

Keynote Lectures

Personalised medicine: needs, challenges, and considerations*

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Resum. La proporció de població mundial més gran de seixanta anys doblarà l'actual l'any 2050. Això implicarà un augment de la prevalença de les malalties cròniques, que són de les més costoses, i que constitueixen una creixent pressió sobre els sistemes de salut. En aquests temps de restriccions pressupostàries, l'envelliment de la població condueix a la necessitat d'un canvi en l'assistència sanitària. Cal un enfocament triple basat en el disseny de programes que millorin l'experiència del pacient, així com la salut de la població, alhora que en redueixin els costos. El desenvolupament de la biologia molecular ha revelat els mecanismes subjacents de moltes malalties, i ens ha conduït cap a la medicina personalitzada. A mesura que la porta a l'atenció predictiva i preventiva s'obre, els problemes d'accés, lliurament i assequibilitat a l'atenció sanitària també s'alteraran: del tractament de les malalties a la preservació del benestar; d'un sistema reactiu, orientat a la malaltia, a un sistema de salut predictiu, personalitzat i preventiu.

Paraules clau: medicina personalitzada · envelliment de la població · sistemes de salut · innovacions disruptives · centres d'innovació terapèutica (CTI)

Summary. The proportion of the world's population over the age of 60 will more than double by 2050. By extension, this means an increase in the prevalence of chronic diseases, which are among the costliest and constitute a growing pressure on healthcare systems. In this time of budget constraints, aging populations drive the need for change in healthcare. A triple-pronged approach is needed consisting of the design of programs that improve the patient experience as well as the health of the population while lowering the costs. The development of molecular biology has revealed the mechanisms underlying many diseases, in turn leading us towards personalised medicine. As the door to predictive and preventive care opens, the problems of access, delivery and affordability of healthcare will be correspondingly altered: from treating sickness to preserving wellness; from a reactive, disease-oriented healthcare system to a personalised, predictive, and preventive one.

Keywords: personalised medicine · aging population · healthcare systems · disruptive innovations · centres for therapeutic innovation (CTI)

Around the world, life spans are increasing and populations are aging. The proportion of the world's population over the age of 60 will more than double by 2050, to more than 1 billion people—or 37% of the active population (Fig. 1). By extension, this means an increase in the prevalence of chronic diseases, such as cardiac and pulmonary diseases, stroke, cancer, diabetes, and dementia, which are among the costliest and constitute a growing pressure on healthcare systems. We are heading towards a situation in which 10 % of the population accounts for > 70 % of the healthcare costs (Fig. 2). How are we going to maintain the quality and type of health-

care systems that in the past effectively met the demands of the respective populations, when healthcare costs have regularly outpaced the gross domestic product (GDP) for around the last 30 years in a row? Healthcare currently accounts for approximately 10 % of GDP spending in most member countries of the OECD. In the United States, it is about 17 %.

There is a definite and imperative need for change. Since the global financial crisis hit in late 2008, the situation has become particularly dramatic. The crisis has taken a severe toll on the system's input (funding from the government, companies, and taxpayers) and placed output (innovation in business, quality of healthcare delivery) under intense strain, raising questions as to how we shall pay healthcare costs in the future. In this time of budget constraints, aging populations drive the need for change in healthcare. This is a challenge that also opens up a wealth of opportunities for innovative approaches to the shift in healthcare delivery. For the elderly, for example, we must move from reactive care, which is typically hospital-based, to proactive care, at home and integrated with social care.

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To do so requires the following:

- Innovative ways to achieve compliance
- Early diagnosis
- Integrated care models for chronic diseases (remote monitoring)
- Increase uptake of technology-based solutions for independent living
- Corresponding integration of these concepts in the planning of buildings, cities, and environments

Active and healthy aging is a priority in Europe, as addressed by the program ‘European Innovation Partnership (EIP) in Active and Healthy Aging,’ which seeks to integrate projects addressing this issue from social, clinical, technological, and economic points of view.

There are many different perspectives regarding how healthcare can become more sustainable. According to Harvard Business School professor Clayton Christensen, in his book

The Innovator’s Prescription, healthcare management is an issue in which ‘disruptive innovation’ is needed to change the way healthcare is accessed, delivered, and paid for; to provide treatment for unmet clinical needs; and to bend the cost curve for healthcare. Innovation should provide not only improvements in care but also value, defined according to patient outcomes and the impact on healthcare system resources. ‘Disruptive innovations’ could come in the form of new technological enablers that simplify processes, or as new business models, or in the form of economically coherent value networks, all of which redesign the way we treat patients.

Wireless sensors and devices, genomics, social networking, mobile connectivity and bandwidth, imaging, health information systems, the Internet, and big data are the top technological trends in the digital revolution that are transforming healthcare (Fig. 2). There is a convergence of the potential of all these technologies and over time their level of development will make them more affordable. For example, in the space of 10 years, the cost of sequencing a genome has gone from more than 10 million USD to less than 1000 USD.

Billions of data points per individual are being generated with these new technologies. The great challenge of medicine in the 21st century is complexity: How do we extract useful information from these data? How do we make correlations? How do we interpret the data? Medicine is increasingly becoming an informational science: through systems and holistic approaches we will be able to understand wellness and disease, by attacking complexity efficiently; emerging technologies will allow us to explore new dimensions of the patient ‘data space’; and with the aid of transforming analytic tools we will be able to decipher the billions of data points for the individual, by acquiring, storing, transmitting, integrating, mining, and creating predictive models.

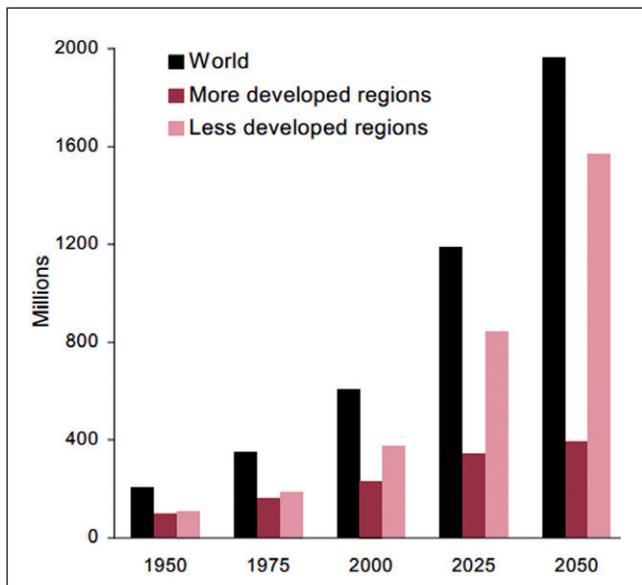


Fig. 1. Population aged 60 and over: world and development regions, 1950–2050. Source: Department of Economic and Social Affairs, United Nations.

Personalised medicine

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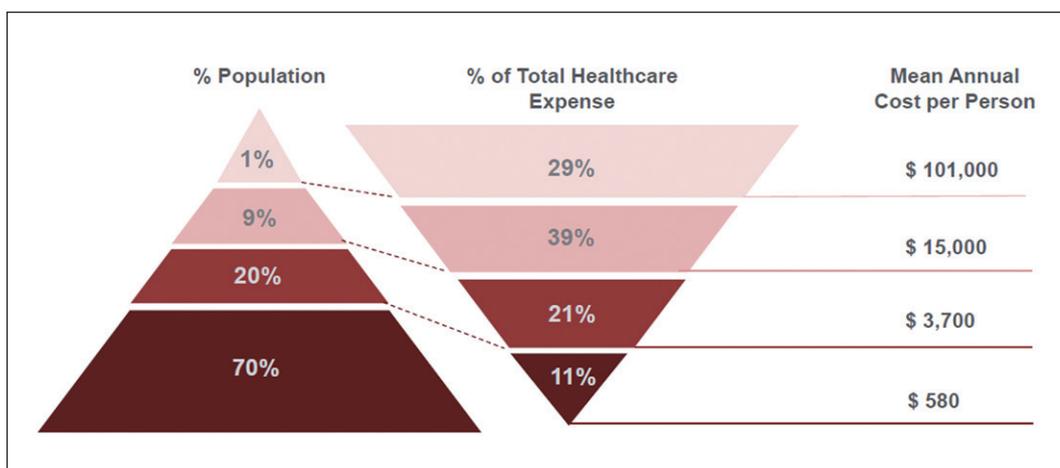


Fig. 2. Imperative for change: the few cost the most.

will be correspondingly altered: from treating sickness to preserving wellness; from a reactive, disease-oriented healthcare system to a personalised, predictive, and preventive one.

The digitalization of biology and medicine is transforming the way we treat patients in what is now called P4 Medicine: *predictive*, because from the available information we can predict the phenotype or the pathology of a patient's disease; *personalised*, because we can treat patients individually, according to their specific condition; *preventive*, because the emphasis will expand to include disease prevention; and *participatory*, because it enables patients to be an active part of their own healthcare.

Since 2003, coinciding with the Human Genome Project, we have progressed from understanding the structure of genomes to understanding the biology of genomes and subsequently the biology of disease. This new knowledge is the key to advancing the science of medicine and to improving the effectiveness of healthcare. The goal of personalised medicine is to be able to distinguish between patients who, while they may have the same symptoms, differ in the pathways underlying their disease. Moreover, we know that patients react very differently to therapeutics, reflected in differences in the percentage response to therapy. With personalised medicine, non-responders can be identified prior to treatment, thus sparing these patients unnecessary discomfort and the healthcare system unnecessary costs.

Let us take lymphoma as an example. Only 100 years ago, lymphoma was described as a disease of the blood. But thanks to molecular biology we have been able to discriminate between lymphoma and leukaemia (80 years ago) and between different types of lymphomas and leukaemia according to the dysfunctional mechanisms—from a total of five types 60 years ago to the 38 types of leukaemia and 51 types of lymphoma recognised today. But of course, all these studies take time and need to be conducted through huge consortiums based on collaborations between researchers from different fields. Here in Catalonia, these research groups include that of Professor Elías Campo. Dr. Campo's laboratory is financed by the NIH and is leading a huge effort in the study of chronic lymphatic leukaemia (CLL). This group recently published a report on the types of cells that give rise to CLL and the elements that cause certain cells to develop this pathology. Another group is that of Professor Roderic Guigó, co-head researcher of the ENCODE project and a leader in bioinformatics who works at the Centre for Genomic Regulation. An example of the new business models is *Inbiomotion*, a spin-off of the Institute of Biomedical Research (IRB) and the Catalan Institution for Research and Advanced Studies (ICREA). Headed by Professor Roger Gomis, the company has just obtained venture capital to fund the development of an assay for use in validating the capacity of a biomarker to predict bone metastases in cancer patients.

Redefining business models

The rules under which the healthcare industry has operated since its inception have changed completely because of global economic trends, policy revisions, marketplace demands,

and technological breakthroughs. Consequently, companies have been compelled to devise new strategies to ensure their continued success.

Biopharmaceutical companies are under pressure to reduce expenditures, as drug development costs increase, patents expire, competition from generics increases, regulations become stiffer, and pipelines dry up. The pressure is causing these companies to redefine completely their approach to innovation, in turn realigning the roles of the different stakeholders, such as academia, venture capitalists, and biotech. Faster and cheaper ways to bring new drugs to the market are needed. The era of blockbusters such as Pfizer's *Lipitor* is over. As the annual sales trends of traditional pharmaceuticals decrease and the sales of bio-therapeutics increase, the pharmaceutical industry is shifting from medium efficiency/overall-patient medicines to an increasing focus on high efficiency/patient-targeted and personalised therapies. As such there is a move away from internal R&D to approaching external resources for new ideas, e.g., through greater reliance on partnerships with biotech and academia as sources of innovation. Pharmaceutical companies are no longer able to generate and access all the information underlying the different pathologies they consider to be of interest. Instead, they are financing collaborations with different research groups and universities but also with smaller companies to be able to more efficiently access innovation. For example, Pfizer has established a CTI (Center for Therapeutic Innovation) at the University of California-San Francisco and another at New York University. The company has invested US\$50M over 5 years to finance an open network of researchers from universities, hospitals, and Pfizer itself to identify and advance promising experimental drugs to proof-of-concept stage. This strategy is expected to accelerate pre-clinical development.

Similar approaches have been initiated by the other major pharmaceutical companies to achieve the same goal: bringing new technologies to the patient. Johnson and Johnson, for instance, has launched a new incubator, Janssen Labs, in San Diego, California, which finances research that comes out of public laboratories, typically in the form of small biotech companies. This is more efficient in terms of access to basic research, in particular the elucidation molecular pathways. In addition, the industry is increasingly turning to other strategies, including the use of virtual models, the variabilization of fixed costs, and outsourcing non-critical steps in drug development. Strong project management, research and clinical oversight, and the taxpayers' involvement are critical in the new ecosystem. Pharmaceutical companies must also work on a more equitable level with diagnostic companies, e.g., by involving them at earlier stages of drug development, as companion diagnostics become more common. Diagnostics accounted for less than 2 % of healthcare spending but affected more than 60 % of critical decision-making. Interest in these measures is also being shown by large research institutes. Francis Collins, the director of the NIH, has launched the National Center for Advancing Translational Sciences (NCATS) to develop innovative ways to reduce, remove, or bypass the many time-consuming, costly bottlenecks in the translational pipeline. Again, the goal is to shorten the path to clinical phases.

Genomic medicine, education, and society

The imperatives for genomic medicine are:

- Making genomics-based diagnostic routine
- Defining the genetic components of disease
- Comprehensive characterization of cancer genomes
- Implementing practical systems for clinical genomics informatics
- Understanding the role of the human microbiome in health and disease

Certainly we have to move from healthcare based on data collection to a system that is more proactive, in which the data are integrated. Bioinformatics and computational biology are the tools that allow us to analyse, integrate, and visualize the data. Moreover, training and education are essential. Clinicians are not trained to deal with all the genomic information that is available, nor do they possess the skills needed to cope with the possible social, communication, legal, and ethical impacts of this information. In the coming years, primary and secondary education must incorporate this type of training, equipping students with general information about the genome, its ethical use, and the concepts of risk and probability. Public outreach is crucial to truly sensitise the population about the opportunities but also the risks involved with the advancement of these new technologies. It is also important to train and build the genomic competences of genomic providers, clinicians, nurses, etc. And of course, the next generation of genomic researchers must be trained in statistics, computer science, and other, related fields that are currently not part of the biological and medical science curricula.

Similarly, with regard to genomics and society there are many ethical, psychosocial, legal, and public policy issues that need to be dealt with. The ability to identify an individual's genetic background and the possible outcomes of it could significantly influence the behaviour of that person, the many implications of which must be taken into account.

Drivers. There are many drivers in the healthcare system. The main ones are: (i) patients, who want safer and more effective drugs but also a more active role in the own healthcare; (ii) payers, who need to be certain that the money spent generates significant medical benefit for the patient; (iii) regulators, whose approval of a drug is based on its safety and efficacy; and (iv) industry, which by reducing development time and costs can increase its success and thus their success rate.

Barriers. Of course, there are also barriers that hinder the full integration of personalised medicine into medical practice. These include: (i) *scientific and technical barriers*, such as data management, storage and analysis; (ii) *regulators*, whose knowledge does not evolve at the same pace as scientific and technical progress demand; (iii) *reimbursement processes*, as clear guidelines specifying reimbursement for services provided are lacking, including the assurance to molecular diagnostic companies that they will be paid for the value they contribute;

(iv) *physicians*, who are challenged by structural barriers in which incentives are not aligned to prioritize prevention versus treatment and who are thus not trained accordingly; and (v) *pharmaceutical and diagnostic companies*, who must recognize the need to work together to provide value to the system.

A more holistic strategy is needed, such as the top down approaches used in some countries to implement genomics in healthcare. In the United Kingdom, for example, a joint strategy for the National Health Service (NHS) was recently commissioned with the aim of incorporating genomics into the healthcare system. Thus, the Human Genomics Strategy Group (HGSG) is responsible for monitoring advances in genetics and genomics research, both basic and translational, to evaluate their benefit to the healthcare services within the NHS: translating research into quality-assured care pathways; developing a service delivery infrastructure (from commissioning initial tests to counselling patients and their families); providing a bioinformatics platform to store and manage data; training the NHS workforce; addressing the legal and ethical issues; and raising public awareness.

Challenges ahead

A triple-pronged approach is needed consisting of the design of programs that improve the patient experience as well as the health of the population while lowering the costs. This is likely to best be accomplished by moving from a data-collecting healthcare system to one that is data-driven. We must develop both medium- and long-term strategies (at the policy and clinical levels). Performance must be monitored by linking technology to health outcomes. There needs to be a realignment of incentives such that waste is punished and quality and results rewarded. Other issues to be addressed include those dealing with reimbursement and the need to better promote the role of health technology assessment in verifying that innovations introduced into the system bring value to it and justify the additional cost. The technological revolution is limited by economic, organisational, and technological disparities among countries, and the capacity of these countries to overcome them must be taken into account. But there will also be a new range of competences, in the form of systematic thinking, project management, communication, clinical genomics and IT. These will involve everyone who participates in the healthcare system, from clinicians to patients.

If we really want to have a continuously adapting healthcare system, one that is able to incorporate innovation and assessment, we must begin by being efficient, specifically at the level that connects care, research, and evidence, and in building networks between clinicians, patients, researchers, and society at large.

References

1. Biotech 2012: Innovating in the New Austerity (2012) Burrill & Company

2. Biotech 2011 – Life Sciences: Looking Back to See Ahead (2011) Burrill & Company
3. Chanock S (2012) Towards mapping the biology of the genome. *Genome Research* 22:1616-1625
4. Christensen CM, Hwang J (2009) *The Innovator's Prescription: A Disruptive Solution for Health Care*. McGraw-Hill, 496 pp
5. Ministry of Health (2012) *Genomic Technology in Healthcare: Building on Our Inheritance*, 83 pp
6. Institute for Systems Biology [www.systemsbiology.org]
7. MedTech Europe [www.medtecheurope.org]
8. Misfit [www.misfitwearables.com/references]
9. Green ED, Guyer MS (2011) Charting a course for genomic medicine from base pairs to bedside. *Nature* 470:204–213
10. Smith M, Suanders R, Stuckhardt J, McGinnis M (2012) *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*. The National Academic Press, 416pp