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# Future of Medicine: Models in Predictive Diagnostics and Personalized Medicine

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**Abstract** Molecular medicine is undergoing fundamental changes driving the whole area towards a revolution in modern medicine. The breakthrough was generated the fast-developing technologies in molecular biology since the first draft sequence of the human genome was published. The technological advances enabled the analysis of biological samples from cells and organs to whole organisms in a depth that was not possible before. These technologies are increasingly implemented in the medical and health care system to study diseases and refine diagnostics. As a consequence, the understanding of diseases and the health status of an individual patient is now based on an enormous amount of data that can only be interpreted in the context of the body as a whole. Systems biology as a new field in the life sciences develops new approaches for data integration and interpretation. Systems medicine as a specialized aspect of systems biology combines in an interdisciplinary approach all expertise necessary to decipher the human body in all its complexity. This created new challenges in the area of information and communication technologies to provide the infrastructure and technology needed to cope with the data flood that will accompany the next generation of medicine. The new initiative 'IT Future of Medicine' aims at driving this development even further and integrates not only molecular data (especially genomic information), but also anatomical, physiological, environmental, and lifestyle data in a predictive model approach—the 'virtual patient'—that will allow the clinician or the general practitioner to predict and anticipate the optimal treatment for the individual patient. The application of the virtual patient model will allow truly personalized medicine.

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## Contents



## 1 Introduction

The emergence of modern technologies in molecular biology has triggered a paradigm shift in the life sciences. The major breakthrough in this field has been the sequencing of the human genome. In a concerted worldwide effort the first draft of the human genome was published in 2001 [1, 2]. The development process of the sequencing technology and gathering of genomic data lasted over 10 years at a cost of 3 billion USD. Since then genome research has been in a phase of rapid development. The modern high-throughput technologies in the 'omics' field for high-throughput analyses of genomes, transcriptomes, proteomes, or other aspects of biological information are now more powerful and efficient and are used to unravel the inherent complexity of living systems. These technologies allow an analytical depth that was not predictable 10 years ago. With this huge spectrum of analytical tools and the increasing throughput, the amount of data produced from biological samples increased tremendously with the effect that new ways had to be implemented to handle, analyse, evaluate, and interpret molecular biology data. Bioinformatics as a new scientific discipline has been established to facilitate data handling and support with tools and methods. As the amount, complexity, and heterogeneity of the data increase it has become a new challenge to integrate the information and generate an understanding of the whole biological system. Systems biology as the next wave in molecular biology addresses these issues and generates computational and mathematical tools to elucidate the functional and regulatory networks [3] of complex biological systems. Today, modeling

approaches are employed to understand fundamental principles in biology and allow predictions about the functioning of, for example, the human body. These novel approaches in biology create a demand for software solutions and computational power that is unprecedented and will become a new driver for innovation in the information and communication technologies [4].

The transfer of these innovative technologies from molecular biology to the medical field caused a paradigm shift and opened the route for a new medicine. With the first draft of the human genome and the subsequent technological development the tools are now available to create a fundamental understanding of diseases in light of this molecular information. Also the entire field of human diagnostics is changing according to the tools that are available today [5]. This newly available spectrum of diagnostic tools exceeds by far what was possible only a few years ago. Recent advances in the 'omics' technologies drive the development even further towards whole genome, whole proteome, or whole metabolome analysis of a given cell, tissue, organ, or even the whole body [6]. Cutting-edge technology drives the development of the instruments towards an increase in speed and precision at a higher throughput of samples that can be analysed at the same time. To bring these cutting edge technologies to the bedside and into clinical practice still needs further development and investment for the analytical machinery to implement easy-to-use molecular diagnostics at a reasonable price per patient sample. The sequencing technologies again take the lead in this; very recently two market leaders in sequencing technology announced the launching of a new product that is able to analyse a human genome within 1 day at a price of 1,000 USD. To produce the sequence of an individual human for 1,000 USD was the dream of the scientific community, and today, only 10 years later, we are for the first time close to the point where it will be possible to generate the genomic sequence of every patient. The availability of this technique will finally allow us to establish the basis for truly personalized medicine [7].

Personalized medicine can be provided as novel tools for molecular diagnostics become increasingly available at an affordable price. With appropriate diagnostics the clinician or general practitioner can tailor a medical treatment or a prevention strategy to an individual patient according to the responding markers on the gene, protein, or metabolite level. Personalized medicine can be considered as a paradigm shift transforming treatment-centered medicine to patient-centered disease management [8]. The 'omics' technologies, especially the sequencing of the individual human genome, will be of primary importance as they offer a comprehensive set of data about each single patient to the clinician. Stratified medicine will be replaced by decisions on therapy and medical treatment on the basis of the individual molecular make-up of patients [9].

From pharmacogenomic studies it became obvious that the common drug blockbuster strategy ('one drug fits all') must be revised according to individual responses. Observations with treated cancer patients indicate that only 25 % of the patients respond positively to the applied drugs; for most other cancer patients a treatment will only generate severe side-effects without leverage for the disease itself [10].

The new model-based approaches in human life science emerging out of the systems biology field are so promising that they are expected to induce the next paradigm shift in modern medicine towards individual-centered health care. Based on molecular methods, systems medicine will break boundaries deciphering the complex mechanisms of diseases, accelerate the discovery of new treatments, and support the evaluation of clinical trials. But systems medicine can also be used to design new molecular diagnostic tools [11–13].

## 2 Molecular Diagnostics as a Driver for Systems Medicine

As life can be regarded similar to a computational process, a biological system computes the phenotype out of the genomic information given a specific environment [14]. Following this paradigm the analysis of the molecular basis is one of the major cornerstones in modern medicine.

The joint effort of sequencing the first human genome had a huge impact on molecular biology and transformed the whole field. Following the central dogma of biology, the biological information stored in the DNA is translated via the RNA into the building of proteins [15, 16]; the metabolites that are found in a given organ, tissue, or cell are determined by the presence and activity of proteins in the given context. Technology development for deciphering biological information has now reached a level that enables the access and measurement of components on all levels and even beyond striving to analyse the complete set of molecules in organelles, cells, whole pathways, or even organs to get a comprehensive view of a biological system. The 'omics' technologies also comprise methods to detect protein–protein interaction, protein glycosylation, or the phosphorylation status of a given protein [17–20]. The development of the 'omics' technologies aims at precision, throughput, parallelization of processes, speed, miniaturization, as well as reducing the amount of sample needed for the analysis, but also reduction in costs for the machines and the price per sample [21].

After a decade of research following the publication of the first draft of the human genome the next elementary milestone in DNA sequencing was reached in early 2012 when technology developers published that the magical threshold had been reached to allow the sequencing of a human genome within one day at a price of 1,000 USD. This 'third generation' sequencing technology opens the gate for implementation of whole genome sequencing for routine molecular diagnostics in clinical application [22]. Further development of this breakthrough technology will allow, for example, the detection of single molecules omitting the amplification step for the libraries; real-time detection will speed up the analytical process beyond the recent timeframe giving rise to possibilities such as online sequencing during surgery, detection of structural variation, mutations and genetic variability, modifications, epigenetics, and transcription factor analysis. Transcriptomics reflects the current status in a given tissue or organ of a patient, and it employs the same technological basis and is additionally striving for sample reduction towards

single-cell and single-molecule analysis with possible transcriptional modifications. Of great importance will be the instant comparison of tissues or organs also in a time-dependent manner. Therefore, simultaneous transcriptome analysis of different samples in real-time will be a future challenge. Real-time PCR as an example has been a powerful technology to meet these demands, but has not yet been introduced in routine clinical bedside diagnostics. The limiting factor for the roll-out of third generation sequencing is the bioinformatics, that is, the mathematical analysis and computational basis behind it. Computer hardware and software solutions are not yet available to enable genome sequencing, for example, instantly at a patient's bedside.

Also the sector of protein analysis is developing fast towards whole proteome detection in cell tissues and organs, as well as the subsequent modifications and interactions. The use of mass spectrometry and NMR for protein analysis have been a major breakthrough, and mass spectrometry has developed now to a leading technology in the analysis of proteins and other biological molecules. These technologies are advancing fast, and it will soon become routine in clinical applications to employ mass spectrometry more frequently for diagnostic purposes. Similar to nucleic acid analysis, further technological breakthroughs are needed in the analysis of whole proteomes in complex samples, or single cells, simultaneously detecting modifications and interactions, and also taking time dependency into consideration. Also methods to analyse protein kinetics in a high-throughput approach are still needed for in-depth understanding of the complex system of cells. Awareness of metabolites as indicators for metabolic activity and energy status in a cell, tissue, or organ has increased over the last decade, and mass spectrometry was again a major technology allowing a much more comprehensive analysis than it was possible before [23]. Although the dream to get a full metabolome analysed in one analytical step cannot be fulfilled with today's methods, but precision and throughput are advancing tremendously, and have now reached a point where transfer of this technology to the bedside as one important molecular diagnostic tool seems to be approaching fast. Efforts to bring protein and metabolite analysis into clinical practice are increasing because these types of biological molecules will reflect the physiological status of a patient in contrast to the genomic information that represents just the 'blue print' of a body.

Microarray technology followed sequencing technology and is a powerful tool for a highly parallelized analysis of a broad spectrum of biological molecules, from nucleic acids via proteins down to metabolites. The most recent advances have been achieved in the employment of array technology for glycomics, the detection of carbohydrates and oligosaccharides in a given tissue or cell as important biomarkers. In the future, array technology will also be one of the major platforms that allow the transfer of molecular assays to clinical practice as 'lab-on-a-chip'. Small and integrative handheld devices such as the ivD platform [24] are an interesting target for engineering to provide cheap and fast diagnostics close to the patient and nearly real-time with a minimum of sample needed for each analysis.

As the future of medicine is shifting from a reactive to a more pro-active and therefore preventive medicine, information about lifestyle and environment will

become increasingly important. In this respect imaging and sensor technology develop into very important life science technologies as they allow monitoring of patients over time. A new spectrum of non-invasive diagnostic tools will emerge from this fast-expanding field. These new approaches advance analytics to the whole-body level. Through new and fast computing systems, the imaging and sensing techniques enable an immediate interpretation of the body and its parts, as well as its biological functions. The combination of molecular data with the imaging and sensing data generate an interior vision with a resolution of the information in space and time. At the moment these techniques are advancing rapidly in speed, precision, and application range, but it is still an engineering, information and communication technologies (ICT) challenge to develop and adapt these techniques for real-time data collection, transfer, and processing [25–27]. In addition, appropriate interfaces among the patient, data, and health care professionals are needed to produce the appropriate information output. These methods will give rise to the hope that in the near future more sophisticated non-invasive diagnostic tools will be available, with the possibility of integration of monitoring the health status and environmental aspects. As technologies advance, other sample sources in addition to blood and biopsy become accessible to provide the necessary information via non-invasive diagnostic tools. In the future, urine, blood, saliva, perspiration, and breath can also be analysed via portable devices that do not require high-tech machinery such as fluorescence microscopy, surface plasmon resonance, or colorimetry. The new devices will enable the monitoring of body fluids or breath at the bedside and as point-of-care (PoC) tools in the general practitioner's office or even at home. Connection of the devices to personal health records is a necessary requirement to integrate the recordings directly and in real-time with existing information and allow the general practitioner a faster evaluation of the results.

The combined use of monitoring systems and enhanced data analysis will be necessary to further advance in vitro diagnostics systems to provide precise and complex analysis and follow-up. The in vivo systems address specific needs of continuous monitoring *via* sensors; they help patients with chronic diseases or senior citizens to live an autonomous life. This type of technology supporting the use of remote systems and mobile computing technology also opens the perspective for better health care in remote areas, for poorer regions, or developing countries where citizens have only limited access to health care. The basis for the implementation of these technologies of ambient assisted living require a central data repository including a personal health record and advancements in hardware and software. With the approach of these technological opportunities legal and ethical frameworks have to be discussed concerning the accessibility and use of the data for the practitioner or other representatives of the health care system.

Immunohistochemistry and fluorescence in situ hybridization are techniques with many variants that have already arrived in clinical practice to localize proteins and nucleic acids in cells and tissues and monitor their distribution. Remaining challenges are the automation of sample preparation, resolution beyond subcellular levels, and the automation of image analysis with high precision and

fast data output. Technologies to analyse features such as detection of mutant genes and transcripts, interacting sets of molecules including complexes of nucleic acids and proteins, as well as variants introduced by chemical modifications of specific nucleic acids or proteins also remain to be developed. Today positron-emission tomography (PET) or PET-MR images already provide the possibility for a quantitative analysis of the localisation of certain active substances in the body. The new integrated PET-MR scanners allow the integration of complex, multi-parametrical, multi-resolution data for 3D reconstructions. The new developments in detection techniques and algorithms will improve both resolution and sensitivity by an order of magnitude or more. X-ray tomography provides volumetric information about the body or a particular organ. When used in conjunction with the injection of a contrast agent and with an appropriate data analysis, it enables, for example, efficient cardiovascular, pulmonary, and tumor imaging [28–30].

An issue that is gaining increasing importance is the multitude of micro-organisms interacting with the human body. New publications [31, 32] show that the metabiome—the microbes living in our intestines—has much more influence on human health than expected. In a few years time we will have access to knowledge regarding how the microbiome interacts with the human body and triggers or influences health status or certain diseases. The study of the microbiome (the identification of the specific micro-organisms and their composition in the intestines) was very demanding in the past because these microbes prefer anaerobic conditions, and it was very difficult if not impossible to cultivate the specific intestinal microbes in the lab for characterization. The fast and cheap next generation sequencing techniques now open up the possibility to study these microbiomes via metagenomics approaches to characterize the composition of the population in a given environment and with an appropriate time resolution. To transfer metagenomic approaches into clinical practice new approaches in automated data assembly and annotation are needed.

One essential prerequisite to implement personalized medicine *via* a patient model is the use of electronic health records (EHR) of patients. Today, in most European countries we face the situation that the patient data are distributed and fragmented, and most of this information is only available on paper. Finland, Sweden, and Scotland as well as regions such as northern Italy have already implemented EHR for their citizens, and more countries will follow. The EHR will be the information core where all the data from a patient is collected and will constitute the interface between patient and health professionals. In particular, the monitoring of risk patients or patients with chronic diseases via sensors and imaging needs a central repository connected to an alert system and to to clinicians. With higher mobility of citizens, EHRs are necessary to ensure patient data can be accessed and updated independently from various locations and times. Given this perspective of future personalized medicine it is important that platforms implemented in different countries work according to standards and allow interoperability between systems. The consent of the citizens in a society on legal and ethical issues connected to an EHR are of crucial importance for the set-up of EHRs, and one of the main questions will be related to the safe storage of the data

and who has access to those data. The legal and ethical framework might differ substantially between countries, therefore initiatives such as the European Union–United States eHealth initiative are very important to start a discourse about the set-up of new systems between countries at the earliest possible stage to facilitate the mobility of citizens (http://ec.europa.eu/digital-agenda/en/about-health).

All these technologies contribute to the generation of highly detailed information about an individual's genetic make-up and physiological status and allow unprecedented insight into the functioning of an individual as a whole [33].

For all these tools enabling molecular diagnostics it will be highly important to define generally accepted standards and protocols to eliminate errors and false responses of the systems. The standardization of all upstream and downstream processes in molecular diagnostics gain highest priority when the data are integrated in the EHR and the virtual patient model to support decision making in the clinical routine. Sample preparation, measurements, data generation, data handling and processing, and mathematical analysis must follow the standards strictly to avoid false responses or predictions based on the model [34–36].

## 3 Systems Medicine: A Paradigm Shift in Personalized Medicine

Systems biology is a novel approach to decipher biological complexity on a systems level. In systems biology, methodologies and tools for mathematical analysis, integration, and interpretation of biological data as well as simulation and visualization methods are employed to build mathematical models of biological processes such as cellular interaction networks [37–40]. The present analytical tools need enlargement to address more complex questions and the integration of aspects not yet considered to be relevant, including environmental conditions and lifestyle data [41].

Mathematical models support the integration and interpretation of increasingly large datasets and combine these with existing knowledge to allow the interpretation of the data. Model approaches have been used widely for pattern recognition, data mining, and network analysis of complex and heterogenous molecular data. The novel approach of systems medicine using a virtual patient model will drive this approach further to reach the level of simulation and subsequent prediction of possible scenarios that cannot be measured directly.

Systems biology represents a complement to the current 'reductionistic' way that science is performed and how the results are transferred to medicine [41]. The systems approach includes the dynamics and nonlinear behavior of networks in biological systems. One prerequisite is knowledge about all the components that are determining and influencing the behavior of a biological system, how they interact, and their resolution and behavior in space and time. Biological systems use mechanisms to achieve robustness and stability while being flexible and

dynamic: These are feedback control, structural stability, redundancy, modularity, and adaptation [42–44]. Because biological systems are multiparametric, complex, and dynamic it can easily be recognized that complex diseases such as cancer or asthma are not monocausal. Diagnosis as well as treatment and prevention decisions must be based on this nature of biological systems and the individuality of patients, demanding tools to support health professionals for optimal use of the knowledge [41].

Modeling approaches help us understand the function and behavior of these highly complex biological systems, and also support predictions for parameters or situations that are not possible to measure and analyse with current methods. Therefore, modeling approaches are also recognized as powerful tools in future medicine to integrate the available data of a patient and support health professionals in their decision making. The translation of these novel approaches into clinical application will allow a general practitioner or a clinician to identify the optimal medical therapy or prevention treatment for each person based on the individual data that are available.

## 4 The 'IT Future of Medicine' Approach

The international research consortium 'Information and Communication Technology for the Future of Medicine' (ITFoM) anticipates the medicine of the future and is based on molecular, physiological, and anatomical data from all individual patients. The aim of the ITFoM project is the creation of the 'virtual patient' model integrating all different layers of genomic, physiological, and other relevant information to support health professionals in their decision-making process for therapy and prevention strategies for each individual patient.

ITFoM (www.itfom.eu) is a flagship pilot project developing a research programme to achieve truly individualized medicine in 2025. Initiated by a call from the European Future and Emerging Technologies programme, the ITFoM pilot connects the experts in Europe and worldwide to address this challenge and enable data-driven personalized medicine in the future [4, 9, 45].

Systems biology offers the methodologies and tools to analyse, integrate, and interpret biological data, providing mathematical concepts, and models, of biological processes which are then subjected to computational simulations. The ITFoM project will establish the 'virtual patient' system allowing for integration of all relevant data not only to improve and facilitate personalized medicine, but also enabling the prediction of the consequences of lifestyle choices and medical interventions on a tailored case-by-case basis.

To implement this vision and see the use of 'virtual patients' become part of standard clinical practice, substantial advances must be made in underpinning hardware and software infrastructures, computational paradigms, and human–computer interfaces, as well as in the instrumentation and automation of techniques required to gather all relevant information useful for the model approach.

ITFoM is a consortium of more than 160 academic institutions and industrial partners with unparalleled expertise in ICT, life sciences, public health, and medicine. This consortium will address for the first time the ICT implications of worldwide individualized patient care in combination with genomics and medical requirements on a large scale. This joint effort will contribute to a revolution in the health care system with enormous benefits for prevention, diagnosis, and therapy. It is expected that this model-based approach will also lead to increased efficiency in patient treatment by individualizing combinations of a limited number of drugs and reducing side effects of treatments. On a long-term perspective, the model-based approach of integrating the patient's genome data and other information on diseases, lifestyle, and environment could develop into an efficient system for prevention, and avoiding treatment, thereby playing an important role in concepts to reduce health care costs.

The resulting innovations emerging from the joint effort in ITFoM will answer to the European Digital Agenda and major health and societal challenges by building consistent value chains such as drug development, diagnostics and prevention, health devices, and PoC diagnostics; intelligent hardware and software solutions together with robust and secure data pipelines support the flow of the circulating medical data.

ITFoM aims at creating the new ICT that is necessary to enable models of human biochemical pathways, cells, tissues, diseases, and ultimately of the human as a whole.

## 5 Modeling Approaches for the Virtual Patient

Modeling approaches have been developed for all areas in the life sciences; we find anatomical, physiological, and molecular models. For an appropriate 'virtual patient' the integration of all information and models is a central challenge.

### *5.1 Anatomical Models*

Imaging methods are the core to build anatomical models. Imaging technology and computer hardware and software recently developed very quickly in this field; for example, magnetic resonance imaging (MRI) and positron-emission tomography (PET) offer a whole spectrum of technologies increased by the possibility of combined approaches [46]. Other innovative approaches such as ultrasound and electromagnetic imaging or (nano)sensors increase the number of opportunities for high-resolution imaging and are efficient and inexpensive alternatives for existing technology. Anatomical models consider cells, tissues, organs, or even the whole human body. Some models are already used in clinical practice; they are used as support in surgery for careful planning and execution as in cancer or heart surgery

[47]. An example recently published is the PREDIBIRTH model software that uses MRI image analysis to predict if a mother might face difficulties during the birth process. The MRI images of the mother's pelvis and the fetus are integrated and analysed in a 3D model providing different scenarios of the expected birth process. These predictions or scenarios will help the clinician to prepare optimally for the birth process and support decisions in critical situations [48].

## *5.2 Physiological Models*

Physiological models study the parts and functional behavior of the human body using physical and biological knowledge of the underlying processes. Physiological models are based on metabolic information and integrate population data that have clinical relevance [49]. Physiological models study the dynamic processes and the functional behavior of the physiological state of a tissue, an organ, or even an organism. Information about the structure and composition of the object of interest is relevant for the physiological models, but also the nature and functioning of the relevant elements, as well as growth processes. Knowledge of the physical parameters of the system including forces and electrical charges and how they are transmitted are of crucial importance for the models. Also thermal energy and its influence on the system can be studied with physiological models. A prominent example is the Virtual Liver Network, a scientific programme across Germany that is financed by the Federal German Ministry of Education and Research. A predecessor programme—HepatoSys—started in 2004 to quantitatively study the liver as one of the major organs in the human body and elucidate the cellular processes underlying detoxification, endocytosis, iron regulation, and regeneration in mammalian hepatocytes (www.hepatosys.de). The Virtual Liver Network (www.virtual-liver.de) followed this approach as a multidisciplinary research programme aiming at the development of a whole-organ model of the human liver and describing the physiological functions under normal and pathological conditions [49, 50].

The Virtual Physiological Human is a European scale initiative developing patient-specific computer models for personalized and predictive health care. Computational tools are the core that enable modeling and simulation of human physiology in healthy and disease-related physiological processes (www.vph-noe.eu). Projects under the VHP umbrella address diseases of the heart, brain, and intestines, but also develop infrastructure for data generation and ICT, and work on the enabling of data integration and modeling. An issue to further advance physiological models is information about how the different parts interact, such as cell–tissue interaction or interaction of different tissues in the human body. The integration of molecular data into these models will allow comprehensive understanding of the mechanisms and the pathophysiology of diseases.

## 5.3 Molecular Models

Many diseases have molecular causes. Therefore knowledge about the genetic make-up of the human body, the molecular components on all levels along the line of the flow of biological information, as well as their behavior and interrelations, need to be integrated in consistent approaches to understand the underlying mechanisms of diseases. As only a limited number of diseases are monocausal, the challenge now is the understanding of the high number of multifactorial diseases.

Molecular models address individual pathways including information from different layers of biological information such as metabolic and signal transduction pathways and cell-cycle regulation among others. With the new technologies already available for research purposes it is expected that in the near future these technologies will also enter clinical practice and will be increasingly used for patient health care. The genome is the basis, but depth and complexity will increase tremendously with integration of new data from transcriptomics, proteomics, metabolomics, and the other 'omics' analyses. Still there is a lack of knowledge about how these components in the system interact and depend on each other and how control and regulation mechanisms achieve stability and robustness of the system. This still existing lack of knowledge is a limiting factor for full implementation of molecular models in the medical field. But world-wide research efforts in this area continuously complement existing knowledge. The integration of Monte Carlo approaches in molecular models is currently established to fill the existing gaps in knowledge and use simulations and predictions to account for missing experimental data [51].

PyBios is a currently implemented model approach using an object-oriented modeling environment (pybios.molgen.mpg.de). It is based on interacting molecular models representing different cells or tissues integrating the patient's personal genome and other data. Individual models describe different objects representing the biological modules within the complex biological network acting in the cell in interacting compartments. These objects might represent different characteristics; for example, one object could describe the Ras protein representing one set of functions, whereas an object representing the mutant Ras protein shows altered functions resulting from the mutation. The PyBios system uses a Monte Carlo approach to simulate and predict the elements that cannot be measured yet. In a current pilot project (2010–2013) on melanoma patients in Germany (TREAT20) the PyBios modeling approach is used for the first time in a clinical setting [52]. The cancer model used in TREAT20 is based on the publications by Hanahan and Weinberg 2001 (with an update in 2011) [53, 54] representing the signalling pathways relevant in cancer. Tumor tissue collected from each patient is sequenced for the genome and transcriptome, respectively, exome data. These data are the basis for establishing an individual patient model that is later combined with a drug database to predict a possible drug response (Fig. 1). In addition, with this approach drugs that are unusual in clinical practice or even new drugs can be tested for their possible efficiency with these 'virtual patients'. The results from the

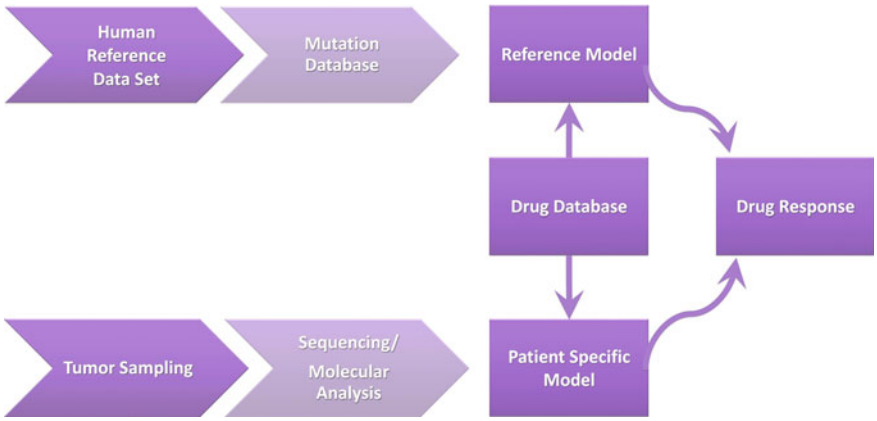


**Fig. 1** The individualization of the virtual patient model and subsequent modeling for the prediction of possible drug responses in the individual patient

modeling approach and the predicted drug response support the clinician in the decision on drug treatment strategy.

With the new analytical technologies and the different model approaches that are already available, the next challenge is the issue of integration. Integration must be achieved in many different aspects including integration of data, technology, and models, but also existing knowledge on the functioning of the human body as well as on biomarkers or diseases. Only an intelligent strategy for achieving integration in an efficient and reliable way allows the transfer of this knowledge into clinical application via the ‘‘virtual patient’.

The reliability of the information output using the ‘virtual patient’ model also depends strongly on the quality of the existing data and information. The construction of the model, therefore, needs a very careful proof and quality check of the data before their integration into the system. New reference datasets need to be generated to feed the model with highly precise and reliable information. For the whole workflow a consensus for standards from the clinic via the analytical technologies down to data processing and integration has to be developed and agreed upon by all participating entities across Europe and even worldwide. Many steps within the workflow are still handled and controlled manually, but a system that will process and maintain the data of millions of patients needs the development of automated processes such as sample preparation, data processing, and analysis.

To achieve real-time health care in the future, these developments must be supported by an adequate infrastructure not only in biomedicine, but also in the ICT field. Data must be made available from the individual, and also a broad range of sources such as population-based data, environment, and lifestyle must be integrated in the system if sufficient support of health professionals is the aim.

To make full use of these novel modeling concepts in clinical practice, we have to solve the problem of demand for computing power that exceeds by far the

capacities of existing systems. Therefore, one of the most important challenges for the computer hardware and software fields is the development of solutions for the data-rich next generation medicine. The aim must be to speed up the computational processes and reduce power consumption dramatically before this virtual patient model can be used in clinical applications.

Only a concerted effort involving all necessary scientific disciplines from biomedicine to engineering and hardware and software system specialists can achieve this aim.

## 6 Information and Communication Technologies Are the Drivers for Systems Medicine

The ITFoM initiative aims at developing the data-driven 'virtual patient' model not only for European countries, but with the long-term perspective to be available to all patients worldwide. To achieve this aim it clearly needs enormous advancements in the ICT field to handle, store, and process all the data of the patients in the system. Already today we face bottlenecks in many areas that will be addressed in the ITFoM initiative.

To demonstrate the needs we face in the near future, a calculation example might elucidate the situation: The European health system includes around 500 million citizens. For each person the genomic information has to be generated, and transcriptional information at least needs to be collected continuously from each individual. If other information on the proteomics and metabolomics levels also needs to be included, the amount of data per person increases tremendously. To run an appropriate model, at least 1,000 cell types under 1,000 conditions per person have to be considered. If the model needs to be used at least twice per year (when the patient is consulting the clinician) the computing time is in need of around $10^{14}$ core years. Google uses 900,000 servers with estimated 100 cores per server; this infrastructure consumes approximately 0.01 % of worldwide electricity. Using the 'virtual patient' model for every European citizen, 100 times the worldwide electricity production would be needed to run the simulations (personal information H. Lehrach).

To allow 'virtual patients' to become part of standard clinical practice, substantial and intelligent advances must be made in hardware and software infrastructures, computational paradigms, and human–computer interfaces, as well as in the instrumentation and automation of techniques and processes required to gather all relevant information [4, 9].

When forming foundations for large-scale ICT, computing science was driven by 'large' physics and commercial applications, and medicine played only a minor role. ICT requirements of the new, data-rich, individualized medicine will soon surpass the demands of all other (ICT) fields. As data-intensive analysis and computer-intensive modeling technologies become common clinical practice,

medical ICT implementation will require far more resources. The enormous demands of computing power to perform the necessary Monte Carlo simulations or other mathematical approaches to describe biochemical systems and allow predictions and simulations of the whole human being pose unprecedented challenges to ICT, that is, in hardware and software constructions for storage, retrieval, and management of data, but also for communication, visualization, governance, and policy issues.

## 7 Implementation in the Health Care System

The future health care system—the patient in the first line—will increasingly benefit from these novel approaches, but our attitudes and daily routines will also change dramatically with respect to health. Despite the rapid development of modern information and communication technologies, an eHealth system to collect patient information in a central repository has not yet been implemented in most countries of Europe and worldwide. An eHealth system provides the huge advantage that general practitioners and clinicians do not have to rely on a patient's personal memory to report earlier diseases or which drugs are prescribed; an eHealth record provides all important information about a patient instantly to a GP or clinician which can be especially important and highly advantageous when an emergency case occurs. The implementation of an eHealth system certainly has to follow a strict legal and ethical framework, and it needs the consent of the citizens in a country to accept such a system. An eHealth system also provides the chance to allow elderly patients or patients with chronic diseases a more independent life. Concepts for Ambient Assisted Living are rapidly emerging along with a huge spectrum of technologies that provide independence for the patient [55]. In diagnostics the devices have increasingly implemented the possibility for a wireless connection to central data repositories where the data are processed and linked to patient data [24]. More and more web services also provide platforms where a person can collect and monitor his or her body functions such as blood pressure, pulse, and body weight. If we expect that in the future the lifestyle and environmental data will be an important element integrated in the 'virtual patient', then these data become increasingly important as background information for decisions regarding therapy and prevention [56].

Pilot projects to integrate molecular information in these patient records have been started recently in some countries in Europe, respecting all the legal and ethical implications connected to these projects. As molecular information becomes available for a reasonable price *via* advanced analytical technologies, it can be anticipated that soon it might become routine for patients to agree to include their personal genome information in their health records. Initiatives such as '23 and me' (www.23andme.com) offer a sequencing service and an analysis for disease risk factors and predicted drug response for the customer. Since services like this emerged, there has been an observable trend of increasing numbers of

customers, indicating the citizens' interest in this type of personal information, thus raising the hope that in the near future it will be possible to integrate molecular information on a broader—e.g. genomic—scale if the legal and ethical framework is carefully respected.

With the availability of modern communication technologies we are able to distribute and share information in a way that was unthinkable only a few years ago. As a consequence we face a situation where the general prescription or clinician is no longer the only group having proprietary information about health, diseases, or drugs. The average patient has become more autonomous and now demands participation in the decision-making process about therapy approaches and drug prescription. For the provision of specific treatment on an personalized basis, co-decision and empowerment are key terms [57]. As a consequence citizens assume increasing responsibility for their personal health with all the advantages, but also the disadvantages of this new situation.

The research in pharmacogenomics has shown the diversity of responses to drugs [10], and with increasing knowledge in this area it becomes obvious that the stratified medicine approach is no longer sufficient. The 'virtual patient' approach with the integration of molecular information and computational evaluation *via* the model will decrease the number of non-responders and make medical treatment more safe and efficient [58]. If a consequent information policy is followed by all stakeholders and parties involved, patients will have the freedom to participate actively in the decision process about their medical treatments and, consequently, also about their individual (health) behavior. To realise this, opt-in mechanisms on different levels and with the possibility to individually access the information must be developed, accompanied by an adequate informed consent. This framework will allow the individual to have decision power over the knowledge that can be potentially obtained.

The new concepts and developments in medicine empowering the virtual patient model open the perspective for truly personalized, efficient, safe, and less cost-intensive health care in the future. On the technological basis all necessary disciplines such as life sciences, engineering, ICT, and the like combine their expertise and efforts to achieve this ambitious goal to enable the patient model as a powerful tool in medicine. Cooperation with and integration of all stakeholder groups is also of crucial importance to allow implementation of the patient model in the health care systems on a sound ethical and legal basis for the benefit of the citizens. These new routes to personalized and efficient medicine will transform existing health care systems and change business models and markets in the near future.

This innovative approach will benefit not only European and first-world countries, and it will be the duty of the scientific community to transfer and actively support the access and use of knowledge for less-favoured countries worldwide to address global challenges in health and leverage the powerful new tools to eliminate inequalities [3].

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