

# Do we understand the personalized medicine paradigm?

*Personalized medicine marks the beginning of a new attitude in medicine*

Krešimir Pavelić, Tamara Martinović & Sandra Kraljević Pavelić

**M**uch has been made about the impending arrival of personalized medicine: it is predicted to revolutionize health care and promises a bright new future in which people live longer and healthier lives. The concept of personalized medicine and the expectations it raises are based on recent advances in the life sciences—notably high-throughput technologies and the various ‘omics’ that these have spawned—that could yield insights into how a given disease will progress for an individual patient. These high-throughput analytical methods have begun to trigger an important drift in medical practice towards presymptomatic diagnosis and preventive medicine. However, the ultimate goal of personalized medicine with a strong focus on prevention and individualized care will require massive investment in both basic and translational research into the biology of disease. More money will then be required to translate this knowledge into benefits for patients, citizens and health care systems, and the implementation of these benefits will require drastic changes to the medical profession, to the public acceptance and understanding of medicine, and to how we train a new generation of scientists and physicians.

Biomedical research is quickly evolving to co-opt other life science research fields into so-called ‘big science’ projects. Research at this scale requires international collaboration, expensive infrastructure and technology, and interdisciplinary expertise to produce and analyse vast amounts of biological data. The starting point for these kinds of projects was the US\$2 billion *Human Genome Project* that deciphered the nucleotide sequence of the human genome,

followed by the Hap Map project, which catalogued the human genome haplotype map. Next was the *Encyclopedia of DNA Elements* (ENCODE), finished in 2007, which identified and analysed functional elements in the human genome. 2008 saw the launch of the *Thousand Genome Project*, with the goal of sequencing 1,000 different human genomes to map differences between them; it has already delivered more than 79 million variant sites that include not just biallelic polymorphisms, but also indels, short substitutions and other structural variants based on sequence data from 2,535 individuals from 26 different populations around the world. Turning such a large quantity of data into useful and meaningful information will represent a major scientific and societal challenge, especially when it comes to implementing it into medical practice and health care. Complexity at every level is therefore the main challenge for this new concept, from research to medical practice; even the life sciences have not fully made the transfer from reductionism towards a more integrated view of life.

**O**n the other side of the equation, the concept of personalized medicine is not fully understood by the medical community either. Use of the term most often implies pharmacogenomics and pharmacogenetics, and recently pharmacoproteomics. The term is also often identified with genomics medicine or medicine based on genotype, individually tailored therapy, integrative health care, medicine based on high-throughput analytics and predictive medicine. Lately, expressions like precise medicine, systems medicine or translational

medicine have entered the fray. In fact, personalized medicine should be understood as a much wider movement that encompasses all of these terms. For example, genomic medicine is an important component of the personalized paradigm, but it is mainly based on genomics and to a lesser extent on transcriptomics data from many human genomes, as a single sequence cannot explain the multitude of disease symptoms and pathogeneses.

“... the concept of personalized medicine is not fully understood by the medical community either”

The more recent term, ‘precise medicine’, describes the idea of stratifying patients to identify genomic, biological and environmental factors that influence disease progression, with the ultimate aim to prescribe the most efficient treatment at the right time. The term thus implies the use of ‘omics’ methods to assess the patient’s disease status. Again, precise or stratified medicine is only a part of personalized medicine—one that is restricted to identifying subgroups of patients who are likely to respond to certain treatment. For example, the drugs gefitinib and erlotinib are used in targeted treatment of certain sub-groups of patients with non-small cell carcinoma bearing the EGF-R mutation [1]; the drug vemurafenib is used in the treatment of metastatic melanoma patients with the mutated BRAF gene V600 [2]. Personalized medicine will



therefore also challenge the pharmaceutical industry, which has largely developed its drugs on the basis of ‘one drug for all patients’. Instead, drugs should be developed and prescribed at least in accordance with the pharmacogenomic profile of the patient.

*“What has been neglected is a comprehensive view of the patient as a person and his or her overall functions”*

The term ‘integrated medicine’ or ‘integrated personal care’ comes closer to the concept of personalized medicine, but has been widely used to describe a combination of classical and alternative medicine. In the context of personalized medicine, it should include the integration of ‘omics’ profiles and classical diagnostics with individually tailored therapy. We now know that there are more than 20,000 genes in the human genome and at least several hundreds of thousands of proteins in each cell, many of which play a role in pathological processes. It is naïve to presume that, based on a few parameters, we can learn about the mechanism of disease and, in such a way, prevent or cure it. The personalized medicine paradigm could thereby contribute to early—even presymptomatic—diagnosis, the development of new, more efficient drugs, and exact disease prognosis. In summary, true personalized medicine is a new approach to classification, understanding, treatment and prevention of a disease, based on individual biological and environmental differences. It is clear that this innovative approach in

medicine opens up a range of scientific and social questions [3], including the potential legal and economic implications—particularly with regard to human genetic research—of introducing electronic medical records and biobanks, personalized genomic data for clinical use, physicians’ access to electronic decision support tools, personalized health plans, personalized treatment and making personal clinical information available for research.

The paradigm of personalized medicine therefore represents not a scientific or medical movement, but a social one: from the hitherto simplified view of a group of patients who share the same disease, to a view that focuses on the individual patient. The principle of ‘one cure for all’ can no longer satisfy the needs of modern medicine; the drug or treatment should be created and prescribed according to the comprehensive patient profile and status. This will challenge medicinal practice in the same way that the historic fragmentation of medicine into sub-disciplines—cardiology, urology, orthopaedics—resulted in a fragmented approach to the patient. What has been neglected is a comprehensive view of the patient as a person and his or her overall functions. Moreover, medicine has already reached a high level of technological sophistication using advanced diagnostic instruments, but it has become depersonalized in the way the medical system approaches its patients. Personalized medicine should resolve some of the moral criticism against this modern, high-tech approach by refocusing attention on the person being treated and tackling their specific disease in the context of their overall profile.

Technological developments and increasing scientific knowledge will eventually have

to start a larger discourse about the social, educational, ethical and legal challenges that will inevitably come with implementing personalized medicine. First and foremost the discussion will need to overcome the scepticism among medical professionals towards implementing new knowledge from scientific research into their practice.

Physicians make diagnostic and treatment decisions based on their ‘classical’ medical school training, practical experience and measurement and conversation with the patient. This stable therapy algorithm is reinforced by the historical successes of blockbuster drugs with the one-size-fits-all strategy. The fate of personalized medicine, however, will depend on the ability of physicians to integrate complex information from multiple sources, such as high-throughput technology and data management, to select the most appropriate treatment from a wider range of options. Consequently, physicians will need to master new skills and embrace new knowledge.

*“Physicians make diagnostic and treatment decisions based on their ‘classical’ medical school training, practical experience and measurement and conversation with the patient”*

Today, professionals in the field should admit a collapse of the blockbuster system of drugs. The earliest example of how the one-size-fits-all approach is failing is linked to Herceptin, a drug used against breast cancer cells that overexpress the HER-2 receptor. Successful therapy requires previous

testing of the HER-2 receptor status. The scepticism towards this approach in Europe was clearly visible 10 years ago when only 6% of breast cancer patients were tested for HER-2 overexpression in the UK, in comparison with 40% in other European countries [4]. In the meantime, the test has become a standard in breast cancer diagnostics.

Current educational systems for scientists, clinicians and other professionals will have to adopt new curricula to prepare them for the challenges of personalized medicine. They will also have to engage and encourage students to move into this new and complex field. The major issues are multidisciplinary and the complexity of tasks. For example, health professionals should be educated to make decisions based on complex biological, environmental and lifestyle information. Bioscientists and technological experts should be educated to understand the real needs of patients, from which this group of experts can develop therapeutic solutions. Doctors will have to develop communication skills and a willingness to understand and collaborate with other experts. The question is how a single person can cope with biology, mathematics, physics, bioinformatics, imaging, and 'omics' technologies and master communication skills that are needed to support personalized medicine. Current education is fragmented, specialized and produces experts in particular fields who do not have the skills, capacities and knowledge to understand a broader picture. New education curricula should address this lack and focus on a more holistic approach to health. To ensure this, we propose to promote health literacy in general among public and specific interdisciplinary study programmes at the earliest stages of professional development, that is a complex approach to diagnostics by the use of novel algorithms, re-classification of disease based on systems biology and integrated scientific data or economical and legal aspects.

Many other factors reinforce scepticism: policy makers who do not understand the personalized medicine paradigm, wrong interpretations of scientific discoveries, excessive optimism and irresponsible claims. Other factors that influence the implementation of personalized medicine include current regulatory regimes, an economy based on spending for drugs instead of encouraging diagnostics, prevention and

education, multidisciplinary, research and health infrastructures, revised disease classification, and compensation models of health services.

Personalized medicine will open a range of social, legal, regulatory and moral challenges. Since diagnosis and treatment will be based on a range of genomic and other biological data from patients, the questions of data ownership, informed consent and privacy come to the fore. How will access to this information be managed for clinicians planning treatment and researchers seeking to better understand disease progression? A possible solution could be a shift of ownership rights of individual health records and other health-relevant information from physicians or health care systems to patients. Any other control system will inevitably end up in inadequate control of citizens, a medicalized society controlled by business interests or public health care systems and loss of the right for free choice. This would address the lingering risk that insurance companies, banks or employers, for example, might abuse the medical data on their customers or employees or that the personalized medicine movement inadvertently becomes a source of additional society medicalization, such as obligatory medical check-ups, grouping of people according to biological data or even denying people the basic right of free choice on how to live their lives. On the other hand, more emphasis on individual responsibility might lead to victim blaming of people who willingly choose not to live healthy. These issues should be stringently controlled by society. A long-term personalized medicine movement goal would be a true personalization of health and decisions along the course of life and not just a personalization of disease and its treatment. Furthermore, the differences between countries in terms of legislation and regulations could become a hindrance for international scientific collaboration and sharing of data.

Personalized medicine must also become accessible to a wide population and not only to countries or societies that have the appropriately developed technology, science and sufficient finances. Indeed, it might easily be hampered by a need to pay for the technology or services and generate even deeper inequalities. Current financing schemes are inadequate. It would be better to use grant money to address true needs and not only in

words and terminology such as a new cure for cancer or new treatments for Atherosclerosis that ultimately benefit patients and not just the pharmaceutical industry.

*“A long-term personalized medicine movement goal would be a true personalization of health and decisions along the course of life and not just a personalization of disease and its treatment”*

All participants in this process will be faced with new roles. Medical professionals will be forced to make decisions based on a wide range of complex biological data, environmental information and life style. Scientists will have to cooperate closely with physicians to fulfil their requirements for patient care. Politicians and regulators will have to better understand the nature of personalized medicine and the underlying technology to support and regulate it appropriately. Citizens will have a larger responsibility for their own health through active monitoring, prevention, lifestyle and treatment choices. Thus, one of the biggest challenges of personalized medicine that must be addressed is a true interdisciplinary dialogue [3]. This dialogue should be begun first with health care professionals and scientists on one side and economists and legal experts on the other side on general interdisciplinary questions related to personalized medicine. A dialogue will also be needed between health care professionals and citizens, and with health care providers and industry. A good incentive for these dialogues might be a well-shaped European scientific policy, but here the question remains what bodies and structures would have the power and the strength for such a vision.

We are witnessing a profound transformation in the molecular life sciences as we finally begin to understand the molecular background of many diseases. The application of this knowledge to personalized medicine and the move to introduce high-throughput analyses in medical practice have the potential to considerably change the lives of both patients and healthy people. Yet, the

research that precedes personalized medicine often raises both unrealistic expectations and fears, each of which leads to misunderstandings or misleading interpretations. It raises the danger of replacing a current lack of knowledge with greater insecurity owing to incomplete or unusable knowledge—a risk prediction for a disease for which there is no treatment, for example—thus worsening or complicating a patient's life. The best approach to handle these problems is to start a wide dialogue and objectively inform the public.

Finding ways to address these problems and challenges will not be easy, but we think that the social sciences and humanities have much to offer in this regard. The path to personalized medicine should be paved through tight collaboration between scientists, medical professionals and social scientists, with all directly involved in research. This issue will be highly relevant when scientific and technological solutions for personalized medicine will be ready to be implemented in an everyday environment. Here, different solutions will be needed, including a regulatory framework with emphasis on privacy rights regulation and reimbursement frameworks for non-pharmaceutical therapies and prevention

schemes. Finally, a large society debate with experts on the social sciences and humanities could help to diminish fears among citizens. Policy makers, health authorities and other public bodies must enter this debate and facilitate the public dialogue.

.....  
*“The path to personalized medicine should be paved through tight collaboration between scientists, medical professionals and social scientists, with all directly involved in research”*  
 .....

We are not sure, however, whether the social sciences and humanities are sufficiently aware of the developments and challenges to undertake this task. They should reach out and learn more from their colleagues in the natural sciences and vice versa. Science is part of our daily lives; it is therefore neither detached from life, nor does it claim to provide ever-lasting truths. Crucially, therefore, the application of science benefits from the involvement of social scientists,

philosophers and ethicists, in particular when it comes to implementing personalized medicine with its large social challenges.

### Conflict of interest

The authors declare that they have no conflict of interest.

### References

1. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I et al; North-East Japan Study Group (2010) Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 362: 2380–2388
2. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M et al; BRIM-3 Study Group (2011) Improved survival with vemurafenib in melanoma with BRAF V600 mutation. *N Engl J Med* 364: 2507–2516
3. ESF Forward Look (2012) Personalised medicine for the European citizen. Towards more precise medicine for the diagnosis, treatment and prevention of disease (iPM). European Science Foundation, Strasbourg November
4. Hedgcock A (2004) *The Politics of Personalised Medicine: Pharmacogenetics in the Clinic*. New York: Cambridge University Press