

How to cope with complexity and adapt new scenarios to patient care

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Summary. The last 60 years have been characterised by an increase in life expectancy and an improvement in the quality of patients' lives. Such advances, to a significant extent, can be attributed – up to 40% of the total – to the results of pharmaceutical research. However, many treatment needs remain unsatisfied: tumoral pathologies, AIDS, neurodegenerative diseases, psychiatric pathologies and rare diseases are only a few of the challenges facing research in its attempt to make new and effective therapies available. The knowledge necessary before a new medicinal product can be made available is becoming increasingly complex, in line with the rising costs of clinical development. In such a scenario success is the result of the commitment made by large groups, aided by the innovative capacity of the SMEs and the active role played by public centres of excellence. A fundamental passage represented by this new model is the part played by clinical studies, which while maintaining the highest standards of efficacy and safety are in a position to identify genetic characteristics and processes before initiating large-scale patient trials. In any case, therapeutic progress is closely dependent upon the choices made to fund research and, therefore, raises the twin question of rationalising expenditure and the sustainability of the NHS. In this framework, where any kind of wasteful spending harms the right to health, every health management inefficiency is intolerable and administrative optimisation undeferrable.

Key words: patient care, medicinal products, translational research.

Riassunto (*Come affrontare la complessità e adottare i nuovi scenari alla cura dei pazienti*). Gli ultimi 60 anni sono stati caratterizzati dall'aumento dell'aspettativa di vita e dal miglioramento della qualità della vita dei pazienti, attribuibile in maniera significativa – fino al 40% del totale – ai frutti della ricerca farmaceutica. Tuttavia, sono molti i bisogni di cura non ancora soddisfatti: patologie tumorali, AIDS, malattie neurodegenerative, patologie psichiatriche e malattie rare rappresentano solo alcune delle sfide che la ricerca sta affrontando per rendere disponibili terapie nuove ed efficaci. Le conoscenze richieste per rendere disponibile un nuovo farmaco sono diventate sempre più complesse, così come elevati i costi delle fasi di sviluppo clinico. Uno scenario nel quale il successo è il risultato dell'impegno dei grandi gruppi, affiancato dalla capacità innovativa delle PMI e dal ruolo attivo dei centri pubblici di eccellenza. Snodo fondamentale di questo nuovo modello è costituito dagli studi clinici che, sempre mantenendo elevati standard di efficacia e sicurezza siano in grado di identificare caratteristiche e processi genetici prima di avviare *trials* su un numero molto ampio di pazienti. Il progresso delle terapie è, comunque, strettamente vincolato alle scelte per reperire le risorse necessarie, e, quindi, al tema della razionalizzazione della spesa e della sostenibilità del SSN. In questo contesto, ogni spreco lede il diritto alla salute rendendo insopportabile qualsiasi inefficienza nella gestione e non più rinviabile la sua ottimizzazione.

Parole chiave: assistenza al paziente, medicinali, ricerca traslazionale.

INTRODUCTION

From 1951 until today for every 4 months lived in Italy, an additional month of life has been earned (*Figure 1*). Italy's population is one of the most longaevous in the world. Italy has the highest average age in Europe together with a satisfactory life quality that continues into old age. Since 1994 the persons declaring themselves to enjoy good health has grown from 19% to 23%; a progress that has benefitted 900 thousand persons.

As in all advanced economies, this phenomenon can

be attributed to a significant degree – up to 40% of the total – to the results of pharmaceutical research, and not only to economic, social and health progress in general [1]. However, pharmaceutical research does not just refer to the major breakthroughs but also includes incremental innovation and interactions between different therapies, which are no less important for continual improvements in the quality of life and the constant progress recorded in the efficacy of treatments, the reduction of collateral effects and ease of use.

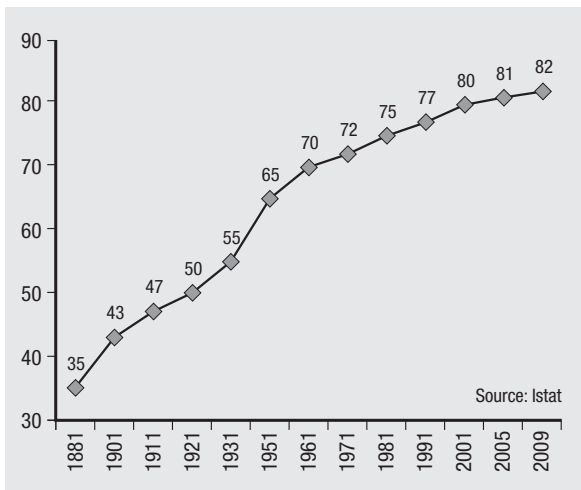


Fig. 1 | Italy: life expectancy at birth in years (male and female average).

Italians are well aware of this progress, as 80% believe that medicines have played a major role in making an agreeable life style possible for persons with chronic pathologies, 76% consider the quality of their lives to have improved and 54% consider that medicines have overcome lethal diseases [2].

Research achievements constitute hopes transformed into opportunities that can change ways of living, and offer a better quality and longer life, less invasive treatments and, therefore, less suffering for the sick and their dear ones.

While it is true that new therapies have reduced the mortality rate in recent years and led to an improvement in the quality of life, it is nevertheless also true that many medical needs are still not fully satisfied. Cancer pathologies, AIDS, neurodegenerative diseases, psychiatric pathologies, diabetes, and rare diseases are only some of the challenges facing pharmaceutical research in its work to make new and increasingly effective therapies available [3].

A thorough knowledge of the population's general health and unanswered medical needs represents the basis for a rational and efficient planning that can address the real needs of citizens given that the aging of the population, on the one hand, and technological progress on the other, generate an increase in health demand. Apart from the greater use of health benefits there is also the recourse to new therapies made possible by growing health investments, which are generally more expensive than those they replace.

These elements, therefore, combine to produce a situation characterized by a high level of complexity and one with which the new scenarios must come to terms, not only in the field of scientific research but also in that of healthcare.

In this regard, the exceptional growth in the prevalence of diabetes is a paradigm of the increase in the chronic illnesses that principally impact the elderly population.

At the international level, this pathology amounts to an out and out epidemic and requires the governments and health systems of individual countries to closely monitor the phenomenon in order to handle it in the most appropriate manner through the use of safe and efficient therapeutic tools.

On the basis of 2005 data and entire population estimates, the prevalence of diabetes in Italy is 4.5%. This figure shoots up to 13% for the 65 to 74 age range and reaches 16% for persons aged over 75 years. This is a health emergency that requires special attention. In practice, over 2 600 000 persons in Italy suffer from diabetes, to which should be added a number of persons, estimated at around one million, who are unaware that they actually have the disease [4].

The analyses conducted in the past decades for the purpose of identifying the factors behind the increase in life expectancy, and which addressed persons, regions and countries, found a positive correlation between income and survival (*Figure 2*).

This relationship is based on a number of factors that are strongly correlated to wealth, such as education, access to information and the individual and collective ability and desire to make use of the best cures available and to search for and experiment new therapies and new institutional solutions in all those cases in which adequate therapies are not available.

Therefore, knowledge, science and technology represent the elements upon which a coherent explanation can be based of the worldwide progress achieved by modern medicine in defeating the principal causes of death. Moreover, in an integrated and synergic manner, they also help define new methodological and procedural approaches aimed at improving experimental scientific investigation able to generate innovation.

THE NETWORK REVOLUTION IN PHARMACEUTICAL R&D

Also the progress made towards future cures largely depends on the transformation taking place in pharmaceutical research, which is increasingly dedicated to specific therapies targeted at individual needs: new technologies to allow researchers to use genetic information to determine not only the right medicine but also the right dose and the right time to use it; genetic therapy, cell therapy and tissue engineering that announce major steps forward in the fight against numerous pathologies [5].

This, for example, is the case of oncology, one of the areas of international specialization of Italian biomedical research, in which the availability of new, more potent and selective medicines is a matter of primary importance among the factors that best explain the increase in longevity and the improvement in the quality of patient lives [6].

The significant increase in the survival rate of cancer patients commencing from the mid 1990s is, in part, explained by the increase in the availability of

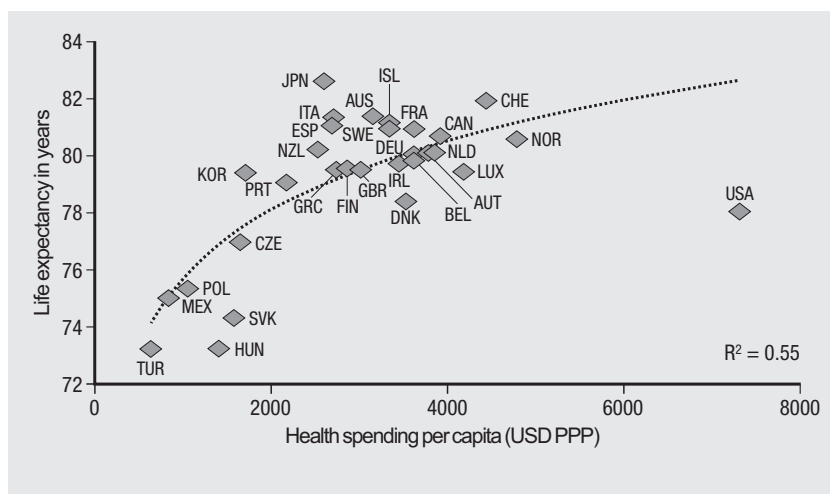


Fig. 2 | Per-capita healthcare spending and life expectancy 2007 (or latest year available).
Source: OECD Health Data 2009.

oncological medicines but above all the greater selectivity and efficacy of the new compounds.

Studies conducted between 2004 and 2008 show oncology to be the leading therapeutic area in Italy for the number of clinical experiments (29.1% of the total), and that these have also grown in number (a 55% increase with respect to 30% in other areas), and for which credit is due to greater public-private synergies.

Another complexity model emerging ever more clearly in the present clinical/healthcare panorama is constituted by rare diseases that together identify a very important area. In social terms this area represents unsatisfied needs, but it represents also an important opportunity of industrial development, especially in terms of the growth in personalized medicine.

In the period 2000-2008, Italy ranked first for the number of publications on rare diseases with respect to the total scientific publications on the life sciences (10.4% with respect to 9.0% in Japan, 8.6% in France, 8.3% in Germany, 5.8% in the UK), and this is also the area to which basic research exhibits an above-the-average orientation, especially as regards the areas of oncology, haematology, neurology, endocrinology, and metabolism [7].

The progress achieved was largely the result of biotechnological applications that make it possible to identify, prevent and cure different pathologies with increasing efficacy and greater safety.

In many cases, furthermore, biotech based treatment constitutes the only therapeutic possibility. There are already 300 million patients being cured worldwide with biotech products, which represents one fifth of those on the market and 50% of those being developed.

The increase in the investments needed to make an innovative medicine (by now in excess of one billion euros), as also, and especially, the costs in its phases of development, the greater complexity of R&D projects and the new scientific discoveries lead to ever greater specialization and division in innovative work (Figure 3).

The knowledge required to put a new therapy on the market is not only increasing but has itself become more complex, and so much so that it is increasingly less frequent that one single company – however large – can command sufficient internal resources to perform by itself all the stages in the long research process in the most competitive manner possible.

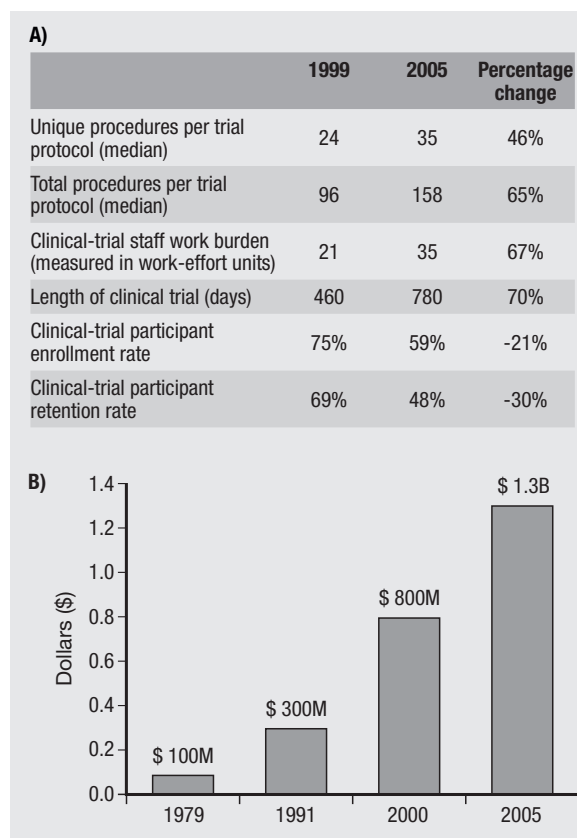


Fig. 3 | A) The growing complexity of clinical trials. B) The investments to make a drug available grow.
Source: PhRMA, Pharmaceutical Industry Profile, 2010.

In such a new and revolutionary scenario a decisive role is now played by the competitiveness of the network, in which the commitment of the major groups is flanked by the innovative capacity of the SMEs and the increasingly active role of public centers of excellence. This is a complex system, which in addition to having a great capability for therapeutic development, also exhibits positive growth synergies among similar sectors because, for example, the use of more targeted medicines calls for a more intense use of increasingly sophisticated diagnostic instruments.

In this new model, success is the product of the capacity to connect one's own excellences to the international network of research, and with a strategy able to exploit synergic relations: from the new technologies, the opportunity to explore advanced scientific paths, and from the pharmaceutical companies, the skills, resources and structures necessary to develop molecules and know-how in order to make innovative therapeutic tools available.

Clinical studies, a necessary stage for the development of medicines, represent an opportunity for curing patients, an occasion for the professional growth of researchers and an important resource for the regions.

In recent years, these studies have shown significant rates of growth in Italy, and a growing concentration upon Phases I and II, which, from 28.7% of the total of clinical trials in 2000, reached 42.2% of the total in 2008 (*Table 1*) [8].

The approach to cooperation established between the Italian Medicines Agency (Associazione Italiana del Farmaco, AIFA) and the Istituto Superiore di Sanità, and addressed to providing incentives to clinical trials held in the country, certainly offers new opportunity for developing the knowledge economy in terms of a capability to attract resources and reinforce public/private cooperation by developing its own culture for the early clinical trials phases.

And this can also be achieved through innovative models able to carry out clinical trials that, while maintaining high standards of efficacy and safety in therapy, can identify genetic characteristics and processes before commencing trials on large number of patients.

Thanks to the new mechanisms (for example conditional approval registers and control models) a more limited but more targeted number of patients should be sufficient to evaluate the risks and efficacy of pharmaceutical products, thus representing a step forward with respect to the method of evidence based medicine.

This model needs a new regulatory approach in which intellectual protection is no longer entrusted to the traditional patent alone but also to more advanced forms of open-source protection so that new discoveries – such as, for example, those in the field of pharmacogenetics and molecular biology – will not be limited to therapeutic use alone but may extend their potentialities to a wider area of applications and contributors.

The products under development in Italy number 233 (89 in pre-clinical and 144 in clinical phases) with a major investments concentrated in specific therapeutic

Table 1 | Number of clinical trials in Italy

Year	Clinical trials	%
2000	562	9.3
2001	610	10.1
2002	570	9.5
2003	579	9.6
2004	624	10.4
2005	662	11.0
2006	774	12.9
2007	780	13.0
2008	851	14.2
Total	6012	100.0

Phase I and II studies in 2008, 42.2% of total.

Source: AIFA, OSsS 2009.

areas (oncology 36%, inflammation and autoimmune diseases 15%, neurology 11%, infectious diseases 11%, dermatology 7%, cardiovascular 6%) [9].

In this “ideas market”, Italy is aware of the difficulties that some major research laboratories are facing, but it also perceives positive opportunities. However, such opportunities will depend upon institutions and companies learning how to leverage their own special excellences such as, for example, their consolidated tradition in pharmaceutical production, international level researchers and clinics and R&D biomedical specialization [10].

No evaluation on the progress of therapies can ignore the choices needed to make the necessary resources available, i.e. rationalizing spending and the sustainability of the NHS.

In Italy the over 65s represent 20% of the population (and 40% of hospitalizations) and by 2045 will exceed 30%, when the percentage of over 80s will rise from the present figure of 5% to 11%.

Therefore, health demand cannot but increase (the over 65 uses twice the average amount of per capita resources) and not least on account of the need to spend more on one's own wellbeing and the growing costs of more innovative medicines [11, 12].

In this new scenario wasteful health spending prejudices the right to health, making each and every management inefficiency and procrastination in health management optimization intolerable.

Data from the Ministry of the Economy and Finance show, for example, where 100 is the average cost index for bed space, that Lazio spends 139 and Lombardy 83 [13].

Similarly, taking the national average for caesarian sections as 100 (whereby Italy with 38% is second only to Mexico in the OECD) the North returns a value of 76, the Centre 88 and the South 125 (practically 1 delivery out of 2 is a caesarian section) [14].

Other examples also illustrate this situation: an acute hospitalization rate (when admission is longer than 1 day) that is 18% higher in the South than in the Centre-North of the country, and statistics showing that old people benefitting from domestic healthcare are twice

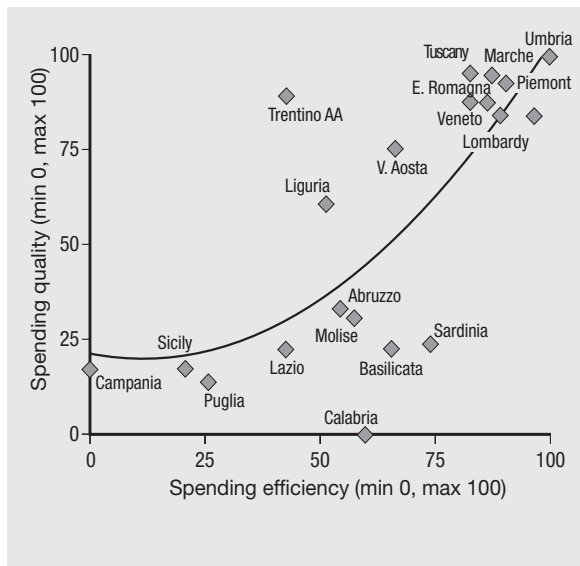


Fig. 4 | Efficiency and quality of health spending by Region. Source: elaboration by Farmindustria on CERM data.

as many in the Centre-North as in the South [15].

This condition has produced a situation such that five regions (Lazio, Campania, Sicily, Puglia and Liguria), with 37% of the population, have notched up between 2003 and 2008 more than 80% the public health deficit (Figure 4).

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A study by CERM reveals that there is a strong correlation between excess spending and poor healthcare quality and that if the regions were to realign themselves onto more efficient levels of spending, net savings of about 11 billion euros would ensue, with the major "corrections" taking place in Campania (whose spending is +31.9% over the efficiency level), Sicily (+24.7%), Puglia (+23%), and Lazio (+17.1%) [16].

Medicines and health are areas with high strategic value, and – in return for the contributions requested for regulating spending – must be guaranteed as such, within an economic framework that rewards investments and research carried out in Italy in such a manner as to: guarantee constant commitment to meeting patient needs in the context of constantly growing health demand; meet the challenges, in the most efficient way possible, represented by the levels of complexity exhibited by socio-health systems; and adapt the new reference scenarios so as to safeguard and improve conditions of health and the quality of life [17].

Conflict of interest statement

There are no actual conflicts of interest or any financial or personal relationships with persons or organizations which can inappropriately bias the findings of this study.

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