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Unraveling human complexity and disease with systems biology and personalized medicine

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Abstract

We are all perplexed that current medical practice often appears maladroit in curing our individual illnesses or disease. However, as is often the case, a lack of understanding, tools and technologies are the root cause of such situations. Human individuality is an often-quoted term but, in the context of human biology, it is poorly understood. This is compounded when there is a need to consider the variability of human populations. In the case of the former, it is possible to quantify human complexity as determined by the 35,000 genes of the human genome, the 1–10 million proteins (including antibodies) and the 2000–3000 metabolites of the human metabolome. Human variability is much more difficult to assess, since many of the variables, such as the definition of race, are not even clearly agreed on. In order to accommodate human complexity, variability and its influence on health and disease, it is necessary to undertake a systematic approach. In the past decade, the emergence of analytical platforms and bioinformatics tools has led to the development of systems biology. Such an approach offers enormous potential in defining key pathways and networks involved in optimal human health, as well as disease onset, progression and treatment. The tools and technologies now available in systems biology analyses offer exciting opportunities to exploit the emerging areas of personalized medicine. In this article, we discuss the current status of human complexity, and how systems biology and personalized medicine can impact at the individual and population level.

Keywords

complexity; human health; 'omics; personalized medicine; systems biology; variability

Historically, our understanding of human biology has suffered from a paucity of data and information content. This has been compounded by the complexity and variability of human individuals and populations. It is salutary to consider that each one of us consists of approximately 100 trillion cells, but approximately 70% of the cells do not belong to us – these are symbiotic bacteria located primarily in our gut. We consist of approximately 210 different cell types; possess approximately 35,000 genes, 10 million proteins (including antibodies) and 2000–3000 metabolites. In addition, each human cell is made up of 95 trillion water molecules,

60 billion proteins, 2 trillion fat molecules, 5 trillion sugars and amino acids, 60 billion RNA molecules and six feet of DNA. A 'simple' organ such as the brain comprises 100 billion neurons, each one possessing approximately 10,000 connections, which creates a synaptic network of 1 quadrillion components. All these numbers demand our attention and emphasize human individuality and complexity. Without technological advances and biological insights, we cannot hope to cure individual maladies.

It is possible to quantify human complexity but, in the case of human variability, we are confounded by the range and subtlety of these differences. Such traits can be transitory or permanent, and influenced in complex ways by both genetic and environmental factors. Sources of human variability include gene mutation (germ-line and somatic), allelic differences, genetic drift, social and cultural influences and nutrition [1]. Common human variations include obvious visible differences, such as gender, age and physical appearance. These differences are determined through poorly understood molecular processes [2]. Such processes are modulated by a wide variety of molecular entities and processes that include but are not restricted to SNPs, DNA copy number variation, alternative gene splicing and protein isoforms, including post-translational modifications [2]. Our basic understanding of these processes have led to the creation of simple semantic descriptors that define such differences and include concepts such as gender, age differentiation (child vs adult) and race. However, such coarse descriptions do not provide adequate insight into the significant and subtle differences that separate us at the molecular level.

As we consider the potential impact of systems biology on human health and disease, and how personalized medicine may impact each one of us, it is reasonable to pose the following questions:

- Why should we consider complexity and variability as being important in personalized medicine?
- What impact does complexity and variability have on our ability to predict and determine molecular events and outcomes in human health and disease?
- How should we address and embrace human complexity and variability in personalized medicine?

We will attempt to consider and discuss such issues, and try to determine how the use of systems analysis and personalized medicine can possibly be of help to biomedical researchers.

Consequence of human complexity & 'omics data

In the past 15 years, the health and life sciences have been inundated with 'omics data as part of the attack on unraveling human complexity and variability. The 1990s saw the advent of genomic, proteomic and metabolomic platforms that provided relatively fast high-throughput capability. These platforms have been extensively employed in the drug discovery process by pharmaceutical companies. Hence, before considering the potential impact of personalized medicine on human health and disease, it is worthwhile to consider the impact of 'omics analyses on the pharmaceutical sector in terms of drug cost and pipeline efficiency. There are a number of parallels to be drawn between the therapeutic treatment of a disease and the use of personalized medicine in influencing overall individual health. However, in the case of the former, the drug-discovery and development process is well described and relatively simple [3]. In the vast majority of cases, a single compound – often with a known biological target – is used in the treatment of a specific disease state. Unfortunately, owing to the complexity and variability of humans, our ability to even develop and provide safe and efficacious therapeutic drugs in the treatment of specific diseases has been widely questioned [4].

Much of this was due to the fact that our understanding of disease etiology and pathobiology was predicated on simple observation of physiological changes and homeostatic imbalance. More recently, this concept has been replaced with an understanding that disease causality and onset is a complex multicomponent process. For example, breast cancer is now categorized into at least five distinct subtypes, and there may indeed be many other unique molecular types [5]. Likewise, it has been well documented with identical twins that one individual may develop a genetically predisposed disease while the other sibling may never exhibit the disease or its early symptoms [6]. In part, this may be explained by the fact that although DNA molecule is relatively simple and well understood chemically, the human genome's structure is extraordinarily complex and its function is poorly understood. Only 1–2% of DNA's bases encode proteins, and the full complement of protein-coding sequences still remains to be established [7].

The consequences of not understanding human complexity and variability have been profound for the pharmaceutical sector. The pharmaceutical industry has been compared with the 'horse and buggy industry' of yester-year [8]. This sector is faced with ever-increasing drug discovery and development costs, as well as the limited efficacy and safety of its products. For example, research and development expenditures by pharmaceutical companies have increased from US \$2 billion in 1980 to \$55.2 billion in 2006. Furthermore, the average cost of developing commercial drugs (including launch costs) has increased from \$1.1 billion (1995–2000) to more than \$1.7 billion in 2000–2002 [5]. The cost is driven in part by a long and tedious timeline to develop new compounds, which can take as long as 15 years each. Unfortunately, the increase in expenditure has not translated into either increased product output or practical developments, such as innovative therapeutics. For example, the number of new chemical entities reached a peak in the mid-1990s and has declined by more than a factor of two. In addition, the number of compounds reaching late-stage clinical trials has decreased during this same time period [5]. According to the US FDA Critical Path Initiative, the number of Phase I compounds that will ultimately be marketed has dropped from 14 to 8% over a 15-year timespan. In addition, according to the FDA, the number of drugs that successfully pass through the costly Phase III clinical trial stage has dropped from 80 to 50% over a 10-year timespan.

Even more disturbing is the fact that, while costs are raising and productivity is falling by any metric of measurement, efficacy does not appear to have been significantly influenced or changed. For example, it is disturbing to note that the death rate due to malignant neoplasms has gone from 170 to 187 deaths per 100,000 people during the period 1960–2005, according to statistics provided by the Organization for Economic Co-operation and Development (Paris, France). In other words, patients appear to be more likely to die after a diagnosis of cancer today than over 40 years ago, despite a significant increase in healthcare spending and biopharmaceutical innovations. In the case of cardiovascular disease, the number one cause of premature death in the USA, trends appear more encouraging: there has been a noticeable decline in mortality from 632 to 223 deaths per 100,000 people during the same period. However, much of this improvement has been primarily attributable to changes in lifestyle and diet, and not as a direct result of new therapeutic treatments. Thus, a threefold increase in the percentage of gross domestic product allocated to healthcare has not translated into better therapies and treatments for some of the toughest, yet most common, diseases in the USA.

Even when large amounts of 'omics data are available, many of the woes hampering the development of the pharmaceutical industry can be directly attributed to a lack of understanding and appreciation of human complexity and variability. It was only recently that the pharmaceutical industry has realized the need for tailoring drugs to subgroups of populations as well as considering the importance of phenotyping effort. The consequences are, nonetheless, manifest, and as the fledgling field of personalized medicine struggles to impact human health, what can we learn from the drug discovery and development process? In

particular, how can systems biology help us address human complexity and variability and augment the tools being developed in personalized medicine?

Systems biology

The 1990s has been defined as the ‘decade of measurements’ [8]. ‘Omic waves flooded through the scientific community as relatively high-throughput platforms were developed for genomic, proteomic and metabolomic analyses of complex biological samples. Such platforms produced massive datasets that were then analyzed and mined using the latest bioinformatics knowledge-assembly tools. In order to produce new understanding and knowledge about complex biological processes and systems and, by extra polation, dissect human complexity and variability, systems biology emerged as a new unifying discipline [9–11]. This nascent field has attracted considerable attention and effort, and appears to be an approach that can offer new insight into the complexities of human health and disease. These developments have helped lay the foundation for the emergence of personalized medicine.

■ Brief history & current status

First-generation systems biology can be traced back to the mathematical theories of systems control in the early 20th Century. In its incarnation, a systems approach to biology was predicated on theoretical considerations of complex systems analysis. Weiner introduced mathematical models of complex systems control and communication in the 1940s [12]. However, von Bertalanffy wrote in 1928 that “... a [system consists of] a dynamic order of parts and processes standing in mutual interaction... the fundamental task of biology is the discovery of the laws of biochemical systems” [13]. von Bertalanffy ultimately went on to develop the ‘general systems theory’ [13]. In the 1960s and 1970s, biochemical systems theory and metabolic control theory (also now known as metabolic control analysis) attempted to create simple mathematical models of biological systems [14,15]. Such a systems-level approach was not able to connect to the then experimental molecular sciences until the availability of quantitative molecular data, provided by ‘omics platforms developed in the 1990s [16].

Second-generation systems biology has its roots in high-throughput ‘omics measurement, bioinformatics, metabolic engineering, computational sciences and mathematics. It is an attempt to establish a more integrated and hierarchical paradigm that facilitates the creation of new biological pathways and networks at the cellular level [17]. This should provide a framework for understanding the holistic system of genetic, genomic, proteomic, metabolic and cellular events that are in flux and interdependent. In order to facilitate such efforts, two distinct approaches have evolved, namely, engineering-based systems biology [9,18] and discovery-driven systems biology [19–21]. The former, which we also refer to as ‘bottom-up’ systems biology, relies primarily on computational modeling and engineering simulations. The latter, which we also refer to as ‘top-down’ systems biology, predominantly utilizes data-sets that are mined to discover new knowledge using a variety of bioinformatics and knowledge-assembly tools [22].

‘Bottom-up’ systems biology initiates the analysis of the system from its constitutive elements. These parts are then integrated and formulated in order to predict systems behavior. The ultimate goal of this approach is to combine pathway models into a global model for the entire system under consideration. This deductive approach was pioneered by Kitano [9]. He defined four essential elements that are needed for systems biology to be useful: systems structure identification, systems behavior analysis, systems control and systems design. More recently, he has extended this to include the importance of biological robustness, which he refers to as a system property that allows it to maintain its functions against internal and external perturbations [23]. As this approach has evolved, the basic biological model is augmented by

incorporating additional processes that contain more mechanistic detail. This is exemplified in the combined modeling and experimental work of Lauffenberger and Sorger on cell signaling in general and signal transduction pathways in particular (e.g., see [24]).

The development of top-down systems biology had to await the advent of the 'omics revolution and the availability of high-throughput platform analysis. However, it has now “emerged as [the] new and dominant method” [25]. This inductive approach attempts to define and determine new molecular mechanisms employing integrated data acquisition, analysis, combination and correlation [21]. Iteration of this process should result in the formulation of new hypotheses concerning co-regulation and inter-regulation of groups of molecules. These hypotheses then predict new correlations, which can be tested in new rounds of experiments or by new rounds of biochemical analysis. Top-down systems biology has been championed by Hood, Naylor and their colleagues [10,21,26,27]. Both have attempted to develop a more applied methodology for systems biology analysis. They have used a variety of 'omics platforms in concert with sophisticated statistical, bio informatics and knowledge-assembly tools to transform the discovery process by studying, in parallel, complex relationships among genetic, genomic, proteomic and metabolic pathways and networks. This approach has been further refined and, more recently, has been used to investigate a number of complex biological problems involving clinical aspects of complex diseases, drug efficacy and animal toxicity [20,28].

■ Definition & opportunities

A specific definition of systems biology appears to vary as a function of the expertise of the individual pontificating on the issue. In part, the lack of a clear definition for systems biology is due to a number of factors and includes the fact that the practitioners of systems biology come from a multitude of scientific disciplines with their own domain-centric perspective. A consequence of this fact is that the language of systems biology needs to be standardized across numerous scientific disciplines. Historically, standards or common language formats have emerged as necessitated by demand. Examples of such established standards include a hypertext transport protocol, relational data model such as the entity-relationship notation [29], unified modeling languages and extensible markup language. In systems biology, a number of data standards relevant to systems biology have emerged and include genomic data modeling, ‘Gene Ontology’ for describing gene function, ‘Minimum Information about a Microarray Experiment’ for describing microarray experiments, ‘Systems Biology Markup Language’ and ‘Cell Markup Language’ for describing bio molecular simulations. The progress in determining standards in 'omics and systems biology has been summarized and discussed in many works, for example, by Chen and Carlis [30] and by Brazma [31].

Progress in standardization continues; nevertheless, the definition of systems biology continues to be debated [32]. Hood defined systems biology as “... an analytical approach to the relationship among elements of a system, with the goal of understanding its emergent properties” [10].

Others have argued that it can be even more encompassing. Naylor expanded the definition of systems biology to “... the process of interrogating the genetic, genomic, biochemical, cellular, physiological and clinical properties of a system to define and create a system pathway or network that can be used to predicatively model a biological event(s)” [33].

More recently, it has also been described as the marriage of molecular biology and theoretical biology [34]. Furthermore, Huang and Wikswo have claimed that systems biology is more than the integration of biological measurements with computational sciences [32]. They propose that “...[systems biology is a discipline] that specifically addresses the fundamental properties of the complexity that living systems represent”.

Huang and Wikswo and others claim that systems biology offers capabilities of “unraveling the ultimate mysteries of life” [34].

■ Informatics tools

Systems biology aims to utilize a broad, comprehensive and disparate set of tools and technologies in an integrated manner. These tools can be grouped into broad classifications that include sample preparation, sample analyses, clinical metadata input, bioinformatics, knowledge assembly and mathematical or computational tools. Hood envisioned that a host of tools would be needed in the future to interrogate biological systems that included laser-capture microdissection, PCR, microfluidic and other nanomechanical and nanoelectronic devices [10]. The technological advances and high-throughput 'omics analysis techniques have been described in detail by Kussmann *et al.* [35]. However, currently, in the case of high-throughput 'omics analysis, the primary platforms used are mass spectrometry and microarrays. Others have also recounted and described technologies with a particular emphasis on proteomics and metabolomics [36,37]. The comprehensive integrated use of genomic, proteomic and metabolomic platform technologies to carry out systems-level analyses on both human and animal subjects has been demonstrated [20,21,26,28]. A plethora of bioinformatics and knowledge-assembly tools are required for the data processing, analysis, integration and interpretation of systems biology datasets [27]. They include examples in knowledge representation [30,38], data processing [27,39], data integration [29,40–42], information visualization [43–45], text mining [46,47] and data sharing [31,48]. The computational technique details of these topics are covered comprehensively in books such as *'Biological Database Modeling'* by Chen and Sidhu [49], *'Biological Data Mining'* by Chen and Lonardi [50], *'Systems Biology'* by Palsson [11] and *'Computational Systems Biology'* by Kriete and Eils [51].

In Figure 1, we show several recent examples of top-down systems biology software tools and databases developed at research laboratories of the Indiana Center for Systems Biology and Personalized Medicine (IN, USA). Figure 1A shows an Alzheimer's disease-specific molecular interaction subnetwork, using protein–protein interactions (as edges) and proteins (as nodes) and methods described by Chen and coworkers [52]. The sizes of nodes are drawn in proportion to their network 'topological significance'. Nodes colored in red (or dark gray) represents proteins curated from prior knowledge, while nodes colored in green (or light gray) represents proteins pulled into the molecular interaction network. With the most basic effort of molecular interaction mapping, the disease biology sub network already connected approximately 90% of all Alzheimer's disease genes and can serve as a useful integrated descriptive model ($p < 0.008$) for drug target prioritization or biomarker identification applications. Practically all the 'omics data that capture the perturbations of normal versus altered physiological state of cells can be mapped to a subnetwork graph like this. Such subnetworks can be more useful as a starting point for further biological pathway studies than whole-network models.

Figure 1B shows a visualization of a gene functional category crosstalk network, using proteomics data derived from an ovarian cancer drug-resistance cell line study compared with ovarian cancer drug-sensitive cell line [53]. Different from networks at the more detailed molecular interaction level, gene functional category crosstalk networks represent integrative biology views at a higher level. Colored nodes and code edges refer to significantly enriched protein molecular function classes and significantly enriched protein–protein interaction crosstalk functional category at the functional category level. Therefore, such network visualization is useful for understanding complex interplay and enrichment of gene sets, without making the global network view too crowded to spot trends.

Figure 1C shows a terrain visualization [44] of a panel of candidate protein biomarkers in Alzheimer's disease, which is organized by the protein interaction network for the disease at

the x–y base and interpolated molecular measurement (expression level) at the z-axis. Valleys and peaks (labeled) on the terrain indicate clustered genes and/or proteins that act together in the panel. Terrain visualization enables researchers to sensitively identify effects brought forth by weak yet cooperative effects from gene in mechanistically related network or pathway clusters.

Overall, these visualization tools allow biomedical researchers to interpret complex patterns revealed at different hierarchical levels under different physiological conditions through top-down systems biology analysis and mining (Figure 1).

Systems biology & health

Despite the medical advances made to date, numerous disease states can only be explained by complex, multimolecular interactions rather than by alteration of a single gene, gene product or metabolite. Thus, in order to garner a more complete and relevant understanding of disease, one must obtain a comprehensive perspective of the biological system, thereby uncovering the interdependent and dynamic pathway, network and cellular events that undergo change as a function of disease predisposition, onset and progression. Hence, as noted recently by Lemberger, the application of systems biology to human biology and medicine should provide a “... deeper understanding of the genotype–phenotype relationship; impact of the interactions between environmental conditions and genotype; novel mechanistic and functional insights based on global unbiased approaches; and elaboration of powerful predictive models capturing the intricacies of physiological states” [54].

Since the original suggestion by both Hood [10] and Naylor [55] that systems biology would have a significant impact on the study of pathobiology and medicine, there has been a small but flurried activity in this area. For example, this past year, a special edition of the journal *Molecular Systems Biology* was dedicated to “systems biology in human health and disease” [54]. In addition, studies utilizing a systems approach across most major disease areas have been published in the past 2 years. For example, in cancer biology, studies include mapping of pathways involved in breast cancer metastasis [56]; and the reverse engineering of structures involved in prostate cancer employing computational strategies combined with genome-wide expression profiling [57]. The *Journal of Lipid Research* has been running a thematic series of articles on systems biology approaches to metabolic and cardiovascular disorders (e.g., see [58]). Mechanistic understanding of neuro degenerative diseases has proved formidable, but a recent perspective on the use of systems biology in determining cell cycle processes involved in apoptosis in Alzheimer's disease appears to be useful [46]. Finally, the potential for computer-aided mathematical modeling of biological systems in medical research also offers substantial potential, which is described in detail in a recent review with examples from some of the major therapeutic areas: cancer, cardiovascular, diabetic and neurodegenerative medicine [59]. All these studies indicate the potential of systems biology to increase our understanding of pathobiology. However, one of the hopes is that the increased information content derived from systems biology analysis can lead to more predictive models of disease susceptibility, onset, progression and treatment. Finally, such a systems-level approach can potentially provide paradigm-shifting surges. For example, Loscalzo has described a new approach to classifying human disease that uses conventional reductionism and incorporates the nonreductionist approach of systems biology in medicine [60].

The use of either top-down, bottom-up or hybrid systems biology technologies is also finding more widespread use in other areas of general health. There has been significant speculation, activity and demonstration concerning the potential of systems biology to understand the tenets of host–pathogen interactions [61], toxicology [62] and aging [63]. Wider application of all these systems biology technologies is likely to be instrumental in opening the door to the era

of personalized medicine with tailored strategies encompassing all dimensions of clinical practice, including prevention, diagnosis, treatment and prognosis, as well as defining general health and wellbeing. For example, Nicholson has developed this concept to determine that “Personalized healthcare and molecular epidemiology are thus effectively two sides of the same ‘systems biology coin’”; the essential differences are with respect to the type of medical end points or outcomes that are to be modeled [64]. The concept that systems biology bridges personalized medicine and molecular epidemiology is important, and the ability to take advantage of this fact will require a pragmatic approach.

Clearly, significant advances have been made in second-generation systems biology at the experimental and computational levels, as well as demonstrated practical applications in human health and disease [65]. Such approaches appear to be ideally suited for personalized medicine and human health studies. However, does the potential bear any resemblance to the reality? The industry and scientific community are still waiting for robust applications of the systems biology approach, especially in view of the availability of analytical platforms and bioinformatics tools and their discussion in publications dating back to 2004. There are numerous publications discussing the potential and benefits, yet very few business success stories. Whether this approach will indeed ensure a reduction of drug development timelines remains an exciting open question.

Personalized medicine in the 'omics era

Many would argue that personalized medicine has already been used in practice for over 3000 years in oriental medicine, such as traditional Chinese medicine [66]. Traditional Chinese medicine doctors prescribe individualized treatment using herbal medicine, based on the diagnosis of the individual patient made using measures such as temperature, pulse, pain, tongue, palms and even facial features that have been practiced and known to be linked to the true causes of the disease. In Western medicine, the principle of personalized care was proposed over 2000 years ago. Hippocrates (born circa 460 BC) is known as the father of modern medicine, but he might better be described as the father of personalized medicine. He argued that disease was a product of environmental forces, diet and lifestyle habits, and that treatment should focus on patient care (prevention) and prognosis (prediction) [67]. Ironically, the status of current Western medical practice is rather different and focuses on symptomology and a correlated diagnosis as well as specific disease treatment. While there has been significant enhancements in patient care over the past century, this latter approach has led to ever-increasing health-care costs and has had limited impact on the prevention, prediction, accurate diagnosis and treatment of both acute and chronic diseases. In addition, our limited understanding of causal mechanisms for onset, progression and treatment of many 21st Century diseases has led to a growing awareness of paradigm change. Current medical practice seeks to treat disease after onset, whereas, by contrast, personalized medicine attempts to identify disease prior to clinical pathology and onset at the molecular level. Furthermore, it seeks to carefully classify disease and subtypes of disease such that appropriate therapies can be optimized to a patient's unique molecular profile and physiology.

The advent of personalized medicine in the genomic, proteomic and metabolomic era is complicated by the fact that it is often used as an umbrella term to cover a number of other subspecialties. Hence, the term personalized medicine, as well as the concept of how personalized medicine is practiced, has broad interpretations. In a 2007 *Boston Globe* column, Francis Collins wrote that “Today, we are witnessing a revolution in the understanding of the human genome and the subsequent creation of a map of human genetic variation. And, like most historic movements, this revolution has been given a name: personalized medicine” [101].

The Personalized Medicine Coalition (Washington, DC, USA) defines personalized medicine as “...the management of a patient's disease or disease predisposition, by using molecular analysis to achieve the optimal medical outcomes for that individual – thereby improving the quality of life and health, and potentially reducing overall healthcare costs” [102].

Personalized medicine now encompasses predictive medicine, preventive medicine, molecular medicine, pharmacogenetics and pharmacogenomics, and each is defined in the following ways:

- Predictive medicine is defined as “the detection of changes in a patient's disease state prior to the manifest of deterioration or improvement of the current status” [68]. Predictive medicine is a discipline that attempts to predict statistically what disease a person may get, thereby allowing one to take steps to prevent disease onset or progression. Predictive medicine (similar to preventive medicine) is different from other aspects of personalized medicine primarily with respect to time. Predictive medicine attempts to halt onset and early progression of disease before more invasive procedures are required; other areas of personalized medicine (see later) attempt to tailor therapy to a patient's unique biochemical profile after disease is discovered and is at a later stage of progressing;
- The American Board of Preventive Medicine® (IL, USA) defines preventive medicine as the “specialty of medical practice which focuses on the health of individuals and defined populations in order to protect, promote and maintain health and wellbeing and prevent disease, disability and premature death” [69]. The term preventive medicine, as envisioned by Hippocrates, is a proactive medical practice that attempts to prevent disease onset and mitigates the need for medical intervention;
- The Royal Society of Medicine (London, UK) defines pharmacogenetics as an “emerging science that seeks to determine how people's genetic make-up affects their response to medicines”. Essentially, pharmacogenetics attempts to determine the role and impact of individual genes in drug response differences observed between individuals;
- The National Center for Biotechnology Information (MD, USA) defines pharmacogenomics as “a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a response to a drug, a bad response to a drug, or no response at all”;
- Molecular medicine is viewed as the understanding and treatment of disease at the molecular level. Examples include the levels of such molecules as DNA, RNA, miRNA, proteins and metabolites. Detailing the relationship of such molecules to aberrant cellular processes, such as transcriptional, translational or metabolic events, is a goal of molecular medicine [70].

Obviously, as personalized medicine continues to grow and fracture into evermore subdisciplines, then new areas of endeavor will emerge, such as pharmacotherapeutics, pharmacoproteomics and pharmacometabolomics. However, the broad aim of personalized medicine is to use a molecular characterization approach to create a better system for disease classification. It is anticipated that this work will lead to earlier interventions and more specific treatments predicated on the individual's specific biochemical fingerprint. This is in stark contrast to current medical practice. Since the time of Hippocrates, scientists and physicians alike have viewed and interpreted disease at the ‘visual’ level, namely the organism, organ and, more recently, tissue levels [71,72]. Personalized medicine offers the alluring promise and potential of uncovering the largely ‘unseen’ details of disease causality, onset and

progression. For example, while general disease phenotype is generally the same from patient to patient (tip of the iceberg), the picture is enhanced (e.g., stage of progression) by viewing disease at its onset and monitoring progression at the molecular and cellular level (hidden unseen mass) [73]. The degree of success in individualizing medicine in this manner will depend on the degree to which the molecular aspects of the disease can be elucidated and measured. However, to date, there are some specific examples of personalized medicine approaches currently utilized to benefit patient disease diagnosis and disease treatment.

Current examples of personalized medicine approaches

The advent of systems biology tools and our understanding of pathway and network biology have dramatically changed the way we think about disease causation, onset, progression and treatment. The simple model of one diagnostic marker or one therapeutic agent per disease has been replaced with a realization that such processes are multifaceted in nature. In order to understand disease processes at the individual level, it is imperative to recognize that multiplex assays or combination therapies may be needed. Several examples are provided in the following sections to highlight such approaches in the personalized medicine arena.

■ Drug-dosing chip

Hoffmann–La Roche AG (Basel, Switzerland) states on its website that it aims to “determine disease predisposition, provide information that can act upon to prevent or delay the onset of illness, and even monitor treatments”. The company currently produces the AmpliChip®, a DNA chip-based diagnostic test that aids in individualized drug dosing. According to Roche's company website, CYP450 is the world's first pharmacogenetic microarray-based test approved for clinical use. The AmpliChip CYP450 test provides comprehensive coverage of gene variations, including deletions and duplications, for both *CYP2D6* and *CYP2C19* genes, which play a major role in the metabolism of an estimated 25% of all prescription drugs [74]. It is intended to be an aid for physicians in individualizing treatment selection and dosing for drugs metabolized through these genes. This is yet another example of a currently available personalized medicine approach that allows for a more quantified approach to medicine. This should ultimately encourage more patient drug compliance and, if used on a broad scale, has implications with respect to increasing the efficacy and safety of pharmaceuticals, as adverse drug reactions are a major problem in the current system.

■ Warfarin genetic test

The correct dosage of the cardiovascular drug warfarin is difficult to determine for patients with thrombosis. The problem with prescribing warfarin is that the optimum dosage is different for every patient owing to genetic differences in the approximately 60 different versions of the CYP450 family of genes [75]. One of these is a variation in the gene encoding vitamin K epoxide reductase complex 1 (*VKORC1*), which is associated with the metabolism of warfarin [76]. If a patient receives too much of the drug, there is a chance of death resulting from severe hemorrhaging. Conversely, if not enough of the drug is administered, there is risk of embolism in an arteriole and the occurrence of a stroke. Despite the risks, the drug has the potential to save the lives of many patients; however, patient compliance is absolutely necessary. The company Genelex (WA, USA) currently provides a diagnostic service that screens for SNP variants in *VKORC1* and *CYP2C9*. With such information, physicians are able to more efficiently adjust drug dosage in patients with the attenuated copies of the mutant alleles. Thus, the dosage of warfarin can now be specifically tailored to an individual's genes coding for CYP and VKORC1 rather than relying on an empirical determination. The result for patients is to optimize drug dosage quickly and effectively. This is in contrast to giving the patient a low dosage of the drug, having the patient return some time later and adjusting the dosage until it is correct. Thus, patients can save costly, repeated trips to the doctor, have the benefit of the

correct dosage immediately, and doctors do not have to rely on the patient's explanation to gauge whether the dosage is optimal.

■ Gleevec®

Chronic myelogenous leukemia (CML) accounts for approximately 13% of the 4500 cases of leukemia diagnosed each year in the USA [77]. Gleevec® (Novartis Pharmaceuticals Corporation, NJ, USA) is a tyrosine kinase inhibitor that can be used to treat both CML and malignant gastrointestinal stromal tumors [78]. The drug is indicated for use with Philadelphia chromosome-positive tumors caused by the binding of an abnormal protein Bcr–Abl 12, which causes the uncontrolled replication of white blood cells. The use of Gleevec can be confirmed as the appropriate treatment with a diagnostic that confirms the presence of the *Bcr–Abl* gene complex. The treatment is specific to patients with CML and uses a monoclonal therapeutic. In addition, although not all patients respond to Gleevec, there now exists a test to exclude the approximately 5% of the patients who do not respond to Gleevec therapy. A test by Genzyme (Maidstone, UK) can further exclude nonresponders to avoid unproductive therapies. The drug is a success story owing to its 90% overall positive response rate of which many experience complete remission.

■ Breast cancer diagnosis & treatment

There are an estimated 210,000 newly diagnosed cases of breast cancer reported annually in the USA, according to the 2008 statistics reported by the National Cancer Institute (MD, USA). For much of the 20th Century, our understanding of breast cancer manifestation and progression was extremely limited and it tended to be regarded as a single disease. However, today, it has been recognized that at least five different molecular subtypes of the disease exist [79]. This has prompted a reassessment of disease prognosis and treatment. The development of diagnostics and specific therapies for breast cancer make it an excellent example of a harbinger of personalized medicine.

Molecular classification of breast cancer is essential to obtain the best possible treatment. Thus, several diagnostic assays exist for more concise classification of cancer subtypes. The five well-characterized subtypes include luminal A, luminal B, basal type, HER2 positive and unclassified, which can all be distinguished by immunohistochemical stain [79]. In addition, further categorization exists, providing more specifically characterized types of breast cancer. These include the progesterone receptor- and estrogen receptor-positive cases; the latter is discussed later in the context of tailoring therapies. Of all cases of breast cancer, approximately 30% are characterized by the cell surface protein HER2, which is involved in the regulation of normal cellular growth [80]. However, a mutation in the gene that encodes the HER2 cellular surface protein can cause overexpression of the HER2 protein and abnormal cell growth. The over expression of HER2 has been characterized as a very aggressive form of breast cancer and is associated with poor survival rates. Currently, there are two tests that can confirm the diagnosis *in vitro* for the overexpression of the HER2 protein – FISH and the immunohistochemistry. Once the classification of the specific cancer subtype is found, optimal therapy, such as adjuvant therapy with the monoclonal antibody Herceptin® (trastuzumab; Genentech Inc., CA, USA), can be selected to combat the disease. The therapeutic is accompanied with the HercepTest™ (DAKO, CA, USA) diagnostic that confirms the use of the drug. The monoclonal therapy simply binds to cellular receptor HER2 protein. The binding inhibits cellular replication, thus stopping the cancer in a targeted approach based upon the cancer molecular pathology. Treatment has fewer side effects and is a more efficacious approach to cancer treatment because it is based upon the tumor's molecular classification.

As mentioned earlier, one of the distinguishing characteristics of breast cancer subtypes is the estrogen receptor-positive case that has a diagnostic test allowing patients' physicians to

determine the necessity of costly and painful treatments such as chemotherapy. The assay *Oncotype DX*® (Genomic Health Inc., CA, USA) is most beneficial for women who have stage I/II estrogen receptor-positive cancer and have no lymph node involvement [81]. To date, one problem with the current treatments of breast cancer is that, in an effort to kill tumors, patients are given large doses of chemotherapeutics. Current cancer protocol calls for a one-size-fits-all model of medicine.

According to Randy Scott, Chief Executive Officer of Genomic Health, “We’re giving a tremendous amount of chemotherapy in this country with very little benefit ... Current treatment guidelines recommend chemotherapy for as many as 90% of breast cancer patients, yet 85% don’t need it, because their cancer isn’t going to reoccur. Of the 15% that do, chemotherapy will only reduce the recurrence rate to 11%.”

The test is a reverse-transcriptase PCR assay that uses 21 previously identified cancer genes and can be used to place patients into a low-, intermediate- or high-risk category for recurrence of cancer after initial treatment. These categories can be used to “predict the likelihood of breast cancer recurrence in women with newly diagnosed, early-stage invasive disease and assesses the benefit from certain types of chemotherapy”.

To reiterate the aspects of personalized medicine already present with respect to breast cancer, the *Oncotype DX* and HER2 therapeutic/diagnostic allows for a more precise characterization of the breast cancer based upon molecular characteristics. As mentioned earlier, in a real sense, personalized medicine is already here (or at least several aspects are). Currently, there are a multitude of diagnostic tests and products that allow physicians and patients to customize their treatments to a component of the patient’s personal biochemical profile. However, with information comes decision-making, and this can be a complicated process that requires a clear diagnostic and treatment paradigm.

Conclusion

It is widely agreed that current Western healthcare systems are under siege. Based on current projections, escalating costs will reach unsustainable levels within the next decade. Indeed, there are a myriad of contributory factors, including social, political, technological and clinical issues. However, within the scope of this article, what can be done to reduce costs associated with treating the chronically sick, improve prognostic and diagnostic outcomes, and produce more efficacious and safe therapeutic agents? As previously discussed, there has been widespread recognition that human complexity and variability leads to different responses at both the individual and population level. As individuals, we are susceptible to disease onset, progression and treatment in very different ways from other individuals. At the population level, we may be part of the mean or we may be an outlier, and we may also be within a subpopulation that is dramatically different from other subpopulations. More recently, with the advent of the ‘omics era, we have also recognized the intricate complexity of molecular interactions, pathways and networks. The old model of a single event leading to disease onset, or the single diagnostic being adequately able to diagnose disease, led to an oversimplification of disease models and treatment. In part, this was due to lack of technology and tools.

Second-generation systems biology has pioneered the development of such tools and technologies as we outline earlier. This has facilitated our ability to unravel some of the complexities and variability of humans at both the individual and population levels. It has also led to the emergence of personalized medicine.

Personalized medicine is a rapidly growing arena of activity and awareness. Current thought leaders recognize the potential of personalized medicine to reinvigorate the healthcare system as a whole. In addition, a small but growing number of companies are building business models

around personalized medicine as opportunists and visionaries see the monetary potential of this new thinking. Examples of various companies and business models range from those that provide ‘home-brew’ test kits to walk-in clinics where comprehensive preventative physicals can be performed. There is significant work to do, with the need for increased investment in research and development.

In Table 1, we show a growing and vibrant worldwide academic community already contributing to this exciting new area, with an emphasis in the USA. To compile this table, we searched for major nonprofit academic research institutions that either carry distinct names associated with predictive and personalized genomic medicine, or have a clearly stated mission to develop or apply molecular systems biology techniques to improve disease prevention, diagnosis, prognosis and treatments. We also explicitly excluded centers that currently focus on basic systems biology or molecular medicine research. Centers or institutes that belong in this group are comprehensively listed. However, the list is not exhaustive, as new centers have mushroomed since Chen founded the Indiana Center for Systems Biology and Personalized Medicine in 2007 (Table 1). To search for a listing of commercial companies, foundations, associations or research institutes in this community, the online Personalized Medicine Coalition web portal is a good starting point [102].

Personalized medicine is not just exuberant hyperbole. The recognition that human complexity and variability can be probed using system biology tools has created significant opportunities and has led to a growing practical trend in the use of personalized medicine. The concomitant increase in knowledge and information available about an individual's health and wellbeing and/or disease is providing a new paradigm focused on the molecular level, which provides much greater detail than the macro-level organism/organ tissue system. The potential of this approach to restructure our understanding of individualized human health in the future is significant. Such possibilities include, but are not limited to, the prevention of disease onset and progression, early detection of disease, the development of more safe, efficacious drugs, the determination of optimal drug dosage, and the elimination of costly and ineffective treatments. The story continues to unfold.

Future perspective

We all believe that the current practice of healthcare is broken [5]. Our unwillingness to be pro active and consider individual wellbeing status and how to attain and maintain it has led to pandemics in chronic disease states, such as Type II diabetes, obesity, stroke and hypertension. In addition, the reactive response to symptomology and poor diagnostic capability coupled with ‘hit-or-miss’ treatment regimens has left all stakeholders frustrated and, in some cases, angry. The scientific, clinical and healthcare communities all believe that personalized medicine has a huge potential to impact prevention, diagnosis and treatment of disease. However, for the first time in recorded history, an individual in London (UK), Tokyo (Japan), New York (USA) or Rio de Janeiro (Brazil) understands that they are biologically unique and as such need to be treated medically to reflect that fact. Personalized medicine has captured the imagination of the ‘person in the street’ because both science and medicine have concluded that the individual is important and must now be considered in efforts to diagnose and treat disease. Such populism will put pressure on all of us to provide the necessary tools, technologies and insight to make healthcare systems work and provide outcomes for individuals that can be trusted. The next 5–10 years will see a grass-roots, bottom-up demand for prevention programs as well as better tailored (individual) predictive and pharmacotherapeutic efforts. The physician-centric model of healthcare will shift to the patient-centric model driven by tools and technologies developed by the systems biology sector and employed by the personalized medicine model of healthcare. and technologies developed by the systems biology sector and employed by the personalized medicine model of healthcare.

Executive summary

- Human complexity and variability are poorly understood, and have provided significant barriers to accurate disease diagnosis and efficacious treatment.
- The emergence of systems biology in the past decade has provided the necessary tools and technologies to help probe human complexity and variability.
- Current medical practice focuses on symptomology, correlated disease diagnosis and trial-and-error treatment.
- Personalized medicine has been defined as the management of an individual's disease or disease predisposition by using molecular analysis to achieve the optimal medical outcomes for that individual.
- Personalized medicine encompasses predictive medicine, preventive medicine, molecular medicine, pharmacogenetics, pharmacogenomics and pharmacotherapeutics.
- The use of system biology tools and technologies has facilitated the development and practice of personalized medicine.
- The increase in knowledge and information available regarding an individual's health and wellbeing and/or disease is providing a new molecular medicine paradigm, which provides much greater detail than the physiology-based medical practice employed in the past.

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Figure 1. Different types and applications of systems biology visualization tools

(A) Visualization of a protein–protein interaction subnetwork for Alzheimer's disease genes. (B) Visualization of a gene functional category crosstalk network activated in ovarian cancer drug resistance. (C) Visualization of a gene-expression panel of candidate molecular biomarkers organized in Alzheimer's disease protein interaction networks for samples derived from a cohort of Alzheimer's patients' brains.

Table 1

A representative list of academic research centers worldwide with a focus on technology-driven and/or systems biology-driven personalized medicine.

Name	Academic institution	Main focus
Abramson Center for the Future of Health	University of Houston (TX, USA) and Methodist Hospital Research Institute (TX, USA)	Advances knowledge of the effectiveness of pharmaceutical products, services and policies, with a particular focus on personalized medicine technologies
Berlin Institute for Medical Systems Biology	Berlin, Germany	Develops new high-throughput methods with which researchers can quickly generate system-wide data and systematically evaluate it, in order to predict the behavior of biological systems in health and disease
Center for Biomarker Research and Personalized Medicine	Virginia Commonwealth University (VA, USA)	Develops biomarkers to improve disease understanding and for drug efficacy and/or safety
Center for Biotechnology and Genomic Medicine	Medical College of Georgia (GA, USA)	Develops and uses technology for preventive and predictive medicine
Center for Computational Medicine and Bioinformatics	University of Michigan (MI, USA)	Facilitates interdisciplinary research in computational medicine and bioinformatics to develop new hypotheses
Center for Genome Medicine	Duke University Institute for Genome Sciences and Policy (NC, USA)	Conducts genome-based personalized medicine research
Center for Genomics and Personalized Medicine Research	Wake Forest University (NC, USA)	Investigates genetic mechanisms in the development and progression of complex human diseases
Center for Medical Systems Biology	Various Genomics Initiative locations, all based in The Netherlands	Applies innovative multidisciplinary genomics and bioinformatics approaches to improve diagnosis, therapy and prevention of common and rare diseases
Center for Personalized Genetic Medicine	Harvard Medical School (MA, USA)	Empowers genetics/genomics-based human clinical care
Center for Personalized Healthcare	Ohio State University Medical Center (OH, USA)	Integrates gene-based healthcare with predictive/preventive medicine
Center for Predictive Medicine	University of Louisville (KY, USA)	Studies new diseases and looks for ways to prevent, control and treat them
Center for Systems Biology	Massachusetts General Hospital (MA, USA)	Analyzes, at a systems level, how biological molecules, proteins and cells interact in both healthy and diseased states
Charles R Bronfman Institute for Personalized Medicine	Mount Sinai Medical School (NY, USA)	Integrates genomic, molecular and preventive medicine; biomedical informatics to advance clinical practice, delivery and economics of healthcare
Computational Medicine Center	Cincinnati Children's Hospital Medical Center (OH, USA)	Integrates genetics, medicine, computer science and biological science
Genomic Medicine Institute	Cleveland Clinic (OH, USA)	Drives genomics-based personalized healthcare
Indiana Center for Systems Biology and Personalized Medicine	Indiana University Purdue University (IN, USA)	Integrates systems biology for predictive modeling in genome-based medicine

Name	Academic institution	Main focus
Institute for Computational Medicine	Johns Hopkins School of Medicine and Whiting School of Engineering (MD, USA)	Develops powerful tools to transform the practice of medicine
Institute for Genomic Medicine	Texas A&M University (TX, USA)	Uses SNP-based predictive medicine to accelerate biomedical discoveries
Institute for Genomics and Systems Biology	University of Chicago (IL, USA)	Accelerates the transition of basic discoveries in genome science into practical benefits for society
Institute for Personalized Medicine	Fox Chase Cancer Center (PA, USA)	Matches emerging targeted drug therapies to the unique genetic profiles of individual patient tumors
Institute of Genomics and Integrative Biology	Council of Scientific and Industrial Research, New Delhi, India	Translate concepts developed in basic biological research to commercially viable technologies for healthcare
RIKEN Center for Genomic Medicine	RIKEN, Kanagawa, Japan	Investigates individual gene variation in the genome and identifies the relationship to disease onset and drug response in order to develop preventive and therapeutic techniques to suit individuals
Shanghai Center for Systems Biomedicine	Shanghai Jiao Tong University, Shanghai, China	Integrates techniques from biology and clinical medicine to physics and engineering to enable basic research translation to clinical applications, as well as postgenomic research and personalized medicine
The Genomic Medicine and Individualized Therapy Center	Translational Genomics Research Institute (AZ, USA) and Arizona State University (AZ, USA)	Translates genomic discoveries into advances in human health