speciliazation in personalized medicine.

4.4. Conclusions

Personalized medicine is inevitable. It will come gradually and stealthily, but within ten or fifteen years it will be seen as a great revolution in medicine, hence also in the health of the population and its quality of life.

The FTF recognizes that it will bring a great many changes. There will be effective treatment for a greater number of illnesses, with an increase in life expectation, quality of life, and, as a percentage of GNP, expenditure on the part of the health system. The participation of the public sector in overall health spending will decrease, the private sector will have more weight, there will be new agents and business models in the pharmaceuticals industry, there will be a moderate increase in the number of medicines approved, and these medicines will be more profitable.

These changes will have great social and economic impact, not only because of their weight in a country's GNP but also because their influence on people's health and behaviour will have a greater or lesser effect on all economic sectors.

In this setting each industry will have to assess impact and adopt a strategy in line with personalized medicine. Given the uncertainty regarding the rate of its development, the present report seeks to provide some indicators that could help in this regard. The members are sure that the rate of development will depend especially on technological factors. Also important and requiring attention will be social and institutional factors that could facilitate or impede technological advances in the health system.
It is hoped that reference in this chapter to scenarios, indicators, economic impact, and social impact will throw some light on the question as to how firms and industry should respond to the inexorable approach of personalized medicine.

5

CHAPTER 5

Appendices

5.1 The Genome

As early as the third century BC, Aristotle conjectured that matter strove to turn an inherent possibility into a reality; that the egg, in some way, contained the information on how to build a chicken.

Introduction

Our generation will be the first to read the secrets contained in the human genome. We are currently seeing what is undoubtedly one of the greatest scientific revolutions of all times

On 26 June 2000, British prime minister Tony Blair and US president Bill Clinton, gave a joint press conference via satellite in which they announced that the first draft of the human genome had been completed. The language in which the instructions for building a human being were written was being deciphered. The press conference was also attended by the director of the human genome project (HGP[1]), Francis Collins, and the controversial Craig Venter, president of Celera Genomics, the first private organisation to sequence the genome. Japan, China, Germany and France, which had also participated in the project, all announced this historical milestone at the same time.

My Notes

The project of sequencing the human genome had begun ten years before, with an initial budget of over three billion dollars and a deadline of 15 years. Six countries formed a consortium with the aim of determining the sequence of all of the more than three billion chemical bases that made up the molecules of deoxyribonucleic acid (DNA), identifying the approximately 20,000 genes contained (according to the latest estimates), developing methods and technologies for making these tasks faster and more efficient, and developing new methods for storing and processing these enormous amounts of information.

Subsequent rapid technological advances and the competition between the public consortium and the private company Celera to conclude sequencing of the genome as quickly as possible, finally resulted in a reduction in costs.

1. *The genome is the "instruction manual" for building a living being*

The genome is the instructions manual to build a life.

A short history of the genome

In 1865, an Augustinian friar called Gregor Mendel published his well-known laws of inheritance. Only a few years before, in 1859, Charles Darwin had published his theory of the origin of the species as a result of natural selection, leading many scientists to wonder what might be the secret behind the transmission of this hereditary information.

Darwin demonstrated that the present variety of the species is a consequence of evolution, starting from the most common and primitive of organisms: as a result of competition between them for scarce resources such as food, those that had some advantageous natural mutation survived better. They were the ones that had most chance of engendering offspring.

At that time, before Mendel's ideas came to be understood, the prevailing theory on sexual inheritance argued that a "fusion" of the paternal and maternal characters was passed on to the children. Naturally, this theory did not support Darwin's idea, since a random advance in a species would not live on in the descendants, but would instead be diluted when mixed with that of its mate.

Mendel, experimenting in his vegetable garden with thousands of plant specimens, realised that inheritance is not simply a matter of a mixture of two species, since there are features which are not mixed, but rather are passed on to the descendants by their ancestors in accordance with certain laws [2]. There were even characteristics that disappeared entirely in one generation only to re-emerge in the next one. It was as if something indivisible, atomic, was transmitted in the genetic characters. This was the dawn of the atomic theory of biology.

However, while these scientists devoted themselves to the more general aspects of development and genetics, others began to analyse the smallest elements, cells-simple units which came together in their millions to form the tissues and organs of living beings. They discovered the micro-cosmos that exists within every cell, where a small inner nucleus has strand-like structures called chromosomes.

2. Offspring from a blue-eyed father and a brown-eyed mother do not inherit a mixture of both colors: a percentage of the offspring will have blue eyes and another percentage will have brown eyes.

However, it was not until scientists began to understand that life was not only chemistry and morphology, but above all information, that they began to untangle the secrets of genetics.
In the 1930s, an American scientist from the University of Texas, Herman Muller,

discovered that it was possible to artificially induce mutations in the genes contained in the chromosomes of living beings. To do this, he bombarded specimens of drosophila, better known as fruit fly, with X-rays and observed that, after certain mutations were induced, it was possible to fix this feature which would then be passed on to the descendants, entirely in line with Mendel's laws of genetics.

People began to conjecture that genes were not indivisible particles, but instead contained a certain internal structure.

Years later, two scientists, the American James Watson and Francis Crick from the United Kingdom had similar ideas about the important role that the DNA molecule, found inside genes, played in the way they functioned. They finally met up and joined forces in Cambridge in 1951, and began to work together on an analysis of DNA. It was certainly one of the most successful collaboration agreements in the history of science.

Not much later they discovered the internal structure of DNA, proving that the molecule contained a code written along a long strand in the shape of a double helix. This code is capable of copying itself and specifying ways of manufacturing proteins. This explained two basic aspects of the concept of life: its capacity to create order, i.e. to reduce the surrounding entropy in its environment, and its capacity to replicate.

This was one of the greatest discoveries in human history, a fact which did not escape Crick: on 28 February 1953 he told his colleagues over a pint of beer in the Eagle Pub that he had just discovered the secret of life.

However, the history of our understanding of the human genome had only just begun. The next step was to decipher that code of a million words, written with only with four letters.

But what exactly is the genome?

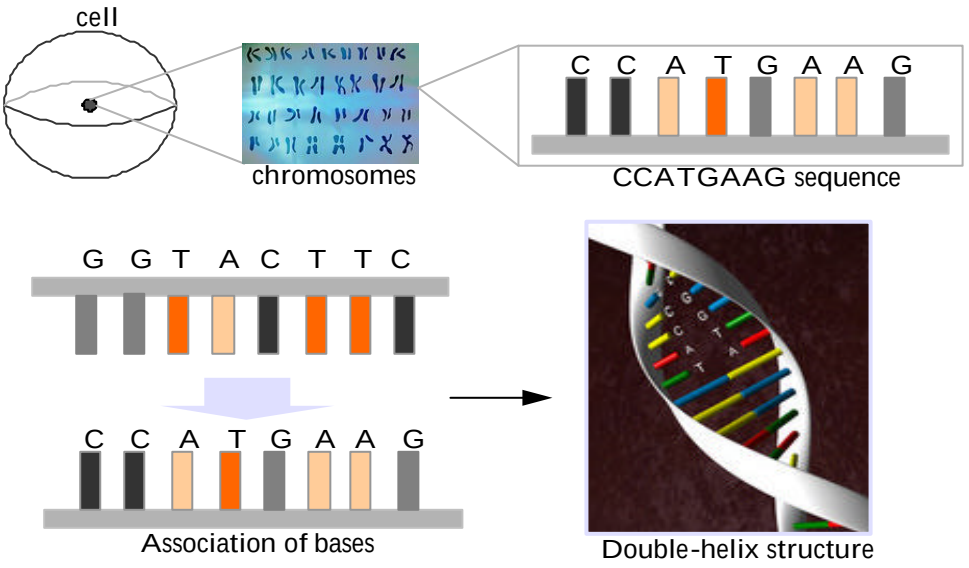
Molecular description

We already now that within the cells there is a tiny black corpuscle scientists call the nucleus. If we analyse it in detail, we can see that inside there is a complex structure formed by tiny strands called chromosomes. The shape and number of these chromosomes is specific to each species and is the same in all its members. All humans have 23 chromosomes, which appear in pairs (i.e., two copies of each chromosome, totalling

46 chromosomes) within the nuclei of the millions of cells that make up an organism[3].

Chemically, these chromosomes consist of long chains of DNA, made up one of four possible chemical structures, called nitrogenous bases: adenine (A), cytosine (C), guanine (G) and thymine (T). These combine with a sugar called deoxyribose and, through bridges formed by phosphate molecules, form a one-dimensional linear sequence of bases (see figure below).

These bases have the property of being able to bond: A can bond with T, and C can bond with G, but no other combination is possible. In this way, two one-dimensional strands of DNA join to form an incredibly stable three-dimensional structure: the famous DNA double-helix[4].
All living organisms contain DNA sequences: animals, plants, bacteria and even viruses carry all their genetic information round in these molecules. All of this genetic material in a single species is what is known as the genome. In humans, the genome basically consists of the 23 chromosomes contained in every cell in our body.



DNA as a digital coding structure

If you go to your local bookshop and browse through any of the books on display, you will find it contains a story, a recipe, a scientific theory or some other type of information. In order to access this information, you need to know how the book is encoded in other words you need to be able to read the language it is written in. There is no

3. There are actually two copies of a complete series of chromosomes in every nucleus of all types of cells in humans, except in ovules and sperms, in which there is only one copy, and in red blood cells, which contain none because they do not have a nucleus.

4. It is the chemical stability of this double-helix that makes it possible to run analyses even on material extracted from Egyptian mummies and insects preserved in amber.

Digital and analogical

direct correspondence between what the book talks about and the parts that form it: for example, a paragraph from a recipe book does not specify a mouthful of cake, otherwise you'd have to read the whole recipe if you wanted to cook it, even if you only wanted to make a mouthful. The book is then said to be *digitally* encoded.

This type of coding is opposed to *analogical* coding, which specifies the information shown as an analogy with reality. For example, a picture like *Las Meninas*, by Velázquez, represents the reality directly, without any coding, which means that you don't need to known any code to understand it.

The genome is very like a book, in that it consists of digital, one-dimensional information[5], written with an alphabet of just four letters-A, C, G, and T-using long chains of DNA to like pages.

The analogy between the human genome and a book can be taken even further: the millions of ACGT bases act like letters in this book. However, direct sequential reading of all those letters does not immediately result in words, sentences or paragraphs; rather, you have to learn to read those letters and interpret them in blocks. There are groups of letters that contain the information which is then translated into proteins (known as *exons*), intersected by other blocks whose letters are not interpreted or which have a structural or support function for the exons (the so-called *introns*). Exons and introns are grouped into larger units called *genes*, which are a bit like the stories in the book, and which are ultimately translated into proteins, the real *bricks* out of which cells are built. Finally the book is arranged into 23 chapters, the chromosomes, each of which contains thousands of stories inspired by the genes.

The meaning of the genome

But what exactly does the DNA in the genome encode? To answer this question, we first need to know that the DNA molecule has two very important characteristics: the first is that it can copy itself (copying process) and the second is that it can be read or interpreted (with the sequential processes of transcription and translation).

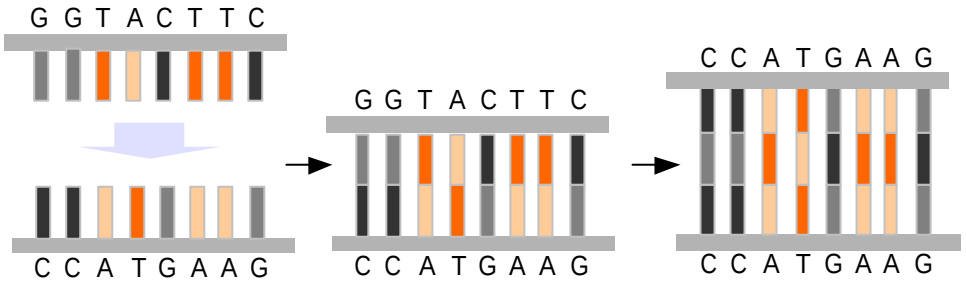
The copying process is based on the capacity of nucleotide bases to pair up in twos (A pairs with T, and G with C), so that, for example, a piece of the chain with a sequence ACGGT pairs with another that contains the sequence TGCCA. In other words, the copy of the copy is always the original chain, proving a process of copying which does not lose any of the original information.

5. One-dimensional in the sense that both a book and the genome are encoded with one letter after the other in a long sequence.

The processes of transcription and translation of the DNA are based on a coupling of the bases in a process similar to that described above, but instead of copying itself in a DNA molecule (based on the letters ACGT), it is copied in a molecule known as ribonucleic acid (RNA). Chemically, this is slightly different to DNA (the sugar it contains is ribose instead of deoxyribose), and in addition, it replaces the nitrogenous bases T (thymine) with a different one called uracil (U). There are various types of RNA with different functions.

The RNA that transports the information from the DNA of the nucleus to the cytoplasm is called *messenger* RNA (mRNA). This is the product of a *refined* reading of the DNA where the introns, which do not contain encoded genetic information, have been removed, leaving only the exons which are placed on after the other, giving sense to the words contained in the gene information. In the cytoplasm of the cell, the messenger is taken in by the *ribosome*, the subcellular structure where the *proteins* are manufactured.

The copying process



My Notes

In the ribosome there takes place a process of translation whereby the information is read and turned into proteins. For this purpose, the ribosome groups the nitrogenous bases in groups of three called triplets or *codons*: these are the words in the alphabet of life.

Each of the triplets is interpreted by the ribosome as one of 20 amino acids which, in chains, make up all proteins.

To summarise, the genome, written on the molecules of DNA, could be said to be a book which tells how the body should manufacture proteins, thus manufacturing itself. For example, the chemical reactions caused inside the organism are catalysed by a type of protein called an enzyme. Other proteins are responsible for activating and de-activating genes precisely, depending on the moment or their position in the body, thus differentiating between the different tissues that form living beings.

We have already mentioned introns in passing: these are chains of DNA which do not specify useful information for the manufacture of proteins and which are eliminated during the transcription process. These introns form 98% of all human DNA, known as *selfish* DNA, and only the remaining 2%, consisting of 20,000 genes, encodes valid recipes for building proteins.

Genes

At this point we are in a position to define a gene as a basic physical and functional unit of inheritance. Each gene is made up of an ordered sequence of nucleotides located in a particular position within a chromosome which specify a given functional product in the manufacture of an organism (a protein).

Mutations and genetic diversity

Mutations

On occasions, when the chromosomes replicate their DNA contents, errors occur in copying, such as the replacement of one base by another, either duplicating it or simply ignoring it. This error in the copying process, if it is not repaired by the cell and remains fixed in the DNA, is known as *mutation*.

Most of these mutations are harmless for living organisms, but on occasions they can alter a base in a gene in such a way that it affects an important protein that the gene specifies. This mutation may be beneficial for the organism in the particular environment it inhabits (hence the evolution of the species) or harmful (with the appearance of diseases and problems due to malfunctioning of the mutant gene).

In an individual, approximately one hundred spontaneous mutations are fixed and passed on to the offspring in every generation.

Genotype and phenotype

During procreation, a phenomenon occurs known as *recombination*, in which fragments of paternal and maternal genome are crossed over, and the child receives a genome which is valid but is not identical with that of either of its parents. This makes it possible to transmit these mutations over various generations, spawning species diversity (by producing different adaptations to the environment).

One interesting example of this genetic diversity can be seen in the intolerance many people suffer to a component in milk known as *lactose*. This natural sugar is metabolised in the surface of the intestine before being absorbed by an enzyme called lactase. If this enzyme is not present, the lactose cannot be absorbed, and causes diarrhoea and other symptoms. Originally, milk was no more than a product mothers used to feed their babies with during the first few years of their lives. After that short period it was removed from their diet and we therefore lost our capacity to assimilate it.

However, people living in communities of livestock farmers, like much of Europe, continued to include milk from sheep or cows in their diets. Individuals who were best able to digest the milk developed and thus survived better, and as a result, only 30% of the European population suffers lactose intolerance.

In contrast, hunter-gatherer communities in Africa did not generally drink milk as adults, and this type of genetic modification did not occur. As a result, 70% of Africans are currently lactose intolerant.

It is important to differentiate between the genotype and the phenotype. The phenotype refers to an observed diversity (the specific characteristic), such as a lactose allergy, for example. It is therefore related to the *analogical* world. In contrast, the genotype corresponds to the coding in genes that generates that specific characteristic, and it is therefore related to the *digital* world.

LUCA

All living organisms store hereditary information in the form of coded genes in chains of DNA. Some genes specify simple functions in an organism, such as the manufacture of a specific protein for a certain fluid, whereas others affect aspects as complex as a person's personality or intelligence.

The most primitive genes, which specify very basic functions of the living organism, are common to the majority of species. As more sophisticated species emerged, new genes were added, possibly through random mutations of existing ones, enabling the best possible adaptations to the local environment. As Darwin explains in his theory of the evolution of the species, this led to the diversification of the different species.

Humans, then, share genes with all other living beings, and no two gene sequences are identical. Two individuals in a species are only differentiated from each other by 0.1% of the sequence of their genome and share the remaining 99.9%. Humans share 99.8% of their genome with the chimpanzee's.

We can infer two important consequences from all this: the first is that many genes are identical among the different species existing on Earth. Furthermore, since these only specify information, they operate like *software*, and are even interchangeable. In other words, we could replace a given gene from a fruit fly with the gene that performs the same function in humans without harming it in any way. We could go even further, introducing genes with a given function in organisms that do not have them; they will receive this function and be capable of translating and interpreting it correctly.

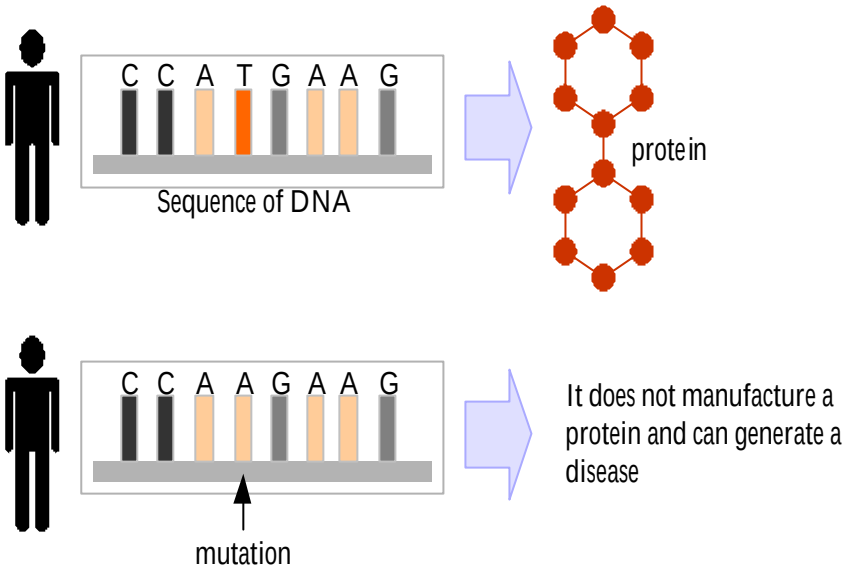
The second conclusion is that all living organisms descend from a single universal common ancestor, who scientists call LUCA[6].

Life has two essential characteristics: the capacity to create order and the capacity to replicate. In this regard, the genome is a living thing, which has been perpetuating itself since it first lodged in LUCA, through different organisms, which are no more than side effects of its operation, and to which it delegates the functions of reproduction and acquisition of energy, as well as the instinct for survival, until finally it programmes the death of the host, to prevent too many mutations from accumulating.

Genes and disease

Genes do not cause diseases. On the contrary, they are responsible for manufacturing life. However, by specifying how proteins are manufactured, they are responsible, to a great extent, for the working of the human body. Thus, a gene that contains an error (for example, the mutation of one base by another) can cause the protein manufactured to be generated incorrectly, as a result of which it does not fulfil its function and can generate a disease, or at least, a certain tendency to suffer from one.

6. Stands for Last Universal Common Acestor



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5.3 Glossary

A

Adenine, cytosine, guanine and thymine (A, C, G and T), the four nitrogenous bases that align in the DNA molecule encoding the information contained in the genome.

B

Biochip, a device which implements a series of miniaturised laboratory tests that are repeated in a matrix known as a micro-array which allows multiple simultaneous analyses to be made from a single portion of DNA.

Biomarker, (in the sense in which it is used in this text) any genetic characteristic that acts as an indicator of a biological process, be it normal, pathogenic or a response to treatment.

C

Chromosome, a structural unit located in the nuclei of the eukaryotic cells which contains the genes responsible for inheritance. The structure of the chromosomes is a long and continuous strand of DNA and associated proteins.

Codon, A sequence of three nitrogenous bases within the DNA or RNA molecule.

D

DEVCOs, Drug Development Companies, companies that develop and supply pharmaceuticals and similar for subsequent supply to patients.

DNA, deoxyribonucleic acid, the molecule that contains all the genetic information on any living being. It is normally housed in small strands in the cell nucleus called "chromosomes".

E

EMEA, *European Medicine Agency*, the agency responsible for assessing and approving drugs and associated elements.

Enzyme, normally a protein which is in charge of catalysing a specific chemical reaction.

Exons, segments of DNA that code proteins, as opposed to introns which intersperse the gene's coding sequence without any known function.

F

FDA, Food and Drug Administration, the US government agency responsible for assessing and approving drugs and associated elements.

G

Gene, the basic unit of inheritance. A gene contains hereditary information encoded in a DNA molecule. It is located in a specific position within a given chromosome. Each gene determines specific aspects of the anatomy and physiology of the organism

Gene expression the process whereby the information coded in a gene is converted into present and operating structures in a cell. .

Genotype and phenotype. The genotype relates to the genetic make-up of an organism. It is unique to every organism and gives it a unique character. The phenotype, in contrast, relates to the physical appearance of the organism.

M

Mutation, an error in replication or other alteration in the copying process of a nitrogenous base of the DNA molecule that constitutes the genome of a living thing. The mutation may cause changes in the individual's phenotype (blue eyes), be completely harmless or generate a disease (such as cancer).

O

OECD, Organisation for Economic Cooperation and Development, international organisation comprising thirty developed countries whose mission is to promote economic and social policies that will achieve sustainable growth, maintain financial stability and contribute to a growth in world trade.

P

Pharmacogenomics, a discipline that studies how genetic inheritance influences the organism's response to a pharmaceutical product.

Pharmacoproteomics, a discipline that goes beyond pharmacogenomics, analysing how pharmaceuticals influence the manufacture of proteins by the genome.

S

Selfish DNA, part of the DNA that does not encode information, i.e., which does not belong to any gene and therefore performs no known function.

Sequencing, process of identifying the order in which the bases A, G, C and T occur in the DNA molecule.

Stem cells. These are the *undifferentiated master cells* from which other types of cells are generated. Every tissue in the body contains a single type of specialist cell. When it is necessary to repair or renew this fabric, the stem cells are responsible for differentiating to repair it.

T

TECPROs, Technology Platform Providers. Companies that provide the necessary technology for developing drugs, in aspects such as database analysis, technologies for identifying the gene sequencing, application and production of biochips and development of automated systems to improve the efficiency of laboratories.

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