Public Health Genomics—
public health goes personalized?

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High five?—5 years ago, we wrote the first Editorial1 and Viewpoint2 on Public Health Genomics for the European Journal of Public Health. We concluded that ‘public health in the future will be quite different from public health in the past’. Today, 5 years later, have we been right? Where are we now?

The highly technology and bioinformatics-driven dynamics of genomics as a ‘moving target’ from the Human Genome Project (HGP) to the Personal Genome Project (PGP) is currently ‘shaking’ public health research, policy making and practice in a very fundamental way. Let us be prepared for rethinking our public health interventions, since we face a time when boundaries of disciplines are crossed and the understanding of diseases is changed as it happened before with the discovery of microscopy and the jump from the macroscopic point of view in anatomy to the microscopic view in cell structure.

Firstly, epigenomics plays a crucial role for public health by bridging social and biomedical sciences and being the blueprint for the understanding and measurement of genome–environment interactions and the interplay of all health determinants in disease aetiology. It suggests measurable mechanisms (DNA methylation patterns) whereby environmental factors such as stress, nutrients or a virus influence gene expression (‘from society to cell’). For example, nightshift seems to be not ‘just’ an environmental risk factor, but also appear to have an epigenomic effect in the aetiology of breast cancer by changing the genome and possibly turning into an inherited risk factor.3 These epigenetic modifications can occur throughout the whole lifetime of the organism, starting with the intrauterine environment, and can accumulate in tissues and cells over time. They may also help not only to explain the differences in health outcomes or disease risk patterns between individuals, but also the changing risk patterns within an individual over the life-course and will provide strong evidence at the individual level as we see it already in the fields of cancer or infectious diseases.5

Secondly, new developments in systems biology indicate that specific cellular functions are seldom carried out by single genes, but rather by groups of cellular components. This network-based research is already starting to change nosology. Seemingly dissimilar diseases and health outcomes are being lumped together. What were thought to be single diseases are being split into separate ailments (‘diseasomes’). The approach offers a novel method for human disease classification. It defines disease expression on the basis of its molecular and environmental elements in a holistic way. Taking the example of breast cancer (and cancer in general), it indicates that every cancer is individual, since individual pathways in systems biology correlate with onset, severity and prolongation of diseases as well as with responses to therapies. Based on this knowledge, individual cancer vaccines are currently developed by using tumour cells of the patient to prime her/his own immune system. Furthermore, the findings on diseasomes demonstrate that one genomic variant (due to a pleiotropic effect) is being associated with a bunch of subtypes of diseases (diseasome) such as e.g. breast cancer, prostate cancer, multiple myeloma and schizophrenia. Thus, there might be no cases of breast cancer in a family, but cases of schizophrenia or autism (as a subtype of schizophrenia). However, all women of this family have a high risk for developing breast cancer. So far, we miss these cases of breast cancer with our current public health strategies.

Trying to translate the impact of these two developments towards personalized healthcare into public health, what does it mean for public health? Why is genomics really ‘shaking’ Public Health?

Obviously, it is a new paradigm, because we start to understand that (i) what we call common complex diseases might be a sum of ‘rare diseases’, (ii) we move from diseases towards diseasomes, (iii) we move from risk factors to individual pathways or networks and (iv) we move from clinical utility to personal utility. Genome–environment interactions change from day to day within an individual, i.e. neither genomics nor the environment is stable. Biological pathways or networks are permanently interacting with environmental networks such as social networks. Thus, does it mean that we move from the approach of the interaction of health determinants to the interaction of networks in systems biology and environmental networks including social networks on the individual level? Will diseases or diseasomes develop just by chance, just randomly within an individual? Is this the end of epidemiology, RCTs and EBPM? Is this the end of primary prevention and health promotion?

For sure, the current shift in healthcare towards a systemic and holistic understanding of the aetiology of diseases or health outcomes (‘systems thinking’) is a scientific revolution. Thus, a comprehensive model of future healthcare taking into account integrative genomics alongside with environmental, social and life style factors will become essential to realize the P4 Medicine as the future paradigm of health-care systems being predictive, personalized, preemptive and participatory.6 At this moment, the biggest challenge is the interoperability and interpretation of a huge amount of data gathered around an individual: what information is at what time relevant for the individual? Hopefully, computational bioinformatics and mathematics (e.g. fuzzy logics) will provide us with solutions in the near future.

Complementary to personalized public health interventions, health protection will continue to be a highly effective and efficient public health task. So far, all stakeholders including...
policy-makers and the private sectors are struggling to translate the emerging knowledge into public health. Public Health Genomics (PHG) is the area of public health ensuring that scientific advances in genomics ('from cell...') triggered by innovative technologies are timely, effectively and responsibly translated into health policies and practice for the benefit of population health ('...to society').

Are we prepared in Europe? The implementation of PHG requires increased concerted actions. The Public Health Genomics European Network (PHGEN I) funded by the General Directorate for Health and Consumer Protection (DG SANCO) (www.phgen.eu) initiated National Task Forces on PHG in over 15 EU Member States. Due to these initiatives, the National Institutes of Public Health start taking a leading role in Public Health Genomics such as in Finland, Belgium, The Netherlands, Croatia, Poland or Germany. Currently, PHGEN II develops 'European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies', which will assist the European Member States. The Hungarian EU presidency will deal with the network thinking in biomedicine and social sciences. No wonder, since the 'father' of the diseases, Albert-Laszlo Barabasi, is Hungarian!

To conclude: today, 5 years later, have we been right? Yes, indeed! Public Health in the future will be quite different from public health in the past and will go personalized. In addition, the level of complexity in Public Health Genomics has even become higher. Maybe this is a philosophical question, but is nature really so chaotic? Or will we learn in the end that there is an ordering principle behind the chaos, as we learned it already from physics in the past?

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Genome-based knowledge and public health: the vision of tomorrow and the challenge of today

Several years after the first human genome has been decoded, the various ‘omics’ technologies struggle to translate basic science discoveries into clinical and public health applications. While several success stories are available, the promise of genomic medicine for 2010 remains largely unfulfilled. Most genomic publications are in basic sciences and little translational research is carried out to feed the pipeline of applications. We need to take a closer look at the way we translate discoveries from the bench to the population and how we process and integrate evidence. This also implies that more realistic expectations are needed to fulfil the promise of genomics to improve health.

Predictive genomics and personalised medicine as a showcase

The area of predictive genomics is currently undergoing substantial change, with a more rapid translation of scientific evidence into products and a sharp decrease of sequencing costs are predicted. With emerging fields like epigenomics and systems biology, we face challenges both within the framework for research and the regulatory response to the emerging knowledge. Ultimately, the policy impact is higher than expected 5 years ago as the merger of diagnostics and pharmaceuticals (theranostics) and the individual risk modulation (in particular in nutrigenomics and toxicogenomics) impact market authorization and market regulation systems currently used in Europe and North America. The personalization of risk prediction, drug response and the understanding of the aetiology of diseases change the role of citizens (in the direction of prevention and self-responsibility) and require increasing emphasis on health literacy, potentially widening health and socio-economic gaps in society. As the new genomics requires an integration of data from various sources, it also questions current data infrastructures and data protection regulations in Europe and beyond. The current re-cast of the European Data Protection Directive will be a Litmus test that will give an indication to what extent the need for data integration and linkage in a secure environment is seen as a priority. Important policy tools such as the precautionary principle or the ‘Health in all Policies’ approach, as defined in Art 168 of the Treaty, may have to follow this trend, creating new legally enforceable approaches.

The current perception is that genome-based knowledge creates expectations, which cannot be fulfilled on the short run. There are large differences in the application of genome-based technologies. While research in certain diseases progresses rapidly, in particular cancer and infectious diseases (pathogen genomics), less progress is visible in cardiovascular and neurodegenerative disorders. The field of cancer is, by far, the most advanced for genomic applications. It has been acknowledged years ago that each tumour is unique and we do not find two patients with identical cancers in Europe. The combination of activated signalling pathways will demand personalized diagnosis and treatment, depending on the level of metastasis and the effectiveness of pharmaceuticals. This makes it difficult to apply traditional procedures of market authorization to ensure safety and efficacy of the drug ‘cocktail’. Data on the different ingredients of the ‘cocktail’ do not provide insights into the interactions of the components and the response of the patient. While researchers gain rapid insights into genes, they struggle to combine the genetic knowledge with environmental factors such as pollution, lifestyle and epigenetic inheritance to understand normal and disease processes and find targets for effective interventions. Evidence standards for a new way of doing research are needed; otherwise we might not close the translational gap between basic and clinical research.

While stakeholders share the scientists’ optimism with regard to the generation of genome-based knowledge, many are reluctant to predict a widespread application in practice due to the complexity of the emerging knowledge and the lack of preparedness in medicine and public health. In USA, the EGAPP working group, an independent multidisciplinary panel that examines the evidence around emerging genomic applications (http://www.egappreviews.org/), has concluded that for several tests they evaluated at so far, an appraisal is not possible due to insufficient evidence. The real take-home message might be that in a personalized medicine setting, our traditional tools for the assessment of technologies do not seem to work anymore. Clinical trials may be more difficult to construct if we assume that there is obvious heterogeneity in patient response to drugs and other medical technologies.

To conclude, we believe that emerging genome-based knowledge requires a more updated policy making and knowledge management processes. A real paradigm shift in public health and medicine still depends on the willingness to restructure policies/approaches and the ability to train practitioners from various professions. Public health therefore needs to develop a pre-emptive approach towards expected structural changes in prevention and care. International initiatives such as GRaPH-Int and European projects such as PHGEN, ENGAGE and EuroGenent are facilitating this process by convening all relevant stakeholders. The P4 medicine vision of Hood is not around the corner yet, but there is a clear urgency to prepare health care systems and policy makers now.

References

Public health genomics and the challenges for epidemiology

While chronic diseases (e.g. obesity, diabetes, coronary heart disease, cancer, etc.), also named ‘complex diseases’, are caused by the combined effects of multiple environmental and genetic factors, it is estimated that the environmental component plays a major role. Nevertheless, the smaller role of inherited genetic factors may partly be explained by the difficulties in exploring this component until recently. The huge amount of genomics data produced by the fast-developing biotechnologies at an unprecedented speed will probably help in dissecting the genetics underlying these diseases.

During the past 5 years, genome-wide association studies (GWAS) identified hundreds of genomic loci robustly associated with common chronic diseases. While this strategy has provided key novel insight into disease biology within a very short time scale, it will take many years before the impact of GWAS findings can be precisely estimated. GWAS, as currently conducted, is not able to identify rare variants, structural variants (e.g. copy number variation), and loci displaying high level of allelic heterogeneity across populations because current standards require associations to be replicated in independent populations. Hence, there is still a large fraction of the trait heritability to be explained, the so-called ‘missing heritability’. The current application of massive parallel sequencing (MPS) is identifying rare variants associated with common chronic diseases. The huge heterogeneity, almost at an individual level, of the genetic alterations found through these new technologies emphasizes the notion of individualized diseases. Epidemiologists are now moving the focus of their analyses from single genetic variants, to rare variants associated with common chronic diseases. The huge inter-individual variability of the genetic alterations found at the individual level, together with extensive information on environmental factors and behaviours.

Regarding the latter, epidemiologists face the important challenge of assessing the complexity of highly correlated environmental exposures. We do not have platforms able to assess environmental exposures with the same low measurement error as ‘omics’ (in particular genomics) platforms do. Rather, we continue asking individuals about their lifetime exposures through questionnaires, which represent soft data. Yet, selected biomarkers represent excellent tools to measure environmental exposures with higher accuracy. A change in paradigm is needed, moving from a candidate to an agnostic/exploratory exposure analysis. Incorporating epigenomics (i.e. modifications in DNA methylation of CpG islands, histone acetylation, etc.) and metabolomics markers should help in better dissecting the still ‘missing exposome’ for most chronic diseases. Tools for standardized collection across centres and across countries will be needed to this end.

Furthermore, the notion that nothing is static during an individual’s lifespan is becoming more and more important. The changes along the time apply to environmental exposures and to ‘omics’ data. Taking such lifelong modifications into account in epidemiological studies is going to be a very difficult task that will necessitate to closely monitor individuals. Once the data is available, its modelling will represent another challenge.

Following the current concept of epidemiological study design and statistical power requirements, very large sample sizes are needed to explore the underlying biological complexity in a meaningful manner. Being provocative, we could argue that instead of conducting large scale epidemiological studies, epidemiologist should focus on fewer extremely very well characterized and bio-monitored individuals. In any case, the integration of several types of data, from environmental exposures to epigenetics, metabolomics and genomics, requires the development of innovative bioinformatics and data reduction techniques. There is still a long way to go.

The extraordinary development of hypothesis-free (agnostic) approaches should not discourage researchers from conducting targeted candidate gene studies. Both approaches should be viewed as complementary and synergistic. Similarly, although most GWAS have included unrelated people, family-based studies may bring valuable information on transgenerational effects, shared environmental factors and parent-of-origin effects. An example illustrating future challenges in terms of study design can be found in the field of pharmacogenomics that aims at identifying genetic variants involved in drug response in order to improve drug safety and efficacy, thus minimizing side effects. There are large inter-individual variations in the activity of enzymes involved in drug metabolism and transport that are in large part genetically determined. In contrast to the small effect of the identified variants associated with the risk of common complex traits, the effect of...
pharmacogenomic-related variants may be larger and clinically relevant. The recently launched Clarification of Optimal Anticoagulation through Genetics (COAG) double-blind, randomized controlled trial will ascertain whether adapting the dose of warfarin therapy based on genetic variants located within the CYP2C9 and VKORC1 genes may improve patient care as compared with a clinically-guided dosing algorithm. Designing such a trial is particularly challenging because the power to detect a pre-specified between-group difference will depend on the genetic makeup of the participants. The challenge comes from the fact that allele frequencies may vary substantially across ethnic groups. To recommend genetic testing, investigators will need to demonstrate that drug dosing based on genetic information significantly reduces costs and morbidity.3

Focusing on a single disease or on a single trait does not allow understanding the full range of phenotypes associated with many genes, for which pleiotropic effects have been described (i.e. one gene may be involved in both cancer and cardiovascular disease). Hence, an additional challenge for epidemiologists is collecting extensive phenotypic data, not only at a single point in time, but longitudinally, again. The collection of high quality phenotypes and more comprehensive phenomes are therefore of utmost importance and will be key to better account for the underlying biological complexity of human organisms living in selected environmental conditions.4,5 The digitalization of patient’s records and imaging technologies, as well as web-based testing, should allow accumulating and linking massive amounts of information for each person. The availability of entire genomes and phenomes may revolutionize the way we classify diseases. There is little doubt that data-gathering technology has dramatically changed and will continue to largely influence the way epidemiologists conduct research. Making best use of all the available information, without harming study participants (i.e. discrimination by insurance companies or employers, undue access to the data by third parties, etc), will be a challenging task in the years to come.

In conclusion, recent advances in genomics have highlighted the polygenic nature of most common disorders. The effects of these genetic variants also need to be studied taking into account time-dependent environmental and behavioural factors.7 As a consequence, any single genetic variant has little impact in terms of disease risk prediction. Yet, polygenic risk scores in relation to continuous traits (i.e. BMI, blood lipid, blood pressure, etc) should stimulate public health researchers to change paradigms and consider integration of multilayer biological data, dynamic designs, agnostic approaches, as well as using quantitative measures in assessing both exposures and outcomes (i.e. continuum of affectedness). Such quantitative thinking leads to a public health model that focuses on prevention on a continuous scale rather than just treating cases. Looking at multivariate continuous dimensions rather than clinical diagnoses using arbitrary cut-offs represent more powerful approaches to decipher the complex etiological mechanisms leading to human diseases. Large inter-disciplinary teams are needed to properly design studies and collect, store and analyse high-throughput data. Whereas the prices of ‘omics’ data production have dramatically come down, the costs of data storage and analysis are very high and often tend to be underestimated. Unless studies are not well funded, epidemiology will not be able to assume the challenges mentioned above. High-quality and continuously updated education programmes are needed to ensure that researchers and health-care professionals are able to critically appraise research findings in the ‘omics’ fields, including ‘epi-omics’.

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A European view on the future of personalised medicine in the EU

At the European Health Forum Gastein in October 2010, personalized medicine was presented as a new paradigm for health care in Europe. I had the opportunity to participate in this session and to listen to the views of my esteemed co-participants on what can be done at the European level to achieve implementation of personalized medicine approaches and other emerging technologies.

Personalized medicine is becoming an ever more important area for the application of genome-based information and technologies identified under public health genomics. The scope and vision of public health genomics, according to the 2005 Bellagio Conference is ‘the responsible and effective translation of genome-based knowledge and technologies for the benefit of population health’. This concept encompasses both population and individual health. It covers prevention, treatment and care. Genomics is clearly an area of innovative research that seeks to close the
that equity and access are also taken into account. The progress offered by emerging technologies and therapies needs to be analysed by the Commission over the coming years in order to keep the EU regulatory framework up to date. We need to constantly look at better ways to address medical needs and one way to do this is by encouraging the development of innovative technologies.

The concept of personalized medicine is an important driver for innovation. It is clear to all that ‘pharmaceutical innovation’ is a crucial component of this concept. It is of key importance in addressing unmet medical needs within society. The lack of adequate treatment for many diseases requires continuous innovative efforts to find new medicines. This equally entails the engineering of innovative in vitro diagnostic medical devices.

But we need collaboration and co-operation. The Innovative Medicines Initiative (IMI) is an excellent example of how collaboration between industry and the Commission can deliver concrete results. We are determined to take this agenda forward.

Our ambition must be to continue our strong support for fundamental pharmaceutical research in Europe to improve chances of translating research results into successful products on the market.

With regard to the regulatory framework for pharmaceuticals, we have a comprehensive EU legal framework coupled with detailed scientific guidance documents, enabling economic operators to foster public health by bringing safe, efficacious and quality medicines to the market.

The Commission has in place several mechanisms to support innovation. The Internal Market framework provides various incentives for innovation. In addition to the Community Code relating to medicinal products, there is the Regulation on orphan medicinal products. This seeks to encourage research and development of medicines for patients suffering from rare diseases. This has proved to be a great success over the past 10 years.

Another example is the Regulation on Advanced Therapy Medicinal Products, adopted in 2007. This legislation aims to speed up the development of regenerative medicine products and promote industry’s competitiveness, while respecting national prerogatives on ethics. This initiative is also starting to yield results.

The Commission funded, Public Health Genomics European Network (PHGEN) has mapped the foreseeable impacts of the evolving genome-based information and technologies in all areas of public health, health care and health systems and is developing the 1st edition of European guidelines for quality assurance, provision and use of genome-based information and technologies due in 2012. Furthermore, we continue with interest to follow developments in science, product development and public discussions on this subject.

In this context, I should also mention that the European Medicines Agency (EMA), together with its network of expertise in the Member States, is an excellent pool of knowledge. At the Commission, we are working across different departments, from Research to Public Health, to share information.

I am convinced that the area of personalized medicine, and its fascinating emerging technologies such as pharmacogenomics, patient-specific modelling and disease simulators, has enormous potential for our citizens. It will lead to Europeans ageing in better health and receiving better health care when necessary.

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Public health perspective: from personalized medicine to personal health

A gradual shift from a ‘one-size-fits-all’ strategy towards personalized interventions is observed in the whole spectrum of healthcare, including personalized prevention, diagnosis and therapy, and the concept of personal health. This shift is caused by two major drivers. The first one is a general societal trend towards ‘personalization’, where individuals demand services or products that are customized to their needs, possibilities and choices. The second driver is rapid scientific and technological advancements in genome-based science and technologies (which is a term that covers the full breadth of knowledge that is being amassed in all ‘omics fields [1,2]), information, and information and communication technologies (ICT).

The future paradigm in health and healthcare has become increasingly visible in the past 10–15 years and has been commonly defined as ‘personalized medicine’ although the exact definition varies among different stakeholders and opinion leaders. In the ongoing communications, the term personalized medicine comprises two separate and independent approaches. The first approach is based on biomarkers and statistical methods subdividing a heterogeneous group into smaller less heterogeneous groups leading to stratified medicine. The stratification into smaller and smaller subgroups is limited by the statistical power, and may therefore, not incrementally lead to individualization. The other approach is based on ‘omics and other data obtained from the individual in conjunction with computer modeling approaches leading to ‘individualized medicine’.

‘Personalized’ mostly refers to the use of genome-based information and technologies for providing more stratified (and possibly personalized) interventions. Some authors put the emphasis not only on medicine but on healthcare as a whole and prefer the term ‘personalized healthcare’, which is mostly used interchangeably with personalized medicine. However, personalized healthcare is much broader in its scope and covers all interventions in a healthcare system including interventions in the medical, as well as, public health setting [3]. The publication of the initial draft and final version of the Human Genome Project in the early 2000s created high expectations for ‘genome-based’ medicine and personalized medicine. But only with the intervention of the new sequencing technologies termed next-generation sequencing, it was possible to analyze the genomes of individuals in larger numbers. Although it is now evident that genomic information has revolutionized our understanding of (human) biology, its translation in drug discovery and medical practice has not been straightforward. So far ‘genome-based’ personalized medicine has provided limited output that can be translated into practice. This led to questioning whether personalized medicine with genome-based information is a ‘myth’ or reality [4,5]. We now recognize that the last decade was more about understanding the biology of genomes, whereas the coming decade will bring more information for understanding the biology of diseases [6]. Clear examples of advancing the science of medicine and improving the effectiveness of healthcare using genome-based information can be expected to start to flourish in this decade, but will probably become more prominent in the period beyond the year 2020 [6].

In addition to genome-based personalization, there are other drivers that will mark the future trends and opportunities in medicine and healthcare, such as prediction by using early markers of progression from a healthy state to...
disease, prevention by personalized early diagnosis and targeting the specific mechanisms that are determining the disease progression in each individual, and participation of the individual in decision-making and management of the disease. Together, these aspects shape predictive, preventive, personalized and participatory (P4) Medicine [7]. It is of note that developments in imaging and sensor technologies will also play an important role in the near future to individualize medicine and healthcare.

There are several issues and challenges in the journey towards this future paradigm of medicine and healthcare. In this commentary, we are addressing some of them that might be critical on the way from genome-based discoveries to real-life implementation with a public health perspective.

**Interaction among factors that surround the individual**

In the initial comments on personalized medicine, genomic information of individuals was the main focus. This was interpreted commonly by media and some scientists in a way that the genome, which is unique for every individual, would be the ultimate means for individualization. The truth here is both shocking and simple: our genome is not the only factor that makes us unique. As genome science evolves, the old truth that the phenotype is shaped by interaction of our genotype with our environment re-emerges and straightforward interpretation of genotypic variation into personalized medicine is ‘confounded’ by multiple environmental interactions. Often genotypic variations turn out to be only minor contributors to disease etiology. The environmental factors surrounding individuals, such as exposure to pathogens or toxins, socioeconomic factors, physical activity, nutrition and other lifestyle factors are constantly interacting with each other, as well as with the genomes. As science progresses, the importance of understanding these genome–environment interactions is getting more and more important. We are moving towards a new understanding of health and disease, showing that these genome–environment interactions change from day-to-day within an individual. Neither genomics nor the environment is stable. Biological pathways or networks are permanently interacting with environmental networks such as social networks. Thus, a comprehensive model of future healthcare taking into account integrative genomics alongside environmental, social and lifestyle factors will become essential to realize the P4 Medicine as the future paradigm of healthcare systems.

Specific examples of environmental factors are the ‘exposome’ of individuals, representing the combined exposures from all sources that reach the internal chemical environment, and can be measured as metals in toenails [8,9]. Pathogens are also strong external factors that lead to disease. A prominent example of interaction of pathogens and the host genome is human papilloma virus and cervical cancer, whereby a pathogen may cause cervical cancer although ‘cancer’ is a disease traditionally classified as ‘noncommunicable’. Moreover, one of the factors that determines if and when progression to the disease will take place is the host’s genomic background [10]. The future is likely to show us more and more of such examples.

The interaction of genome and lifestyle, as well as other environmental factors, may become more visible by studying epigenomics. Epigenomics may also provide insights to interactions with socioeconomical factors and play a crucial role for public health by bridging social and biomedical sciences [11]. For example, nightshift work, which can be categorized as a ‘lifestyle’ or ‘socioeconomical’ factor, increases the risk of breast cancer [12]. This effect may be mediated by an epigenomic change in circadian rhythm genes and ‘night shift’ may also turn into an inherited risk factor for breast cancer with potential effect for future generations [13].

“The integrative approach should not only be a concept for scientific discoveries, but also a main constituent of personalized medicine approaches in practice.”

**From genomic to systems approaches in personalized health**

The path to evolve from genome-based personalized medicine to personalized medicine that takes all the relevant factors into account is the transition from genomic to systems approaches in personalized health. Systems biology is defined as an integrative, interdisciplinary approach to biological science that is built around the concept of close integration of computational methods, technology development and global measurement and analysis of biological systems [14]. The integrative approach of systems biology has so far focused on the biological determinants of health and integrates various levels of information for discovery of disease causing biological
networks. For example, nutritional systems biology [15] integrates ‘nutrition’, which is classified as a ‘lifestyle factor’, into systems biology studies by taking into account all biological mechanisms and processes that are affected by dietary components on all relevant levels of complexity. Integration of other determinants of health into systems biology approaches may provide further insight to understanding the biology of health and diseases. This approach is supported by the Public Health Genomics European Network (PHGEN), which is currently producing the first edition of “European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies” assisting all EU Member States [European Commission. European best practice guidelines for quality assurance, provision and use of genome-based information and technologies (2012). Policy report in preparation] [16,101].

The integrative approach should not only be a concept for scientific discoveries, but also a main constituent of personalized medicine approaches in practice. In order to manage an individual’s health, disease risks and diseases, we need to involve all available information related to the individual; make a 360-degree assessment of the individual’s health, including personal, health, socioeconomic and lifestyle information, biomarkers and ‘omics information; develop a personalized plan; and follow-up the progress made by the individual [17]. There are published and unpublished models indicating similar integrative approaches, which are conceptually developed [3,18], prepared for implementation or developed as a practice model and implemented as a pilot study [17]. It is likely that more integrative approaches will soon emerge around the globe.

“Personal health drives a fundamental change not just in what is known, but also in how we think of ourselves and the way we are living, thus redefining our society.”

Role of the individual
While various attempts are made to understand and manage health, disease risk and diseases, the perspective and expectations of the individual, who is in the center of all, should also be taken into account. Individuals are taking more and more control of their health because they have better access to health-related information and a higher desire to control their own life and health. It is not uncommon anymore to hear about patients who challenge their healthcare professionals with information they have found on the internet or obtained from their ‘peers’ with the same condition and/or symptoms. Social networking platforms such as PatientsLikeMe [102] enable its members to share condition, treatment and symptom information in order to monitor their health over time and learn from real-world outcomes. Furthermore, recently Sage Bionetworks launched a project called ‘Portable Legal Consent’ being a tool for patients to tell doctors, researchers, companies and other stakeholders in the healthcare system, that they, the patients, own the rights to the data generated from their bodies. Portable Legal Consent states that “what the patient desires is for the data to be shared broadly in the public domain, to serve scientific progress as a whole, regardless of the particular individual or institution that makes the breakthrough” [103].

Individuals should have the lifelong skills to find and assess the relevant and reliable information on the internet, which is also related to the concept of health literacy. In Europe the consortium of the European Health Literacy Project (HLS-EU) [104] defined four dimensions of health literacy. Using this definition health literacy can be used as a catalyst to accelerate the accessibility, understandability, appraisal and application of genome-based information matching the needs within different population groups. In this context, examples such as Google [105] provide a powerful health literacy friendly electronic environment facilitating self-management, simplicity and user-centered applications. Thus, the future patient may turn from a passive consumer of health interventions into a proactive consumer or ‘prosumer’ [19,20].

ICT as facilitating factors
ICT plays a central role in the implementation of personalized medicine in real life at several points. The development of a new, data-rich, individualized medicine is likely to surpass the demands of all other ICT development fields. As data-intensive analysis and computer-intensive modeling technologies become common clinical practice, ICT capacity and organization will become key limiting factors in medicine, resulting in shifts of resources from personnel intensive to ICT intensive application. Data-rich, individualized medicine poses unprecedented challenges for ICT, in hardware, storage and communication.
The combined genomic and phenotypic analysis may become very complex and needs algorithms and mathematical models to provide a clear diagnosis and therapy. A doctor’s computational brainpower is not enough to process all of the different factors surrounding the individual where there are hundreds or maybe even thousands of data to be considered, make current status and risk assessments, and based on these, draw personal plans for management of the individual’s health, risks and diseases. ICT is also essential in optimal coaching and patient empowering, both in complicated therapies (compliance) and in lifestyle coaching for prevention and health optimization. In order to facilitate a healthcare professional’s adoption of personalized medicine, we need strong information and communication platforms integrated into healthcare services to collect and analyze data, assess and interpret it, develop personal plans, follow-up the implementation and provide updates and revisions to the plan. At the same time, this should be a closed circuit that feeds science in identifying new hazards, both environmental and genomics, for disease risk and progression [21].

The IT Future of Medicine (ITFoM) provides such a platform for Europe being one of six pilot projects in the European Future and Emerging Technologies Flagship scheme [106]. It produces computational models of individual persons (‘the virtual twin’), which will follow the person during the whole lifecycle through the healthcare systems enabling healthcare professionals to virtually simulate and optimize treatments. In the end, medical decision-making may turn into in silico decision-making.

**Conclusion**
There are several opportunities and challenges on the way to the future vision of medicine and healthcare. One of the key factors for its realization is aiming for an integrative approach towards an individual’s health, risks and diseases, considering all relevant factors surrounding them, such as genome, stages of life (from preconception to old age), exposure to pathogens, nutrition, toxins, physical activity and other lifestyle factors, social interactions, stress and other socioeconomic factors, and healthcare systems. ICT will be critically important at all phases of this journey, including scientific discovery and translation and application to healthcare practices.

**Future perspective**
Personal health drives a fundamental change not just in what is known, but also in how we think of ourselves and the way we are living, thus redefining our society. The political will is there, but we have to prepare for all the various organizational changes. The real paradigm shift depends on the willingness to restructure policies. For realization of P4 Medicine, there is a clear urgency to prepare healthcare systems and policy makers in time.

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* of interest
** of considerable interest

1 Bellagio group. Genome-based Research and Population Health: Report of an expert workshop held at the Rockefeller Foundation Study and Conference Centre Bellagio, Italy, 14–20 April 2005, Office of Genomics and Disease Prevention, CDC, GA, USA.

** First document defining the framework of ‘public health genomics’ and the term ‘genome-based information’.


* Report laying out the differences among the terms genomic medicine, personalized medicine and personalized healthcare.


** Strategy document of the National Human Genome Research Institute, NIH, USA, for 2011–2020. It gives a very concise outline of what has been achieved in the past and what is expected to be accomplished in the future.


** Defines P4 Medicine using the case of cancer medicine as an example.


* Editorial article on the future perspectives of public health genomics and personalized medicine.


* Conveys key factors for realization of personalized nutrition.


* An integrative preventive model, which utilizes an individual’s health information, lifestyle factors, biomarkers and genotype to prevent and detect chronic and complex diseases early in a targeted way. Having been piloted with 500 individuals, it is a very early example of personalized healthcare being practiced in real life.


** Websites


105 Google. www.google.com


** IT Future of Medicine is a very ambitious project, which aims to harness the vast potential of information and communication technologies to revolutionize human healthcare and targets to ‘lead the way towards truly personalised healthcare’. It is one of the six pilot projects in the European Future and Emerging Technologies Flagships.