Personalized Respiratory Medicine: Exploring the Horizon, Addressing the Issues. Summary of a BRN-AJRCCM Workshop Held in Barcelona on June 12, 2014

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Abstract

Go to:

This Pulmonary Perspective summarizes the content and main conclusions of an international workshop on personalized respiratory medicine coorganized by the Barcelona Respiratory Network (www.brn.cat) and the *AJRCCM* in June 2014. It discusses (*1*) its definition and historical, social, legal, and ethical aspects; (*2*) the view from different disciplines, including basic science, epidemiology, bioinformatics, and network/systems medicine; (*3*) the bottlenecks and opportunities identified by some currently ongoing projects; and (*4*) the implications for the individual, the healthcare system and the pharmaceutical industry. The authors hope that, although it is not a systematic review on the subject, this document can be a useful reference for researchers, clinicians, healthcare managers, policy-makers, and industry parties interested in personalized respiratory medicine.

Because personalized medicine (PM) is a trending topic in biomedical science, it is pertinent to review its scope and applicability to respiratory medicine. We summarize the content and main conclusions of an international workshop on the topic coorganized by the Barcelona Respiratory Network (www.brn.cat) and the *AJRCCM* in June 2014. As such, this manuscript is not a systematic review on the topic but rather a potentially useful reference for researchers, clinicians, healthcare managers, policy makers, and industry parties interested in personalized respiratory medicine.

Definition and Historical and Ethical Aspects

It can be argued that medicine has been personalized for the past 3,000 years, whenever an interaction between a "healer/physician" and an ill person occurred (1). Why then the current interest in PM? The answer likely relates to the development of new approaches to predict (and eventually to effectively intervene) the *individual* risk of developing a disease, its severity, its evolution, and/or its response to treatment, in contrast with traditional approaches that predict these risks for *groups* of patients (Figure 1) (1, 2). Other terms used frequently in this field are defined in Box 1.
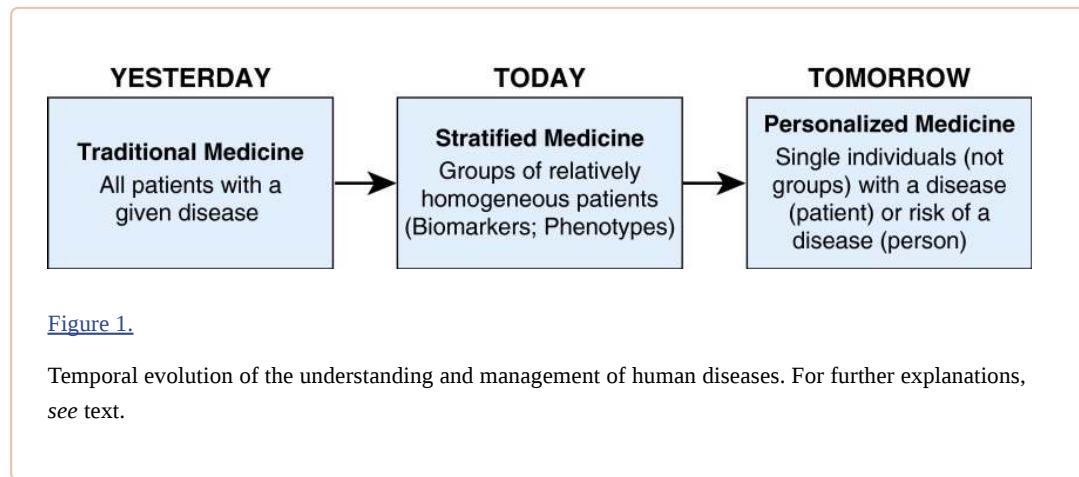

Figure 1.

Temporal evolution of the understanding and management of human diseases. For further explanations, *see* text.

Box 1.

Terminology

The terms "P4 medicine" (Personalized, Predictive, Preventive, and Participatory) (83), "precision medicine" (85), or "individualized medicine" (iMedicine) have often been used interchangeably with personalized medicine (PM).

"Systems biology" is a research strategy that focuses more on the interactions between parts of a biological system than on the components themselves. It seeks to understand and predict the dynamics of a system, and it operates through iterative cycles of quantitative data collection, computational modeling, and experimental validation in model systems (*in silico*, *in vitro*, or *in vivo*) (86–88). "Systems medicine" (also called "network medicine" [7]) is a research strategy that uses a similar approach in humans, both in health and disease (89).

"Stratified medicine" involves the use of statistical and bioinformatic analyses of different biomarkers (molecular, clinical, functional, imaging, and others) to allow clinicians to classify groups of patients (not individuals, like in PM) into more homogeneous groups with similar prognosis and/or treatment needs in a real-life setting; as such, it is not a research strategy but rather is an up-to-date clinical practice.

PM opens great opportunities but also raises significant ethical, legal, economic, and social issues, such as (*1*) there are already companies commercializing predictive genetic information without fully verified analytical and clinical validity (3), (*2*) it is unclear who will have access to and/or own this

information in specific individuals (*4*), (*3*) relevant and current legislation is lacking in most countries to avail and protect the individual (or patient) from the dissemination and potential misuse of predictive information by third parties without the knowledge and approval of the individual, and (*4*) how developing countries will be able to participate in and benefit from PM is unclear.

A Perspective of PM from Different Scientific Disciplines

The path to PM requires (*1*) interdisciplinary cooperation between basic, clinical, and epidemiological research; (*2*) investment in infrastructure and resources, including bioinformatics data handling and systems modeling approaches; and (*3*) decision support systems that allow the effective translation into the clinic of all this new and complex knowledge (5).

The View from Basic Science: Addressing Biological Complexity!

The traditional reductionist approach of biomedical research has produced a vast amount of new knowledge, best exemplified by the sequencing of the human genome in 2001 (6). However, it is now also clear that biology is extremely complex (7). For instance, the recent mapping of the proteome in 2014 (8) and the "resilience projects" to map out why people stay healthy will provide further understanding, and, as shown in Figure 2, the "determinants of a phenotype" include complex epigenetic interactions between multiple spatial and time scales (Figure 3) mediated by nonlinear biological networks that enable, filter, condition, and buffer such complex interplays (6, 9, 10). "Nonlinearity" is the key concept here because it implies that the output of the "system" (e.g., having or not having a disease) is not simply proportional to its "input" (e.g., risk factors) but is modulated in a nonlinear way by different elements of these multilevel networks (Figure 2) (11).
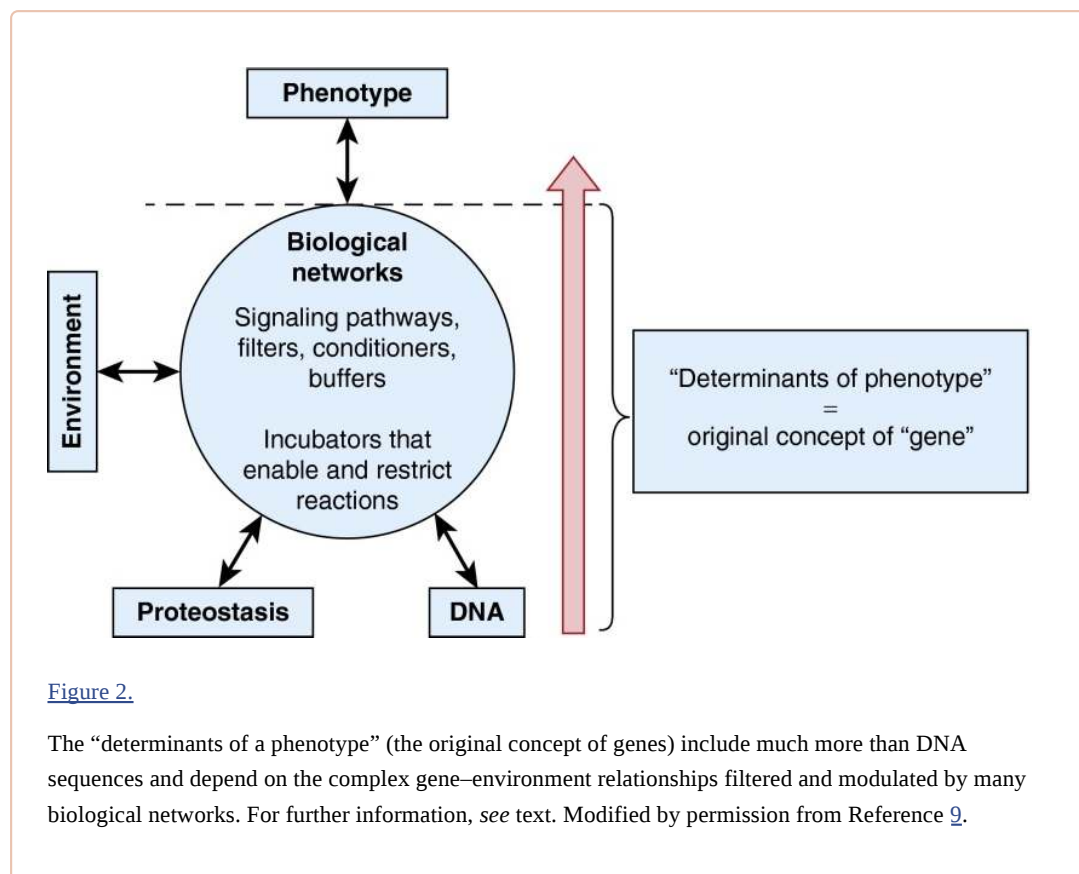
Figure 2.

The "determinants of a phenotype" (the original concept of genes) include much more than DNA sequences and depend on the complex gene–environment relationships filtered and modulated by many biological networks. For further information, *see* text. Modified by permission from Reference 9.
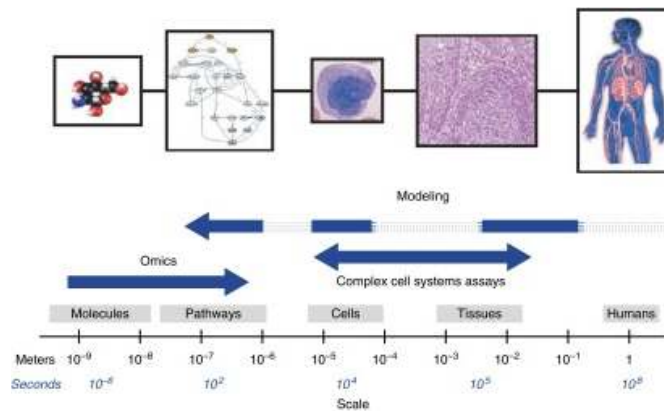
Different levels of complexity (from molecules to networks, cells, organs, and whole body) targeted by different aspects of systems biology and network medicine. The spatial and dynamic scales that apply to each level are also shown. Reprinted by permission from Reference 100.

A network can be represented as "nodes" and "edges" (11). Systems analysis shows that perturbations of these networks may result in distinct functional consequences if they are due to node removal (i.e., complete loss of gene products) and/or edgetic (i.e., interaction [edge]-specific) alterations (12). The complex, nonlinear, dynamic relationships between the parts of the system explain the occurrence of emergent properties, such as health or disease (7, 13). For instance, a mutation can lead to a damaging effect in one tissue and not in another, or two different mutations in the same protein could result in no disease or cause different diseases due to quantitative effects on protein activity, competition for binding, affinity, and relative concentration of binding partners (14). Likewise, exposure early in life to an external or internal environmental stress may have a significant impact on the penetrance of a mutation later in life. Finally, there is an element of randomness (stochastics) that changes dynamically over time (in 20 yr, "you" will be a different "you"). As a result, in biology, the whole is over and above its parts instead of just the sum of them all (14–16). The lack of consideration of these contextual effects and the interactions between different elements and levels of the system likely explain the relatively limited power of massive genome-wide association studies, which show little clinical effect of the majority of associated genetic variants (17–19). The challenge is therefore to integrate multilevel, multitype, dynamic (i.e., different measurements over time in the same individual [20]) information to generate more powerful predictive models (Box 2).

Box 2.

The Challenge from Basic Science: Integration of Different Levels of Biological Complexity

1. Take each type of data for itself (fingerprint) and combine them (using linear relationships or more complex methods) to generate a handprint (90).
2. Start with all raw data in the same scale, consider all potential relationships, and use unbiased methods.

The View from Epidemiology: A Key (but Sometimes Forgotten) Component of PM

Epidemiology can be defined as a population-based approach to health and disease. Starting with epidemiological studies of smoking on respiratory health in the early 1950s (21), modern respiratory epidemiology has largely evolved into a wide range of methods that allow us to understand causal

relationships (at the population level) and to develop prediction models (for risk estimates in groups and individuals). A relevant aspect of this evolution has been the use of biomarkers in molecular epidemiology as a way to incorporate the biological mechanisms as part of the epidemiological causal model. It is not a surprise, therefore, that some epidemiologists embraced genomics with hope. The genome and postgenome respiratory epidemiology has evolved rapidly through genome-wide association studies, the assessment of gene–environment interactions, and the other types of omics ([22], [23]). This has provided new insights and has stimulated research on causal mechanisms and on the use of genetics for screening. However, the exponential increase of molecular and omics studies has increased the amount and complexity of available information without resulting in better strategies for the prevention and treatment of respiratory diseases ([24]–[26]) and has sometimes generated a feeling of being lost in complexity. It is in this context that epidemiology can look to systems biology and PM as an opportunity for more successful integrative strategies. Systems biology has developed a new approach to complexity that includes networks as patterns of interrelationships and the possibility of emergent properties, an approach that could contribute to a better understanding of complex respiratory diseases like asthma. How respiratory epidemiology can contribute to personalized medicine is even more challenging because the traditional risk factor epidemiology paradigm averages the risk of each individual in the population (given their particular attributes) within the overall risk in the population ([27]), whereas personalized medicine requires individual risk estimates, as discussed below. Box 3 presents potential different contributions of epidemiology to PM ([28]).


Box 3.

Contributions of Epidemiology to Personalized Medicine

1. Integration of different levels of biological, social, environmental, and behavioral complexity ([57])
2. Unbiased study of population-based samples
3. Broadening statistical approaches to include bioinformatics analyses
4. Fostering, participating in, and leading multidisciplinary consortia
5. Developing a wide public health/population-based framework for systems medicine (evaluation- and evidence-based)

Bioinformatics: The New Kid on the Block

There are increasingly large amounts of biological and clinically relevant information stored electronically that can be useful to progress to PM ([29]). For instance, there are currently 23 million scientific papers referenced in PubMed, and more than 700,000 are added each year, not to mention additional medical knowledge beyond PubMed, including electronic medical records ([30], [31]). There is, therefore, an opportunity to gain knowledge by overcoming the current fragmentation into "silos" (Figure 4) ([32]). To achieve knowledge integration, a number of strategies and tools can be used that leverage advances in computational, mathematical, and engineering sciences (Box 4) ([32], [33]). The participation and close collaboration of basic and clinical scientists with bioinformaticians and engineers is key for the proper curation and understanding of findings ([33], [34]). Several currently available examples include, among others ([35]–[37]), the identification of novel candidate genes for idiopathic pulmonary fibrosis ([38], [39]), personalized therapies for patients with cystic fibrosis ([40]), and predictive outcome signatures in lung cancer ([41]).
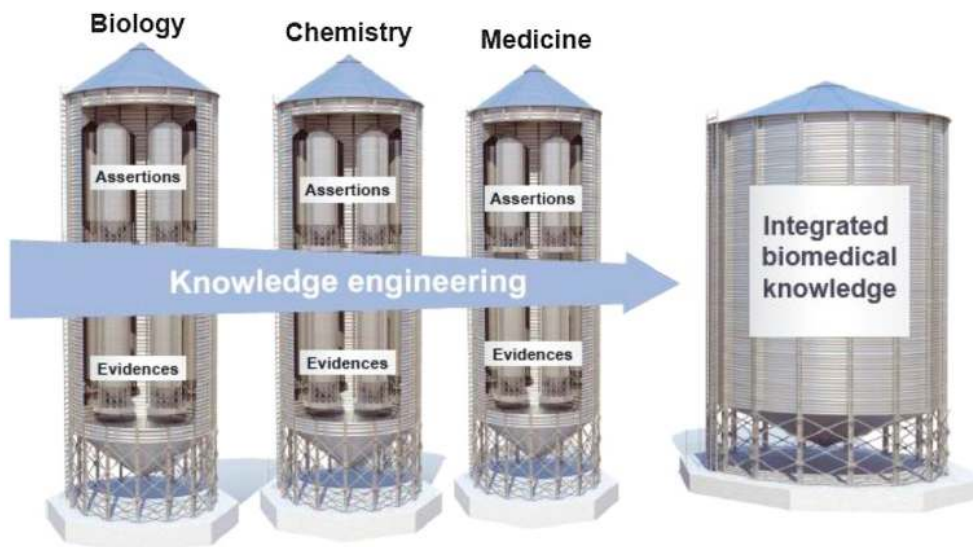
Figure 4.

Knowledge engineering has the potential to overcome inter- and intradiscipline knowledge "silos." Reprinted by permission from Reference 32.

Box 4.

Bioinformatics Strategies and Tools Required to Advance toward Personalized Medicine

1. Seeking (i.e., mining), filtering, and prioritizing of information

2. Annotation and curation

3. Integrative analysis

4. Visualization in formats that are useful and user-friendly

Network/Systems Medicine

Major respiratory diseases, including chronic obstructive pulmonary disease (COPD) (2), asthma (42), and idiopathic pulmonary fibrosis (43), are heterogeneous and complex. In this context, "complex" means that these diseases result from the interplay of several components with nonlinear dynamic interactions, whereas "heterogeneous" indicates that not all of these components are present in all patients at any given time (2). Network medicine (Box 1) is a research strategy to study comprehensively the molecular, cellular, disease, and social networks that underlie human diseases (44), as discussed below (Box 5 shows the key components of network medicine [7]).

Box 5.

Key Components of Network Medicine

1. Holistic rather than reductionist approach
2. Construction of molecular, clinical, and social–environmental networks
3. Consideration of the nonlinear responses of complex systems
4. Assessment of emergent properties from the entire network(s)
5. Investigation of the dynamic responses of networks to various types of perturbations

6. Employment of systems biology methods

Understanding disease pathobiologic complexity and disease subtypes Clinical and unbiased approaches, such as factor analysis or principal component analysis (which identifies disease axes) and cluster analysis (which identifies groups of subjects), can be used to dissect disease heterogeneity (45). Genetic studies may also help us to understand disease heterogeneity and to define disease subtypes (e.g., six genomic regions so far have been associated with COPD [46]). Finally, the use of network analysis allows the creation of molecular (11, 47) and phenotypic (34, 48, 49) networks that could provide new insights into the pathobiology of the disease.

Development of new drugs The reductionist approach to drug discovery has worked well in a number of diseases (e.g., to develop antiretroviral agents for HIV infection) but has not been effective (yet?) in many complex respiratory diseases. Because the latter likely results from multiple genetic, epigenetic, molecular, cellular, tissular, organ, and environmental factors, targeting multiple components of disease pathways may be necessary or even essential (50, 51) (Figure 5). For instance, the sequential use of anticancer drugs enhances cell death by rewiring apoptotic signaling networks (52). Likewise, because oncogenic signaling networks have multiple feedback levels, single protein measurements cannot accurately predict cellular responses to drugs. This is also relevant for complex nonmalignant diseases, such as many chronic respiratory diseases, in which tissue regeneration may be required. In fact, there are respiratory drugs with pharmacogenomic labels, like indacaterol for COPD (53) and ivacaftor for cystic fibrosis (40). Some of the challenges of developing subtype-specific therapy for chronic respiratory diseases (COPD is used here as an example) are shown in Box 6.
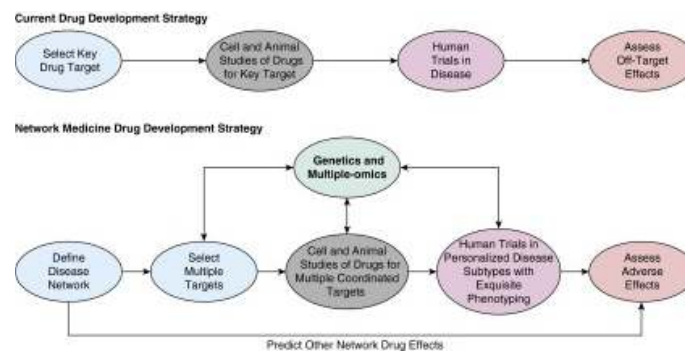

Figure 5.

Current and network medicine approaches to drug development for complex diseases. Reprinted by permission from Reference 50.

Box 6.

Challenges for Developing Subtype-Specific Therapy (Stratified Medicine) for Chronic Obstructive Pulmonary Disease

1. Recognize that complex diseases result from biological network perturbations.

2. Identify subjects who have progressive versus stable disease to target individuals at risk for progression with more intensive or different therapy; patterns of stability may vary between and within biological subtypes.

3. Develop more sensitive and earlier readouts than FEV_1 decline or CT emphysema changes to guide drug development.

4. Acknowledge that some biological mechanisms could be rare, making specific treatment development challenging.

Reclassification of complex diseases When applied within the framework of network medicine, omics technologies have the potential to provide insights into complex disease pathogenesis and to help create reclassifications of disease that more precisely reflect pathogenesis and guide preventive, diagnostic (e.g., imaging), and therapeutic strategies (54–56). Because long lead times are required to develop new drug treatments, we anticipate that the initial clinical benefits of network medicine will be in improved diagnoses based on disease reclassification, followed by renewed disease phenotyping, improved prognostic information based on genomic and proteomic data, longitudinal studies of disease subtypes, and eventually more effective treatments based on tailored therapeutic regimens.

Bottlenecks and Opportunities

There are several biology/systems and medicine/PM research projects currently ongoing in respiratory medicine (57): (*1*) MEDALL (Mechanisms of the Development of Allergy), which aims to generate novel knowledge on the mechanisms of initiation of allergy from early childhood to young adulthood (58–60); (*2*) U-BIOPRED (Unbiased BIOmarkers for the PREDiction of respiratory disease outcome), which hypothesized that biomarker profiles from high-dimensional molecular, physiological, and clinical data integrated by an innovative systems medicine approach should enable the prediction of a clinical course and therapeutic efficacy and identification of novel targets in severe asthma (17, 61); and (*3*) Synergy-COPD (Modeling and Simulation Environment for Systems Medicine), whose working hypothesis is that a systems approach to the understanding of chronic diseases (62) may enhance health outcomes in a cost-effective manner (63, 64). Box 7 outlines potential bottlenecks and opportunities facing these projects.

Box 7.

Bottlenecks and Opportunities of Systems Biomedicine Research Projects to Clinical Practice (Network/Systems Medicine)

1. Incorporate recent guidelines on omics analysis in clinical medicine (91, 92), limiting preliminary discovery with proper external validation.
2. Omics fingerprints have to be integrated with clinical data, requiring a quantitative, multiscale systems approach.
3. Large-scale pooling and harmonization
4. Assessing phenotypes using unbiased approaches
5. Developing appropriate knowledge management infrastructures (93)
6. Integrating pathobiological mechanisms into multilevel, multitissue, and multiscale models

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Implications for the Individual, Healthcare Systems, and the Pharmaceutical Industry

As discussed below, personalized respiratory medicine has implications not only for the individual (who is not necessarily a patient yet) but also for the healthcare system and the pharmaceutical and biotechnology industry.

Individual Risk Stratification: Toward EBM 2.0

Evidence-based medicine (EBM) has affected the practice of medicine because it forced a reevaluation of intuition, unsystematic empirical trial-and-error clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making and, by contrast, has stressed the examination of evidence from randomized clinical trials (RCTs) (65). Yet, by definition, RCTs deal with groups of patients, not with single individuals, which is the essence of PM. EBM 2.0 aims at personalizing

medicine through individual risk stratification and the consideration of personal values and preferences ([66](#)).

The current practice of estimating benefits versus harms in an individual can be arbitrary (e.g., "it may be worth a try"). The decision-making context is often oversimplified because only a single parameter or few parameters are assessed (e.g., through comparing the number needed to treat and the number needed to harm [[67](#)]), and personal informed participation is rare. The latter is particularly relevant in the case of PM, when an individual (not yet a patient) may be offered a preventive treatment with a potentially suboptimal efficacy/safety ratio to reduce the risk (high but not definite) of developing a certain disease. How to deal with the issue of risk-seeking versus risk-averse individuals in this context is unclear. However, to support clinical practice in this scenario, modern methods are emerging that bring together personalized outcome risk assessment (from molecular and clinical characteristics), preventive treatment effects (from RCTs), and personal preferences to estimate the benefit/harm balance for individuals ([68](#)–[71](#)). In any case, it is essential to develop such individual risk-stratified treatment strategies and well-defined translational paths that closely connect basic, clinical, and epidemiological research with evidence synthesis and multidimensional benefit/harm analysis ([Box 8](#)) ([28](#), [66](#)). The goal would be to develop clinical guidelines that support decision-making at the individual level rather than for broader groups of patients, as is the case today. Besides individual risk prediction, it can also be envisioned that individuals who nevertheless develop disease will be treated based on their genomic profile ([41](#)).

Box 8.

Pathways for Individual Risk-stratified Assessment ([66](#))

1. Precise identification of risk factors
2. Research on treatment effectiveness and risk prediction ([94](#), [95](#)) (i.e., combination of biomarkers and clinical information in the prediction of outcomes [[96](#), [97](#)])
3. Multidimensional assessment of benefits and harms to develop risk-stratified prevention and treatment strategies

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Implications for the Healthcare System(s)

Healthcare value Whether or not PM will increase healthcare value for the individual and for large populations is of paramount importance ([Box 9](#)) ([72](#)). Yet, depending on the stakeholder, "value" may be defined very differently. It has been suggested ([73](#)) that there are core elements of value (i.e., elements relating to patient health improvement) and wider elements of value (i.e., elements relating to other benefits for the patient, and to benefits for caregivers, the health and social care systems, and society more widely). The cost of this value is always a concern, although it is likely to vary in different healthcare systems. Development of risk-sharing approaches between pharmaceutical companies and healthcare-providing institutions has to be considered to provide equitable healthcare ([74](#)).

Box 9.

Healthcare Value (Outcomes/Cost) of Personalized Medicine

Outcomes

- Health gain per person
- Number of persons who might benefit from PM
- Access to the benefits of PM

Costs

- Healthcare system sustainability ([71](#))

a. PM may result in increased costs and represent health gains to some but be denied to others ("me" vs. "we" medicine) ([98]).
b. Better prediction and prevention may reduce costs in the long term, but transitional costs will be likely high.
c. Comparative effectiveness can help to determine the effects of PM on the population ([99]).
d. Cost increases do not translate directly in better healthcare quality ([100]).

Clinical practice variability PM may increase clinical practice variability, thereby increasing costs and harms ([1], [75]). Generating the required scientific evidence for personalized treatments will be challenging ([28]). One alternative is the analysis of big databases to identify subgroups of the population who can benefit more (or less) from PM ([31], [76]).

Healthcare system organization PM involves not only the adoption of novel technologies; it also proposes a radically different view of providing healthcare. For instance, disease classification is likely to change ([54], [57]), and, as a result, healthcare organization will have to change ([77], [78]). Likewise, different potential users of PM include patients (i.e., individuals with a disease), relatives of patients (who may potentially have a higher risk of developing the disease), and/or healthy individuals interested in knowing their risk and reducing it. The logistical and financial implications of considering these three potential types of users will have to be addressed. As a result, (*1*) new or redesigned tools may be needed (what will the future hospital/primary care practice look like?), (*2*) professional profiles and roles (specialists, primary care providers, other healthcare providers, etc.) will have to be revisited, (*3*) it is unclear whether healthcare services have enough resources to educate and pay PM-educated staff, and (*4*) information and communication technologies and (wearable) sensors may play a key role. Finally, it is known that life expectancy varies significantly with zip code, emphasizing the likely importance of socio-economic and environmental factors, although zip codes could also track ethnic and therefore genetic differences and would hence need to be handled while respecting privacy ([79]).

An Industry Perspective: Small Is Beautiful?

Introducing PM will be of interest and a challenge for the current business model of the pharmaceutical industry. In fact, it has progressively moved from broad solutions for prevalent diseases to more focused approaches in diseases with major unmet needs and lifelong suffering. Arguably, PM can mark the end of the drug blockbuster era, in which one medication was used for one or more diseases, and the beginning of more "tailored" approaches. However, this could initially drive costs up because it would require the development of drugs for new targets ([Figure 5]) and would probably decrease the market size for a specific medication. Pharmaceutical companies might be reluctant to invest in medications with decreased markets and returns on investment. The question is therefore whether or not these small indications (i.e., orphan diseases) can compensate for financial losses. Yet, the fact that many age-related chronic diseases, the incidence of which is increasing in parallel with life expectancy ([80]), share similar molecular mechanisms ([34], [49]) may reconcile "market size" with a "personalized approach" through the identification of treatable clinical characteristics in these patients with multimorbidities ([2], [81]).

Summary and Proposals for Future Development

Systems biomedicine has the potential to transform biomedical research and clinical practice from a reactive to a proactive practice of medicine ([20], [82]). This transition requires a synergistic integration of basic, clinical, and epidemiological approaches using computational modeling and knowledge management sharing ([83]) ([Box 10]). As illustrated in [Figure 6], PM can be then envisaged as the convergence of three domains: excellence in clinical science and provision of care, omics and/or imaging biomarkers, and network analysis coupled with clinical decision support systems. On the other hand, the active participation of all stakeholders, including researchers, clinicians, other health professionals, industry, regulatory and funding bodies, individual patients, patient organizations, and the

public in general, is necessary to address the associated ethical, legal, and social issues. Eventually, this may result in a more cost-effective, efficient, and sustainable integrated healthcare system. There are already examples of individuals who have managed to anticipate the occurrence of disease and take preventive measures through a regular assessment of their own exposome (which includes their environmental and occupational exposures, nutrition, sleep, exercise, and stress), clinicome (i.e., their biological and clinical features), and integrome (integrated metabolomic, proteomic, transcriptomic, epigenomic, genetic, and genomic features) (84). At this stage, however, it is essential to follow the recent recommendations on the validation and implementation of complex biological information in clinical medicine (3, 4).
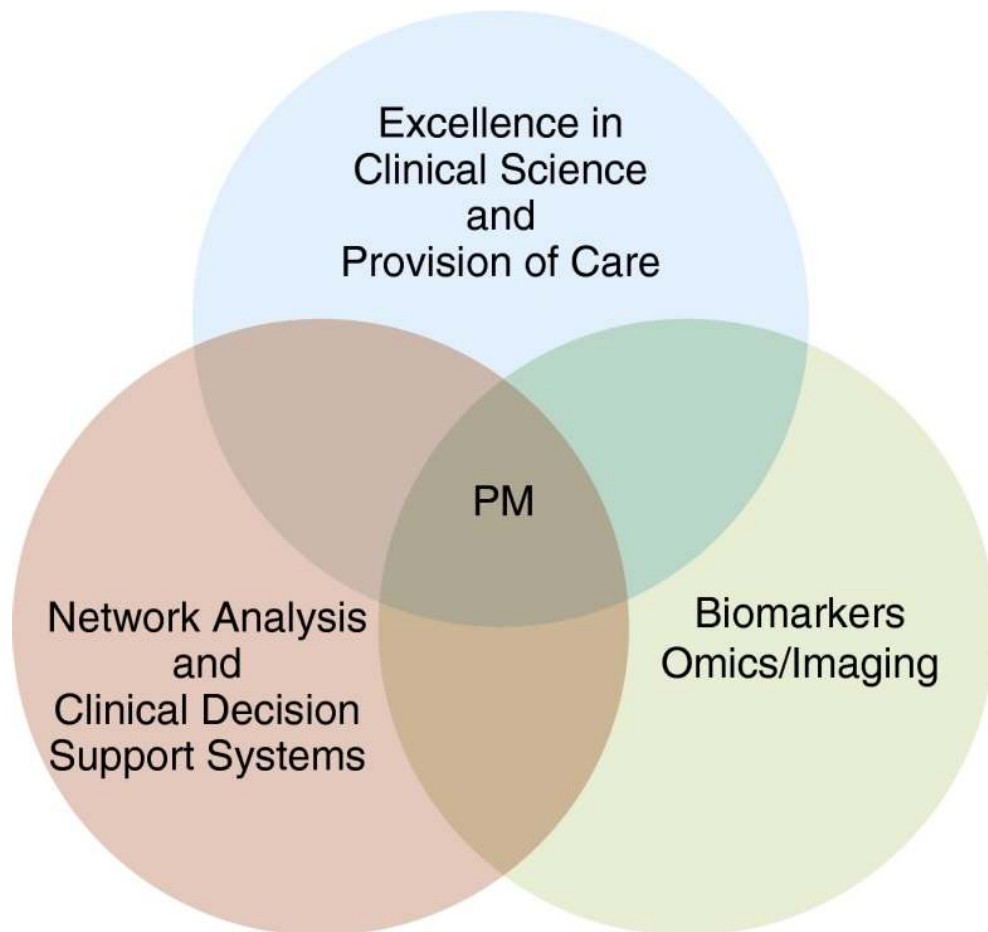
Figure 6.

Personalized medicine as the convergence of three domains. For further explanations, *see* text. PM = personalized medicine.

Box 10.

Key Take-Home Messages

1.To progress to personalized medicine, research is needed and requires the following:

  a. Consideration of key concepts, such as biological complexity (networks), multilevel data integration, external data validation, population implications, and healthcare redesign

  b. Study, from this integrated and unbiased perspective, of the effects of interventions (i.e.,

perturbations of the system in the same individual)

2. In the meantime, stratified medicine using appropriately validated biomarkers appears ready for clinical use (81).

Acknowledgment

Go to:

Go to:

Footnotes

Go to:

References

Go to:

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