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CHAPTER 3

Present Situation and Context of Personalized Medicine

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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 itself¹.

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.

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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 Germany², 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

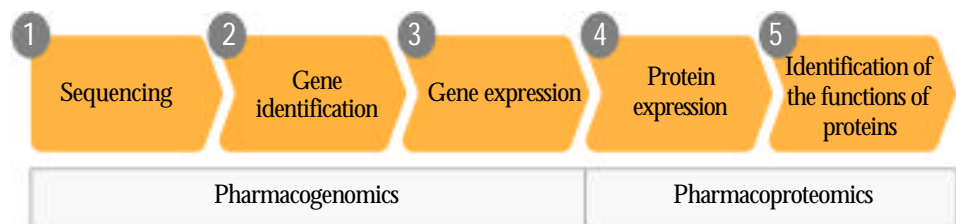
The sequencing of the genome unquestionably marks a major breakthrough and in coming years it will lead to a true revolution in diagnosis techniques using DNA analysis, and in the design and development of new safer and more effective pharmaceuticals.

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

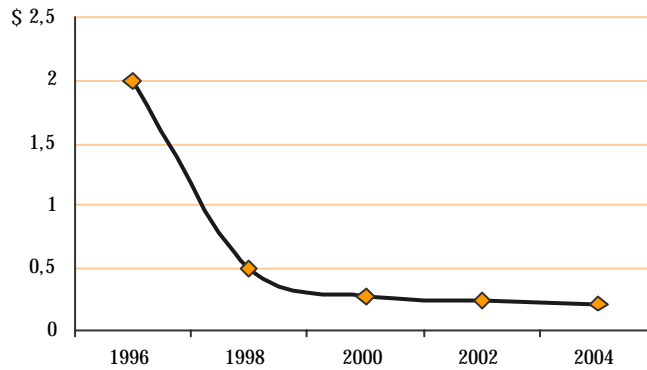
The first step to be taken with the genome consists of sequencing it—in other words, identifying the specific order that the A, G, C, and T nitrogenous bases occupy in the type DNA of a species. This is a bit like identifying the sequence in which the letters of a book are written, an indispensable step 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.

Cost per base sequenced



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.

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

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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

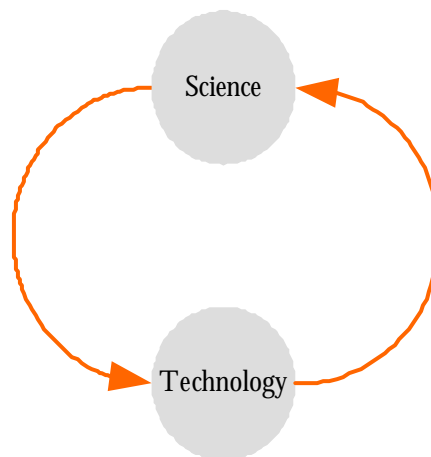
Biochips

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 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

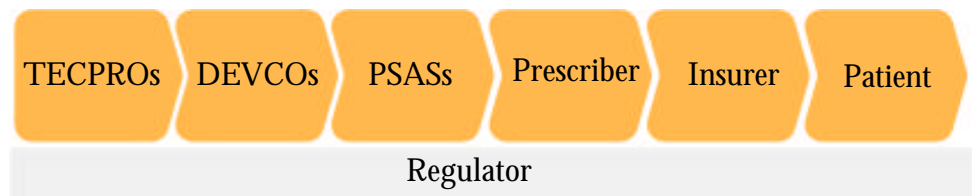
Roche was the first company to bring out a drug developed for a specific genetic profile, Herceptin. This drug is targeted at approximately 30% of women with metastatic breast cancer, which is developed by overproduction of the proteins necessary for cellular growth and division, in this case through 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 organisations 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.

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- 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 industry⁴

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").

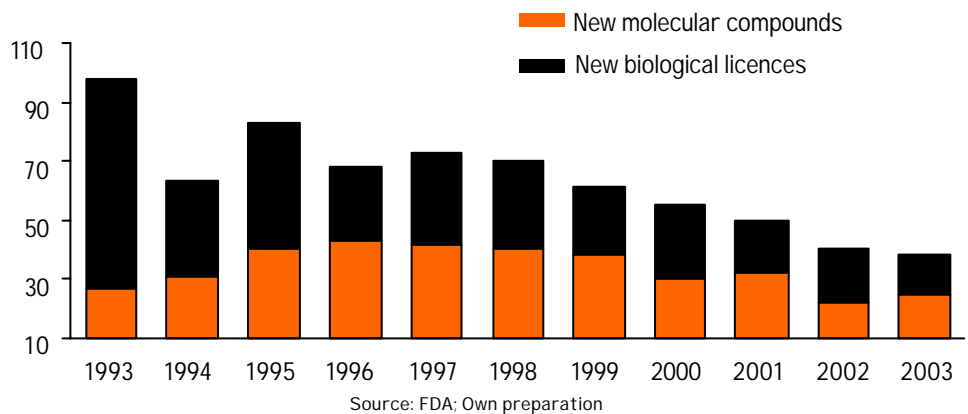
Over recent years this model has lost validity, and this has been reflected in the following factors:

- 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.

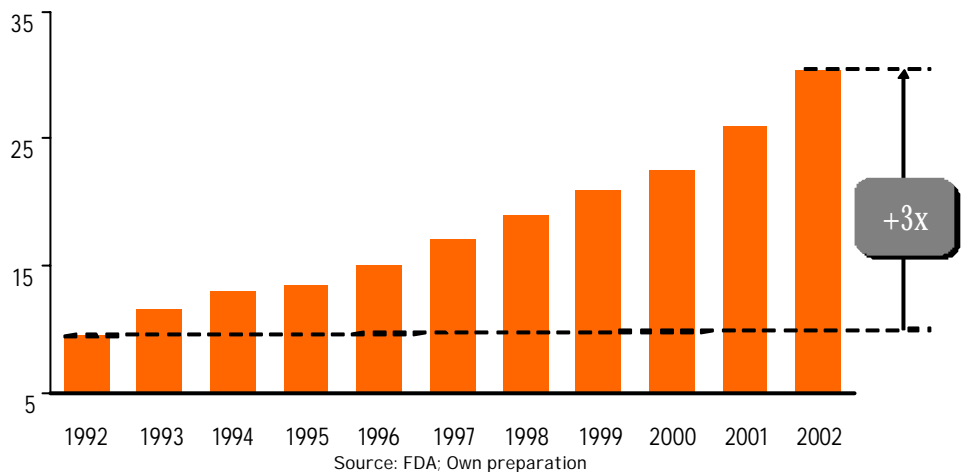


Number of pharmaceuticals submitted for approval

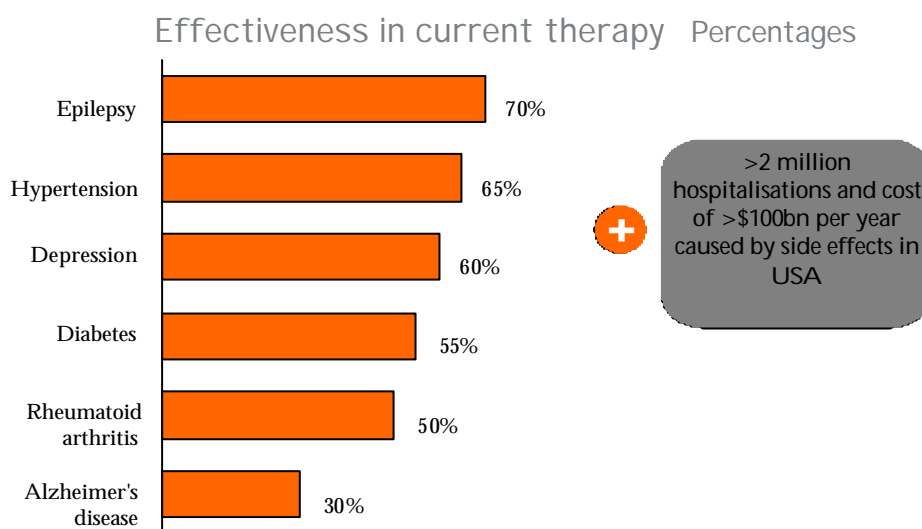


■ A marked increase in the cost of developing new drugs. In contrast to the fall in the number of pharmaceutical products developed, the graph below shows that total expenditure on R&D amongst pharmaceutical companies multiplied more than threefold in recent years, to around thirty billion dollars in 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.

Total R&D expenditure by pharmaceutical companies
Billion dollars



- 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).



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

The response of the pharmaceutical industry

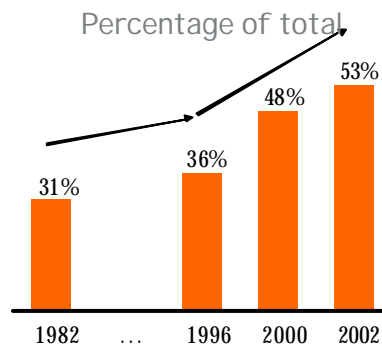
The primary response of the traditional pharmaceutical industry to these circumstances has been a process of consolidation, with a great number of large-scale mergers and take-overs (many to values in excess of fifty billion dollars). As a result, the market share of the ten largest companies in the 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.

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.

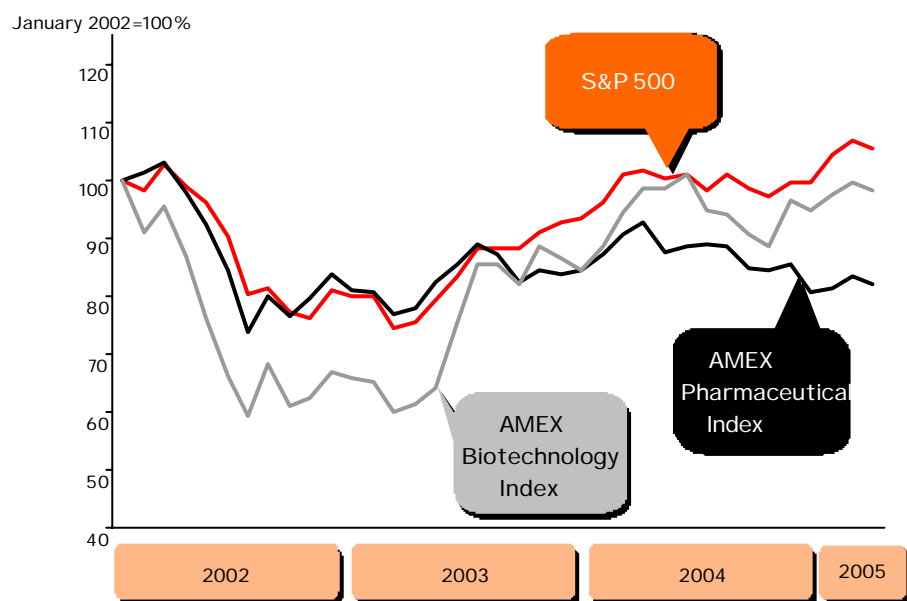


Source: Script's Pharmaceutical Company League Table; Own preparation

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 profiles⁶. 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.

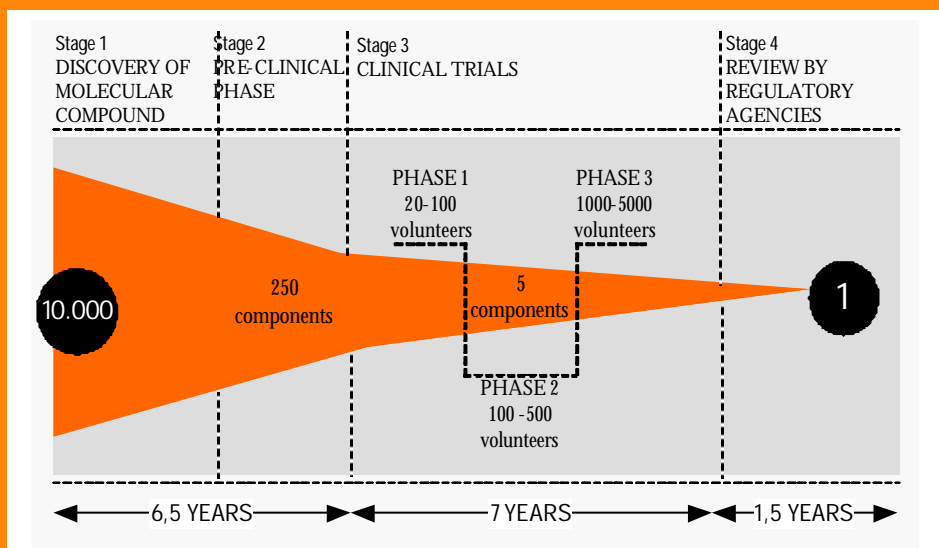
In any case, the effect is the same; where previously one pharmaceutical covered the entire population, there are now four pharmaceuticals to do the job.



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 knowledge 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/critical-path/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

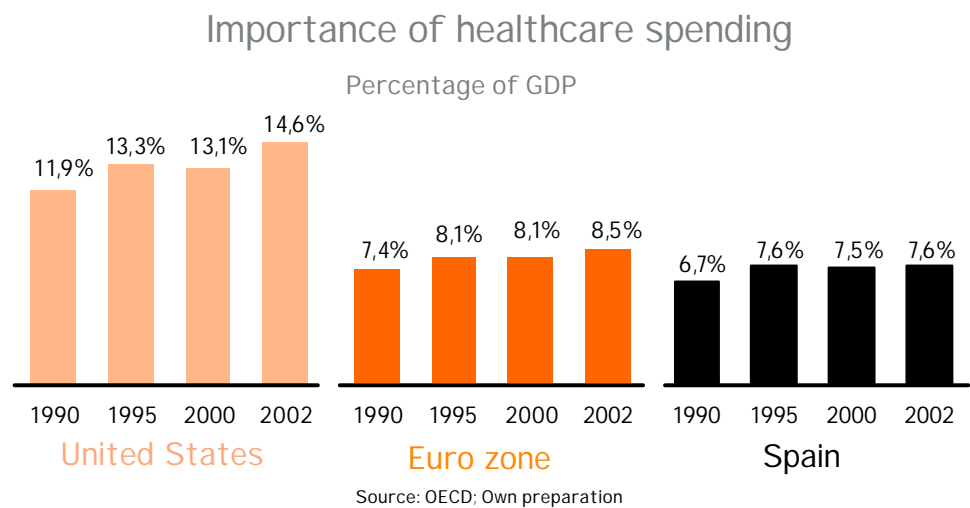
Spending on healthcare⁹ has seen strong growth over the last 10 to 15 years, during this period the percentage of GDP it accounts for has increased by one or more percentage points in the various OECD Countries. This trend has accelerated in the last 2 to 3 years, leading to health spending reaching 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.

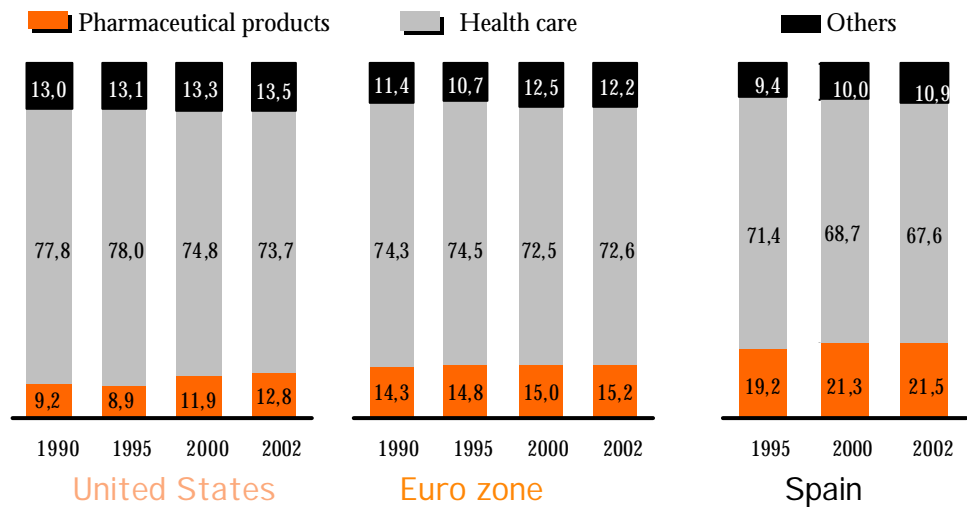


If we look at trends in spending by categories, we can see that pharmaceutical spending has grown above the average, gaining as a proportion of total expenditure. Nonetheless, we can see a certain disparity between the weight of this component in Spain (more than 20%), in other European countries (15%) 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 hospitalisation¹⁰ 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

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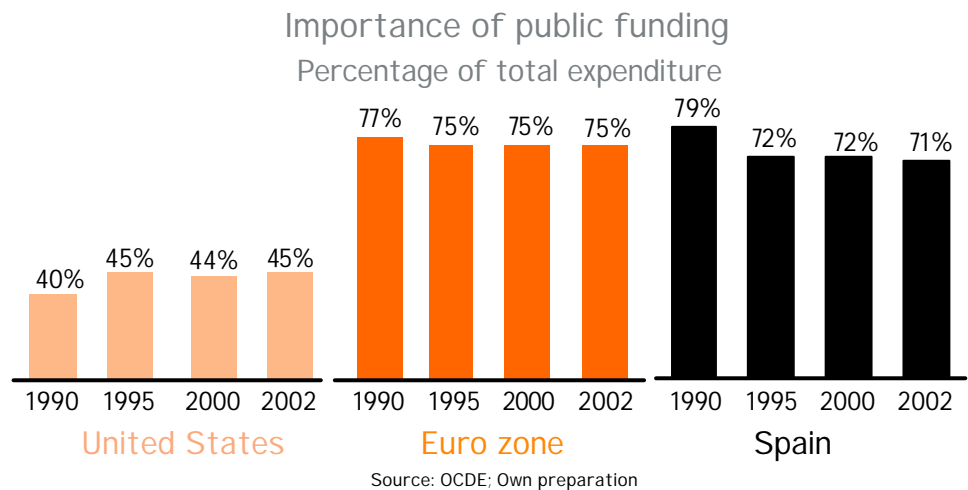


In the area of financing of the healthcare systems, in mainland Europe approximately 75% of the cost is absorbed by the public sector, whereas in the United States the proportion is smaller—close to 50%. The following illustration also shows a slight downward trend in the participation of the public 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.

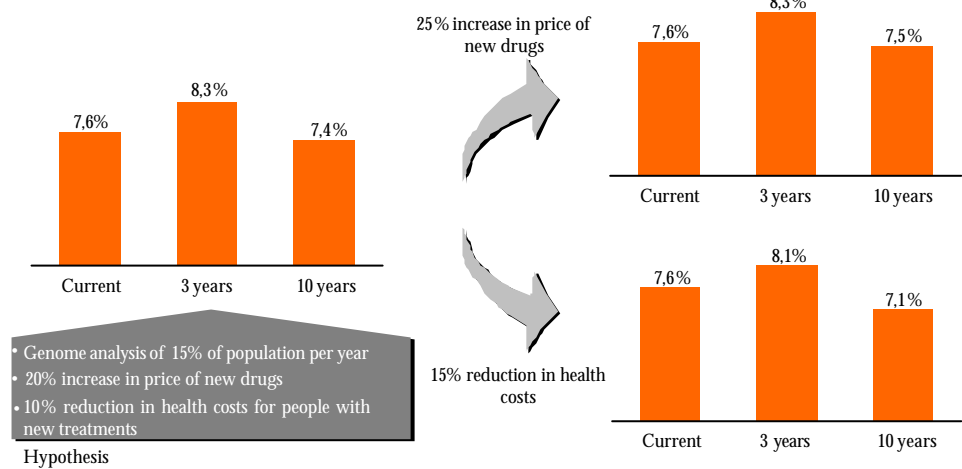


In this context, the development of personalized medicine may have a substantial impact on the development of health spending, as well as on short, medium and long-term financing requirements. Specifically, it may lead to the following repercussions:

- **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 population 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-



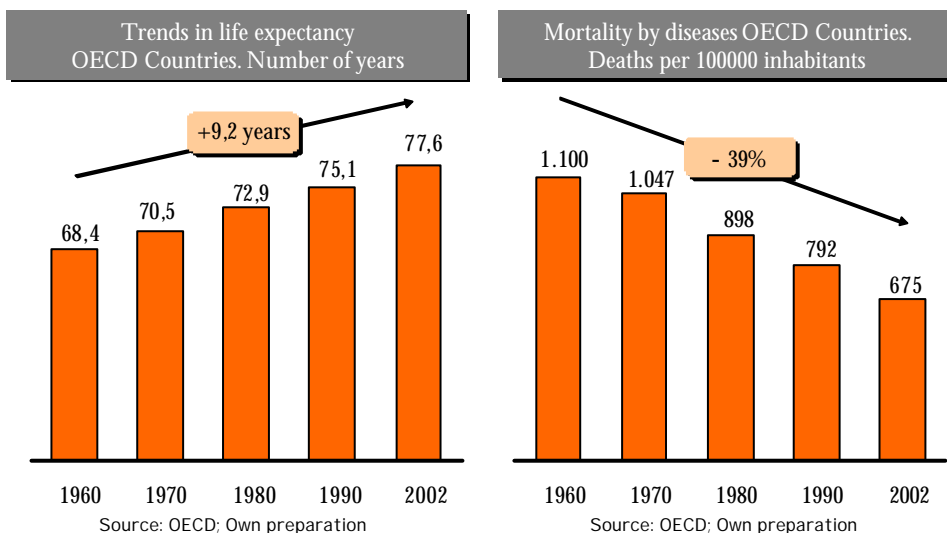
tor, especially for healthcare service providers and the insurance industry.

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.

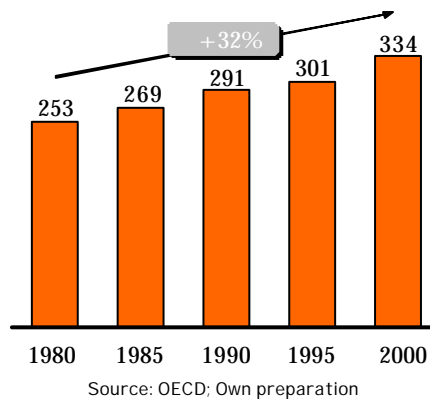
Health and Quality of Life

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



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 medicine 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 resistant 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 information¹¹.

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.

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.