Systems Thinking in Medicine and New Drug Discovery

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Volume Two

By

Robert E. Smith

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This book is dedicated to my grandchildren. I hope they can work with others in their generation to end civilization's addiction to fossil fuels and reverse the damage that my generation has done to the environment.

CONTENTS

PREFACE

Medicinal chemistry is undergoing an important paradigm shift (or way of thinking) from reductionist to systems thinking. This is based on a similar paradigm shift in medicine and the pharmaceutical industry. Network science is an integral part of this. It has led to the emergence of network medicine. It not only aims to develop safe and effective new prescription drugs for patients who become sick, but also to recommend diets, lifestyles and even some dietary supplements that can prevent diseases. Instead of focusing on just one aspect of health, network medicine uses systems thinking to predict peoples' susceptibilities to diseases and find ways to prevent them. In addition, patients who have specific cancer-causing oncogenes are being identified before clinical trials begin. That way, only the patients who are likely to benefit from the anticancer therapy will be recruited into clinical trials. This will increase the success rates of these trials and help to reduce the cost of new drug development and healthcare.

Network medicine also emphasizes precise, personalized treatments, in which patients and their caregivers can actively participate. It recognizes the important human need for patients and caregivers to be involved in preventing and curing their diseases. This is done with the types of extensive teamwork, open collaborations and continuous feedback which are hallmarks of Total Quality Management (TQM) and Total Quality Leadership (TQL) that are used in modern businesses. This leads to new insights. In business, it means that every employee is important because they all make crucial contributions to the organization. It also means listening to the voices of the customers, so their demands can be met. Similarly, TQM and TQL in systems medicine means listening to the voices of the patients and their caregivers, so their health needs can be met. It also means that the needs of every part of the human body are recognized by other parts of the body that interact synergistically and communicate with each other constantly. In addition, there is a deep ecology in the human body in which even the lowliest viruses and Bacteria make crucial contributions to the health of their human hosts and serve as essential parts of the neuroendocrine immune system. So, the human body operates under the principles of total quality, in which every component interacts, communicates and undergoes nonlinear feedback and feed

forward mechanisms. However, the human body is not a machine that is involved in manufacturing. Machines don't make themselves. Humans and other living creatures make themselves in the process called autopoiesis (self-making). So, TQM in the human body means total quality making, not total quality manufacturing.

The main goals of this two-volume set are to inform people with different backgrounds about the new ways that we are looking at human life and medicine, help healthcare professionals do their jobs better, provide background information and references for patients and their caregivers, as well as clarify some serious misconceptions that have emerged. For example, some people believe that the FDA and other governments' regulatory agencies are in a conspiracy with pharmaceutical companies and physicians to keep people sick, so they can maximize profits and continue to sell patients prescription drugs that don't cure any diseases. This thinking can lead some people to avoid seeing physicians, who prescribe 'chemicals'. Some people believe that all dietary supplements are always safe and effective – especially if they are labeled 'natural'. Many misconceptions like these can be exposed by using systems thinking.

The first volume provides an overview of systems thinking. The first chapter compares and contrasts reductionist and systems thinking in biochemistry and medicine. Some basic principles of systems thinking and network science are introduced. The new ways that diseases are prevented, treated and cured are described. This includes changing how new drugs and dietary supplements are being developed. Network science is crucial in this change, as is using one's own body and natural resources to prevent, treat and cure diseases. At the same time, a huge, interactive network supports healthcare. It starts with the smallest viruses and Bacteria. It includes patients, caregivers, nurses, physicians, hospitals, research institutes, universities, industry and many government agencies. It is based on a holistic view. Doctors no longer engage in a man-to-man struggle to cure the disease. Instead, they work with large interdisciplinary teams to focus on treating the whole patient and not just the disease. Moreover, pharmaceutical companies have realized that the former, secretive approach to developing new drugs was inadequate. Now, they collaborate with each other and with academia and even individual patients working at home. Part of this paradigm shift is the realization that there is a deep ecology.

So, the second chapter in the first volume also includes a description of how the human body is an ecosystem, consisting of not just human cells, but also viruses, Bacteria, Archaea, and Eukarya. At the same time, a type

of deep ecology has emerged in science and medicine. That is, biology and medicine are just as important as math, physics, chemistry, engineering and industry.

The third chapter in the first volume describes how systems thinking is used in every stage of new drug development. In this new paradigm, some of the best work is done by people who are educated in more than one field, so they can do interdisciplinary research using systems thinking. They are using 3D printing to produce plastic models based on CT and/or MRI images of patients, so they will know what to expect when they start surgical procedures. Such models are also quite useful in teaching surgical techniques to new residents. Interdisciplinary teams are also using 3D and 4D printing to make devices that are specific for each patient and can alter their shape as young patients grow and recover. In addition, interdisciplinary scientists are using 3D printing to make personalized organs on a chip to test the safety and efficacy of new drugs. This is eliminating the need for animal toxicity testing. Moreover, 3D printing may be able to provide personalized food and feed the world's growing population.

However, it's also important to look for hidden connections. For example, one substance used in 3D printing (UVR-6105) became popular decades ago because it's resistant to photobleaching by UV light. Also, it is less genotoxic than the substance it replaced (bisphenol A diglycidyl ether, or BADGE). However, UVR-6105 can undergo hydrolysis that can be catalyzed by either esterase enzymes or the acid in gastric fluid. The hydrolysis products are produced in an autopoietic system that resembles death more than life. The hydrolysis products are more bioavailable and more carcinogenic than BADGE. Instead, a silicone-based material is resistant to hydrolysis and has very low toxicity. It might be better for regenerative medicine and for making devices that will go into patients' bodies.

CRISPR technology is another important advance. It may be able to produce new cures for diseases as well as make new organisms. Sterile mosquitoes are being made that may eliminate malaria and the Zika virus. Genetically modified Bacteria and algae may be able to remediate pollution and make biofuels. However, there are many potential pitfalls. Just as many fear the uncontrolled dissemination of genetically modified foods into the environment, some fear the release of genetically modified Bacteria and plant seeds. Also, CRISPR could potentially make designer babies and people with super-human powers.

In the meantime, many people think that only natural remedies should be used and chemicals (prescription drugs) should be avoided. As a result, dietary supplements are widely consumed. Some are quite dangerous and

potentially deadly. So, a quick, easy way to see if your turmeric is adulterated with carcinogenic chromium (Cr^{6+}, hexavalent chrome) is presented. In addition, the different ways that prescription drugs and dietary supplements are developed, brought to market and sold are discussed.

Systems thinking is an interdisciplinary process requires scientists to learn other scientific disciplines. So, there is an Appendix in volume 1 that describes some basic chemistry to biologists. There is another Appendix in volume 2 that explains some basic principles of neurology, immunology and endocrinology to chemists and non-specialists.

Volume 2 starts by describing predictive, preventive, personalized and participatory P4 medicine. This includes the use of systems thinking in primary care medicine and an explanation of how our understanding of causality has changed. It also tells what P4 medicine does and how all the stakeholders are collaborating and using evidence based medicine. This includes the Advancing Regulatory Science Initiative and listening to the voices of the patients, in the spirit of TQM. There is also a description of how metabolomics shows what is happening within a patient's body and provides fundamental insight into the causes of diseases. Targeted radiation therapy is also described, along with precision systems medicine that targets cancer stem cells. The second chapter discusses the important role of inflammation. This includes dispelling some previous misconceptions on how dietary antioxidants work to prevent diseases, including cancer. Since nutrition and lifestyle are important in preventing diseases and maintaining good health, they are discussed in chapter 3. This includes an explanation of how the superfood cult is misleading many people – especially women. In fact, the only true superfood is mother's breast milk. The second volume finishes by describing the harmful effects of a toxic environment, with recommendations about trying to reverse the effects of global climate change through systems thinking. Then, there is an Appendix that describes the basic principles of the neuroendocrine immune system.

It's also important to be able to speak each other's languages. So, several examples are given of the same word, abbreviation or acronym being used in very different ways in different fields of science. Also, since many people who don't speak or write English as a native language can easily become confused by the way that numbers are written in English. The English language uses commas (like 10,000) where other languages use periods (like 10.000). So, in this book, the number ten thousand (and all larger numbers) are written using a space (like 10 000) instead of a

comma or period, except when directly quoting sources that were written in English.

This book also provides information that people can use in their work and their lives. For example, if a healthcare professional is ever challenged by someone who believes that he or she is part of a conspiracy to keep dietary supplements out of the hands of people who need them, he or she only needs to talk about folic acid. It's a dietary supplement that physicians and governmental regulatory agencies help people find and take to prevent birth defects and many types of cancer. It can be found in most breads and cereals, as well as vitamins for pregnant women. It tells how mother's breast milk is the only true superfood. Also, many databases, government websites and other internet sources are provided, along with over 1600 references to the scientific literature. There is also a list of hundreds of toxic substances that have been found in dietary supplements and information (*m/z* values that can be seen in a mass spectrometer) that chemists can use to detect them. Moreover, there have been cases where seemingly harmless supplements like vitamin D can be formulated wrong by manufacturers. So, educating physicians and patients on the adverse effects of high doses may be the most important way to prevent unnecessary or excess supplementation. Moreover, the FDA and other governments' regulatory agencies are not in a conspiracy to keep people sick. It is just the opposite. They and many other organizations and individuals are collaborating to make modern medicine predictive, preventive, personalized and participatory.

This work should not be taken as having an impact on the FDA or any other governmental regulatory agency.

CHAPTER ONE

PERSONALIZED MEDICINE

1.1 P4 medicine: predictive, preventive, personalized and participatory

One of the most important aspects of systems thinking in medicine and new drug development is predictive, preventive, personalized and participatory (P4) medicine [1-3]. It is an outgrowth of stratified medicine, in which people are separated or stratified into separate groups, depending on their genomes, so they can receive the proper therapy [4]. It engages patients and helps them prevent diseases, decide treatments and monitor recovery. Diagnostic tests are changing the paradigms for screening and diagnosing rare conditions. As a result, patients' susceptibilities to diseases can be predicted, along with the likelihood that specific therapies will succeed before starting clinical trials. Interventions will start at an earlier stage in the disease process, often pre-symptomatically, when they are much more cost-effective. Costs of clinical trials will drop while success rates increase when they are done on the correct patient populations. Treatments and potential cures for previously incurable diseases are emerging by separating people and diseases into distinct subgroups. So, people who have the appropriate genome and other –omes or biomarkers that will make them more likely to benefit from the drug being tested can be chosen for clinical trials to test the drug [1]. For example, if a drug or new molecular entity (NME) is being evaluated for treating cancer in patients who have a certain mutation in an oncogene, it would be best if the subjects in clinical trials have that same oncogene. In summary, personalized medicine customizes medicine by using molecular information to understand disease patterns more accurately, to diagnose them better, and to tailor preventive and therapeutic intervention more effectively with fewer side effects [2].

P4 medicine is also known as P4 systems medicine (P4SM) [5] because systems medicine is integral to it [5, 6]. The five pillars of P4SM are cutting-edge technologies, digital infrastructure, personalized data

clouds, new analytical tools and systems biology models. Systems medicine emphasizes prevention and individual participation in one's own health care. It is holistic and quantitative. It includes mathematical approaches in the practice of medicine and new drug development. That is, systems medicine emphasizes prevention and individual participation in one's own health care. It recognizes the important human need for patients and caregivers to be involved in preventing and curing their diseases. At the same time, mathematics is being used to analyze huge datasets from patients, while physicists, chemists, biologists and engineers develop the analytical tools needed to generate the data. All of this is linked through the Internet and used in mobile healthcare applications. So, systems medicine is the application of systems biology to the study of human health and disease [1].

The goal of P4 medicine is to prescribe appropriate, individualized drugs and medical devices for people with different types of nutrition, environment, genes, mRNA, miRNA, epigenetics and/or proteins [2]. Such treatments should be designed for the patient's specific anatomy (size), physiology and environment. Diagnostic devices can monitor vital signs, blood glucose, oxygen or other small molecules. They can monitor brain and heart activities with electroencephalography (EEG) or electrocardiography (ECG or EKG) and do diagnostic imaging. Some can even determine part or all of the genome, epigenome, transcriptome, proteome and metabolome of the patient and/or his or her diseased cells. This approach led to four anticancer drugs being approved by the FDA for use in patients who have specific genetic characteristics that can be identified by a companion diagnostic test [2, 7].

P4 medicine can use –omics data and biomarkers from many people to help everyone work with their physicians to make their own medical decisions [2, 7]. It can also use data from many different tissues or the same tissue at different times in single person. For example, the effects of anticancer therapy on a tumor over time can help physicians and patients predict the prognosis and guide subsequent therapy. Pre-emptive genome-based testing of adults and children in personalized health care is becoming very helpful. Diagnostic tests are now available for over 2000 Mendelian conditions. These tests are changing the paradigms for screening and diagnosing rare conditions. They are identifying patients who will most likely respond to preventive treatments or whose diseases or symptoms may progress differently when compared with others in the general population. Personalized medicine can help identify patients who are more susceptible to certain diseases or disease-related symptoms or are pre-symptomatic. Just as important, personalized medicine engages

patients and helps them prevent diseases, decide treatments and monitor recovery. As healthcare continues to be personalized, the public is expressing their desire to participate actively in healthcare decision-making that is based on analyzing their genomes. So, P4 medicine not only aims to prescribe the right medicines, but also maintain the mental and physical well-being of the patient and caregivers. In the process, systems biology and medicine work together to create a cycle of innovation [2, 7].

Sometimes, a combination of predictive biomarkers is used to make clinical decisions. For example, the effectiveness of anti-PD-1 immunotherapy depends on not just the presence of PD-L1, but also an inflamed T cell microenvironment [2]. The popular media have also joined in this effort. In 1995, scientists were on the Larry King show, asking for volunteers who had a history of prostate cancer to allow their genes to be analyzed. The response was wonderful. Many families were recruited from around the world, and their genes were mapped [2].

Moreover, systems medicine is making the care of people with diseases more cost-effective in both human and financial terms [2]. Treatments and cures for previously uncurable diseases are being developed. This is done, in part, by separating people and diseases into distinct subgroups [1, 2]. Genomic and analyses of other –omics and biomarkers can stratify people into subgroups based on their disease risks, likely reactions to drugs and other clinically relevant factors. For example, breast cancer, which was once classified as a single disease, is now stratified into clinically relevant subgroups based on interactions in genetic, molecular and cellular networks [8]. Stratifications of prostate cancer [9] and Crohn's disease [10] are making diagnoses more effective and interventions more cost-effective because they are based on the underlying causes of the diseases [1]. Surgical decisions are also being made based on disease stratification and individual needs. By focusing on the causes rather than the symptoms of a disease, physicians and patients are doing a better job of preventing diseases from occurring in the first place, or stopping them before they can cause serious damage. Moreover, as we identify and understand the biological networks that are perturbed in diseases, systems medicine will continue to provide a stream of new therapeutic targets for the pharmaceutical industry and biomarkers for patients and physicians [1, 2].

The goal is to develop drugs that will be more effective and have fewer costly side effects, because they will be more personalized [1, 2]. They will target specific strata of the populations of people and types of diseases. It will be cheaper for pharmaceutical companies to do clinical

trials if they are done on the correct patient populations. Interventions (including, but not limited to pharmaceutical interventions) will start at an earlier stage in the disease process, often pre-symptomatically, when they are far more cost-effective. The impacts of interventions will be more accurately monitored, allowing for adjustments to improve outcomes and reduce costs [1, 2].

As part of P4 medicine, almost everybody will have a personal data cloud, which will act as a medical record, with all the health data for each individual - including the genome, blood chemistry, lifestyle data (activity levels, diet and stress), transcriptome and gut microbiome [1, 2]. Actionable information will be given to individuals based on the analysis of data accumulated in their personal data cloud [1]. The data will be collected and analyzed to produce a stream of highly personalized information about each person's health and disease. Furthermore, actionable information can be supplied back to individuals based on the analysis of data accumulated in their personal data cloud. This will be given not just to physicians and other professionals, but also to individuals and those with whom they confide. Finally, systems biology and medicine are working together to create a cycle of innovation. As new biological insight inspires the development of new analytical tools, new tools and technologies produce new data, as new data drives the creation of more analytic tools that advance biological insight [1].

This has been happening ever since the decision was made in 1990 to sequence the human genome in 15 years [2]. Bioinformatic tools were developed and implemented to sort the billions of fragmented sequences into the complete genome (shotgun sequencing). This helped the International Genome Sequencing Consortium and others announce the complete DNA sequence in just 13 years, in 2003. Many government agencies, including the US FDA established collaborations with the Center of Excellence in Bioinformatics and Life Sciences (CBLS); Center for Functional Genomics; Center for Structural Genomics; Office of In Vitro Diagnostics and Radiological Health (OIR); and the Voluntary Genomic Data Submission (VGDS) Program and were quite helpful in solving the human genome. Then, in 2004, the FDA created the Genomics and Targeted Therapy Group. Numerous other groups were formed, including the Personalized Medicine Team in the Center for Biologics Evaluation and Research (CBER) in 2011 and the Division of Systems Biology at the National Center for Toxicological Research (NCTR). Also, the FDA has issued at least 21 guidances that relate to personalized medicines. This includes guidances on pharmacogenomics data submissions, tests, definitions, considerations, applying human factors and cGMP requirements

for combination products. However, reductionist thinking led some to believe that once we knew the entire 'book of life', the role of every gene would be identified and a new age of medicine would appear. Surprisingly, when researchers started knocking out individual genes in mice, they often found that it had no effect. Systems thinking was needed to realize that our genes are just one part of a much more complex whole that comprises the human body and influences health and disease [2, 7].

1.2 Systems primary care medicine

Systems biology started with the goal of "making sense of the genome and its relationship to the whole organism (phenotype) through computational and mathematical modeling" [5]. It integrates holistic data into mathematical models. We are now able to make many measurements and determine several –omics at a higher speed and lower cost that was previously thought. So, very large sets of data are generated, while bioinformatics and computer analysis try to make sense of them. Systems medicine is "the emerging medical application of systems biology to medicine" [5]. It views a human as of a dynamic, integrated complex network and a system of systems. It aims to expand the field of personalized medicine so that it no longer uses reductionist thinking to focus on just genes. Instead, it is holistic and integrates many aspects of biology and biochemistry. It is guided by systems theory. In this process, systems medicine hopes to consider the great complexity of human health and disease, while counteracting fragmentation. Even though this may be relatively new in the field of new drug development and in many medical specialties, it has always (and still does) apply to primary care and family medicine. That is, good, effective primary care physicians (general practice or family medicine) have always tried to communicate well with their patients, whom they know as whole persons with their own life circumstances, close relationships, goals and values. Primary care physicians are especially important because they are the first point of contact for patients seeking help. It is also general, unlike specialties focusing on bodily subsystems or single diseases. The generalist aims to provide the best possible, tailored care for each individual as a whole, complex person who often presents previously uncategorized health problems. They try to help their patients achieve the goals that are meaningful to them. The challenges of primary care medicine are strongly linked to the health problems with which it must deal. Non-communicable, chronic (long-term) and costly health problems are seen quite often. They exhibit multimorbidity and even medically unexplained symptoms. The

primary care physician, as a specially trained human professional, models each patient as a whole person, while integrating a variety of fragmented information to make predictions about what is best for that person at that time. This has been done for quite a long time. Even before science became involved in medicine, traditional healers always considered the socially situated whole person. So, personalized medicine has always had a humanistic nature. However, modern systems medicine has added a technoscientific meaning, which has been called technoscientific holism [5].

This has led some to think that computers will eventually be smarter than physicians – especially when it comes to diagnosing diseases and recommending therapies [5]. They ignore the fact that diseases and therapies can't always be reduced to things that computers can recognize as distinct phenomena. In fact, systems biology considers health and disease to be a continuum. Moreover, different diseases are not distinct, but fluid, interlinked and overlapping phenomena. So, a systems view of disease and health requires using more than just computers [5]. It also needs a human touch as well as some theory and/or philosophy.

1.3 Causality in P4SM

For example, P4SM is consistent with "a systems view where no level is causally or epistemologically privileged" [5]. However, some people feel that there is downward causation or biological relativity [5, 6]. That is, "the whole, with its emergent properties, has some sort of causal or constraining influence over the parts by which it is constituted" [5]. This contradicts reductionist thinking that believes in upward causation. That is, the whole person can supposedly be defined and controlled by the individual parts – especially the genes.

There is an intermediate approach that focuses on organs instead of molecules, metabolites, genomes or cells [6]. It is a middle-out approach that views the human body as a total system of inter-connected cells, tissues, and organs. These are connected by biochemical signals and are controlled by combinations of factors. This has led to an increased interest in physiology that incorporates systems biology. Dynamics and control mechanisms are being illuminated as new, advanced laboratory methods emerge. They are able to recognize the metabolic and regulatory activators as well as the metabolites that are produced by the activities of cells. There is much interest in learning on how different parts interact, communicate, and function in relation to one another across subsystems and ordinary boundaries. Multi-level boundaries in cells and tissues are crossed as

information is passed between different parts. This interest in studying regulatory channels, communication methods and cascading molecular networks is modernizing and improving the more traditional mechanistic approach. This is an interdisciplinary approach that includes dynamic theory design and engineering control models [6].

This approach includes the Human Physiome Project (HPP) [6]. It uses a global network of scientists and physicians who are studying physiology and the ways that organ systems function. The goal of the HPP is to study physiologic problems and create models, while continuing further investigations that should include additional parts of the models as they are discovered. Computational modeling is a key aspect of the HPP. As each team of investigators works on their personal areas of interest, they share their results with others to generate a whole picture. Hopefully, this will lead to computational predictive models for individual patients as well as for entire populations. Another important goal of the HPP is to create a Virtual Human Patient model. It will be a computer graphic of individual physiologic models for each patient [6]. This is building on earlier work by Noble and colleagues that became the Cardiac Physiome Project [11]. Eventually, it is hoped that anyone will be able to visit a physician and obtain a computed Virtual Human Patient model so they will be able to discover their susceptibilities to diseases, track their health and the progress of any diseases that they may have and suggest the best treatments or ways to prevent the diseases from emerging [6].

1.4 Explanation, prediction and control in P4 medicine

In contrast, some systems thinkers think that P4 medicine should still have the goals of explanation, prediction and control. They feel that the whole person and his or her health are quantifiable, predictable and controllable. Supposedly, this can be done by quantifying the interactions of biochemicals in networks. However, bioinformatics, machine learning techniques and artificial intelligence may not be able to interpret large data sets without proper theoretical guidance. Moreover, a virtual human is not a real human and not everybody has the same goals or challenges. There are some human factors that most likely will never be quantified [5].

So, personalized medicine has been defined as, “the ability to customize medicine using molecular information to more accurately understand disease patterns and diagnose disease, as well as to tailor preventive and therapeutic intervention more effectively with fewer side effects” [12]. “It includes not only prescribing medicines, but also maintaining the mental and physical well-being of the patient and care

givers. Pre-emptive genome-based testing of adults and children in personalized healthcare is becoming very helpful, especially when studying diseases with Mendelian inheritance. Diagnostic tests are now available for over 2000 Mendelian conditions. These tests are changing the paradigms for screening and diagnosing rare conditions. Personalized medicine can help identify patients who are more susceptible to certain diseases or disease-related symptoms or are pre-symptomatic. It will identify patients who will respond to preventive treatments differently or whose diseases or symptoms may progress differently when compared with others in the general population. Just as important, personalized medicine engages patients and helps them prevent diseases, decide treatments and monitor recovery. As we continue to personalize healthcare, the public is expressing their desire to participate actively in healthcare decision-making that is based on analyzing their genomes" [12].

1.5 What P4 medicine does

Personalized medicine "tailors medical treatment to the individual characteristics, needs and preferences of each patient" [7]. Actually, it has been used for over 100 years to analyze blood types, to ensure that transfusions don't cause hemolytic reactions. Also, over 50 years ago the genetic basis for the selective toxicities of fava beans and an antimalarial drug (primaquine) was discovered. It is a deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD) that is important in metabolism. Then, in 1977, different isozymes of cytochrome P450 2D6 (CYP450 2D6) were found to cause the effects of the anti-hypertensive drug debrisoquine to be exaggerated and last longer in some people than in others. So, genetic differences can cause different pharmacokinetic parameters, such as area under the curve, or AUC. Pharmacogenomics is "the study of how variations of DNA and RNA characteristics affect responses to drugs. It has been a crucial part of personalized medicine for decades" [7].

1.6 Examples of P4 medicine

In chapter 3 of volume 1, some examples of personalized medicine were given. For example, high throughput screening (HTS) is being used in personalized medicine when cells come from the individual patient. So, the potential cardiotoxicities of NMEs that inhibit protein tyrosine kinases (PTKs) were evaluated by HTS that used human induced pluripotent stem cells (iPSCs) to produce cardiomyocytes, endothelial cells and cardiac

fibroblasts. That way, the effects of several FDA-approved PTK inhibitors on different types of heart cells were determined. One unexpected discovery of the study was that cardiotoxicity can be alleviated by activating insulin and insulin-like growth factor signaling [13]. In addition, 3D models are being made from iPSCs that are unique (or personalized) for every patient [14]. Also, organ chips are engineered to mimic and recapitulate important aspects of physiology. They can be used to assess the phenotype of the cells by measuring the expression of genes, as well as the structure, metabolism and function of the cells that are seeded into microenvironments that recapitulate healthy or diseased conditions. When cells are taken from the patient, they can be used to specifically model inherited pathologies at preclinical costs and used on just those who have personalized genetic backgrounds [14]. Moreover, J. Craig Venter has started a new company, Human Longevity Inc™ (HLI) [15]. Its goal is to give "everyone access to the power of data-driven health intelligence". They have already published the results of deep sequencing of 10 545 human genomes [16]. A wholly owned subsidiary of HLI, called The Health Nucleus does extensive testing of clients [17]. They analyze their genomes, gaits and fecal microbiomes. Clients get a prognosis of their present and future state of health. The data gives them information that they can use to modify their diets and behaviors [18]. In addition, Google and Arthur D. Levinson started a company called Calico that aims to "harness advanced technologies to increase our understanding of the biology that controls lifespan. We will use that knowledge to devise interventions that enable people to lead longer and healthier lives" [18]. There are other companies that are using data-driven –omics data to improve wellness and/or longevity by providing personalized advice on nutrition [19]. They include Arivale [20], Day Two [21] and Google Baseline [22]. There are even some companies that do personalized analyses of microbiomes [19]. They include American Gut [23], Enterome [24], Second Genome [25], Seres Health [26] and DELETE Vedanta Bioscience [27]. So, this is another example of how industry is working with people in an open collaboration to improve health. None of these companies or organizations are in a conspiracy to keep people sick.

Instead, they are developing and prescribing different drugs and medical devices for people with different genes, mRNA, miRNA, epigenetics and/or proteins, as well as various levels of nutrition, while living and working in different environments [2]. These treatments are designed for the patient's specific anatomy (size), physiology and environment (be it the home, hospital or Intensive Care Unit). Diagnostic devices can monitor vital signs, blood glucose, oxygen and a

variety of small molecules. Some of these devices can perform electroencephalography (EEG) or electrocardiography (ECG or EKG) and do diagnostic imaging. Some can even analyze the genome, epigenome, transcriptome, proteome and metabolome of the patient and/or his or her diseased cells. Also, the patient's blood or tissues can be assayed for different types of enzymes (including CYP isozymes) that catalyze reactions that can metabolize drugs differently and affect their bioavailabilities, or abilities to bind to different receptors. This genetic approach led to the development and rapid approval of tratuzumab, or Herceptin®, for treating and curing patients who have the HER-2 gene that is involved in many cancer signaling pathways. More recently, it led to four anticancer drugs being approved by the FDA "for use in patients who have specific genetic characteristics that can be identified by a companion diagnostic test" [2, 7]. A similar approach was used to find patients with cystic fibrosis (CF) who would respond to a new drug.

Kalydeco® (ivacaftor) was approved for patients with a specific genetic mutation (glycine to aspartic acid on amino acid 551, or G551D) [28]. Kalydeco® was the first drug to address the underlying cause – rather than the symptoms – of CF. Personalized medicine is also important in pediatrics [28]. Genetic tests are available that can be used before conception to detect mutations that are associated with over 150 genetic disorders. After conception, prenatal tests of the mother's blood can diagnose many genetic diseases. Still, many childhood diseases have multiple causes, so they still need personalized medicine. For example, children with type-1 diabetes must monitor their consumption of carbohydrates and monitor their blood glucose concentrations. Unlike adult-onset type-2 diabetes, which can be caused by decades of over-consumption of sugars, fats and calories, type-1 diabetes is not. Still, both types of diabetes require P4 medicine. It must be predictive, preventive, personalized and participatory. Unfortunately, type-1 diabetes is not so predictable or preventable, but type-2 can be prevented in many cases by adjusting one's diet and lifestyle. Both are personalized and participatory as each patient or their caregiver must provide medicine, control their lifestyle and diet, and monitor their blood glucose. There are also *in vitro* fertilization techniques to help couples have a baby. If the mother has a mitochondrial disease, the nucleus from her fertilized egg can be transplanted into the enucleated embryo of another woman. The embryo has functioning mitochondria and can be transplanted back into the mother [28].

One measure of the advance in P4 medicine is that about 2% of the population of the USA uses or has used genetic tests [29]. There are about

1000-1300 tests available for about 2500 conditions and new tests are emerging rapidly. A survey of healthcare claims data for 32 million people in the USA from 2008–2011 found that the cost grew by 14% per year between 2008 and 2011, primarily resulting from increased utilization. They predicted that genetic testing and molecular diagnostics use will continue to grow in the next five years. Moreover, by strengthening the ability to collect and analyze data in P4 medicine we will promote positive changes that benefit patients [29].

Also, scientists are working to develop hand-held devices that will prick the finger and quantify about 2500 organ-specific proteins from all the approximately 50 human organs [30]. The data will be sent by wireless communication to a file server, which will analyze the data and email a report to the physician and patient. Hopefully, this will enable a rapid evaluation of current health. Also, our genomes and metabolomes will enable predictive and personalized medicine. Physicians will learn how to use drugs to re-engineer metabolic networks that have been perturbed by the beginnings of a disease, before symptoms can emerge. Moreover, education will put patients in the position to take more responsibility for charting their own future health choices [30].

Individualized medical devices are being made, too [7]. Three-dimensional (3D) printing was used to make a bioresorbable tracheal splint for an infant who was critically ill. Furthermore, research on induced pluripotent stem cells (iPSCs) will enable people to use their own cells to biosynthesize their own organs when they need a transplant. So, advances in genomics, medical imaging, 3D printing and regenerative medicine, along with increased computational power and the advent of mobile and wireless capabilities, are allowing patients to be treated and monitored in ways that better meet their individual needs [7]. Many surgeons are now able to print 3D models obtained from MRI and/or CAT scans before they perform the surgery. That way, they can see ahead of time what they will face during surgery. At the same time, 3D models can be used by interns to develop and practice surgical techniques before they do their first real surgery.

There are many examples of personalized medical devices [2, 7]. A customized tinnitus masker tailors audio signals to suit each patient's hearing requirements. Pedicle screw spinal systems can be assembled by physicians to fit each patient's unique anatomy based on MRI and/or CT images. There is a software-based EEG analyzer that predicts one's response to various psychotropic drugs. The device predicts the probable response to various medications to help guide clinical decisions. There is also a Zenith Fenestrated AAA Endovascular Graft for patients with

abdominal aortic or aortoiliac aneurysms having morphology suitable for endovascular repair. Each device is tailored to the patient's individual aortic anatomy. Finally, there is an artificial pancreas under clinical investigation that monitors the concentration of glucose in the blood and delivers the proper dose of insulin to diabetics [2, 7].

The FDA and other governments' regulatory agencies evaluate applications for new medical devices and drugs. So, the following goals were described in a recent report from the FDA [7]: "Personalized medicine seeks to reduce the burden of disease by targeting prevention and treatment more effectively. With the help of personalized medicine, the health care management paradigm will focus on prevention, moving from illness to wellness, and from treating disease to maintaining health. By improving our ability to predict and account for individual differences in disease diagnosis, experience, and therapy response, personalized medicine offers hope for diminishing the duration and severity of illness, shortening product development timelines, and improving success rates. At the same time, it may reduce healthcare costs by improving our ability to quickly and reliably select the effective therapy for each patient while minimizing the costs associated with ineffective treatment and avoidable adverse events" [7].

1.7 Important collaborations in P4 medicine

The US FDA and other countries' regulatory agencies are collaborating with industry and academia to build an elaborate infrastructure to support personalized medicine. This has been described as the five pillars of systems medicine: cutting-edge technologies, digital infrastructure, personalized data clouds, new analytical tools and systems biology models [1, 2]. Advanced technologies and algorithms can gather and analyze data, while setting up user-friendly databases for further analyses. For example, in 2003 the US NIH started the ENCODE project to identify and define the functional DNA elements that are required for normal genome function. In 2012, about 40 articles were published describing the results that came from an international effort. It is anticipated that the Internet and mobile telecommunication will establish a data cloud in the near future – hopefully for everybody who wants it. It will contain medical records, including the genome, blood chemistry, lifestyle data (activity levels, diet and stress), transcriptome and gut microbiome. Actionable information will be given to individuals based on the analysis of data accumulated in their personal data cloud. Attempts are being made to establish quantitative metrics to help decide when a person is healthy, pre-disposed

to a disease, or in various stages of a disease. The data will also help find biomarkers that will be used to suggest the best therapies for each individual, while monitoring the treatment process, making necessary changes when new conditions emerge [1, 2].

Also, the US National Cancer Institute (NCI), the Moffitt Cancer Center and Stanford University School of Medicine met at the Medicine 2.0 conference in Boston in 2010 [31]. They discussed how sociotechnical frameworks, informatics platforms and health-related policies can be used to encourage data sharing and innovation. This built on the Institute of Medicine's vision for a rapid learning health care system that is encouraging an open source, population-based approach to cancer prevention and control. This learning system is based on a sufficiently advanced digital health infrastructure and "rapid, seamless, secure exchange of useful, standards-based information among authorized individual and institutional senders and recipients" [31, 32]. A learning system that is being used in oncology is called the American Society of Clinical Oncology's Cancer Learning Intelligence Network for Quality (CancerLinQ) system [31, 33]. It was designed to address the growing challenge of managing the huge amounts of data that are emerging from P4 medicine for cancer care. It incorporates data from researchers, providers, and patients so comprehensive clinical algorithms reflecting preferred care at a series of decision nodes for clinical decision support can continually improve [31]. There are also immunology datasets that are available at the National Institute of Allergy and Infectious Diseases ImmPort website [34]. To help encourage open collaborations, the US government passed the America COMPETES Act as part of the Open Government Initiative [28]. This has led to unprecedented amounts of data being available to the public. Two examples include the Data.gov platform, which provides public access to "nearly 450,000 datasets…across 172 federal agencies" [35] and one million microarray measurements of gene expression [36].

In addition to sharing data, public and private entities are collaborating to accelerate innovation [31]. At the same time, the US government's NCI and the Office of the National Coordinator for Health Information Technology (ONC) are working together with the federal Small Business Innovation Research (SBIR) grant program to support the evaluation and dissemination of evidence-based applications for cancer prevention and control [37]. They incorporate crowdfunding to encourage further collaborations and perform market validation of innovations [38].

The FDA is also collaborating with other governments, academia and pharmaceutical companies to develop regulatory standards, reference

libraries, research methods, and tools that can be used to integrate biomarker identification into drug and device development and help make clinical decisions [2, 7]. "The biomarker qualification program aims to provide a framework for scientific development and regulatory acceptance of biomarkers for use in drug development, facilitate integration of qualified biomarkers in the regulatory review process, and encourage the identification of new and emerging biomarkers. There is also a project on microarray and sequencing quality control, a genomic reference library for whole genome sequencing (WGS) platforms and a virtual physiological patient. They are also building a high performance integrated virtual environment (HIVE) for next generation sequencing analysis. Also, high resolution human leukocyte antigen (HLA) typing systems are being developed, as well as molecular tools to facilitate blood group typing. The FDA and other governments' health care agencies are working with others to design and conduct clinical trials better. They are refining the design of clinical trial and the statistical methods of analysis to address issues such as missing data, multiple endpoints, patient enrichment, and adaptive designs that often arise when developing targeted therapeutics. They are also looking closely at clinical trials of anticancer drugs. This is complicated because many cancers are heterogeneous, each with their own specific genetic makeup. This heterogeneity is one reason why different people with cancer in the same organ respond differently to the same therapies. The I-SPY 2 trial is a collaborative initiative developed under a unique public-private partnership. It includes more than 20 cancer centers. They are trying to better understand heterogeneity and complexity to provide targeted therapies" [7].

It is also essential to have adequate and robust statistical methods to analyze the data that is produced [2, 7]. So, scientists at Booz Allen Hamilton, the FDA supercomputer center, the Genomics Evaluations Team for Safety (GETS) and the Office of Vaccines Research and Review (OVRR) in CBER have been comparing different methods to analyze genomic data to predict patient outcomes and/or prognosis. CDER and CDRH (Center for Devices and Radiological Health) have also been developing new device diagnostics to improve drug safety. They are assessing new device-based algorithms and biomarkers that can distinguish between benign and malignant drug-induced QT prolongation (time between the start of a Q wave and the end of a T wave) in an electrocardiogram [2, 7].

The National Center for Toxicological Research (NCTR) is also studying the biology of cancer [2, 7]. They found that many tumors carry subpopulations of KRAS (Kirsten rat sarcoma oncogene) in mutant cells.

These mutations can lead to acquired resistance to some anticancer drugs. Effective treatments to prevent drug resistance in tumors are being identified by using defined genetic profiles. Also, researchers at CBER are identifying genetic determinants of immunogenicity in patients with Hemophila A. The eventual goal is to predict each patient's risk of immunological response to a given protein therapy before it is used in treatment. Other researchers at CBER are trying to understand better the effects of DNA modifications on the quality of protein products coded by them. By looking at proteins that are involved in blood clotting as models, they demonstrated that while "synonymous" or "silent" mutations do not affect the protein sequence, they may affect protein concentrations as well as protein folding and function. The goal is to determine which mutations are deleterious and which may be safely employed in the design of therapeutic protein products. Hopefully, this will lead to new tools and methods for evaluating the properties of proteins from the gene sequence [2, 7]. "This could have many diverse implications for developing and evaluating safe and effective protein therapeutics, including biosimilar products" [7].

CBER's Office of Vaccines Research and Review (OVRR), together with the Genomics Evaluations Team for Safety (GETS) are also involved in collaborations to identify genetic risk factors that are associated with adverse reactions to vaccines [2, 7]. In addition, the Centers for Disease Control (CDC) and Northern California Health Care (Kaiser Permanente) are trying to see if there are genetic risk factors that predispose children to febrile seizures (caused by high fever) after MMR vaccination. At the same time, the Innovation Center for Biomedical Informatics (ICBI) at Georgetown University is trying to identify genes that are associated with links between vaccines, vaccine components, and several autoimmune diseases. The goal is to help test the hypothesis that autoimmune diseases might occur as adverse reactions to some vaccines [2, 7]. "Pathway models derived from this data may help predict autoimmune reactions to vaccines and other medical products in the future" [7].

Scientists at NCTR are collaborating with the University of Liverpool (in the UK) and the Huashan Hospital (China) to do whole genome sequencing and genetic analyses to identify susceptibilities to carbamazepine-induced hypersensitivity reactions [2, 7]. They are also collaborating with the University of Maryland to identify genetic factors that might interact with certain aspects of lifestyle in the Amish community to see if they contribute to heart disease. The metabolic responses of volunteers were examined after consuming specific diets and drugs that are associated with cardiovascular risk. This included blood

triglyceride concentrations after a high fat meal, blood pressure after consuming much salt (NaCl) with a meal, and platelet aggregation response after taking aspirin or clopidogrel. The DNA from people in the Amish community who showed abnormal responses was sequenced. Genetic association studies are also being done. This work is ongoing. As possible genetic markers are discovered, they are being validated in another group (cohort) of Amish subjects. Identifying genetic factors that interact with drugs or certain diets to increase risks of cardiovascular disease or the efficacy of treatment will lead to patients and their physicians using personalized medicine to improve health [2, 7].

At the same time, the National Cancer Institute (NCI), the National Institute of General Medical Sciences (NIGMS), the University of Maryland and FDA are trying to see if increasing the dose of clopidogrel can increase antiplatelet responses in people who have genetically reduced CYP2C19 metabolism compared to those with normal metabolism [2, 7]. Also, scientists in the Office of Science and Engineering Laboratories at CDRH are using new methods to analyze electrocardiograms to predict which patients will benefit from cardiovascular therapies such as cardiac resynchronization therapy. They can diagnose problems with electrical conduction and quantify scar tissue in the heart. They use different criteria for women and men, since women tend to benefit significantly more than men from cardiac resynchronization therapy. Similarly, the Office of Science and Engineering Laboratories at CDRH is collaborating with George Washington University to develop a microfluidic, high-throughput microchip to test the interaction of tears with contact lenses, care products, and microbes. They aim to provide individual testing results that can guide the prescription of lens materials and hygiene products for patients. So, from the perspective of the FDA and other governments' regulatory agencies, the era of personalized medicine has arrived [2, 7].

So, the FDA has a website with information on personalized nutrition and medicine provided by the Division of Personalized Nutrition and Medicine (DPNM) [2, 39]. The Division has two areas - Biometry and Biology. The main function of Biometry is to develop biometrical methods for all aspects of the FDA's mission, goals and objectives. A subgroup within Biometry analyzes all data from the National Toxicology Program (NTP). The Biology area is studying the broad areas of pharmacogenomics and nutrigenomics - how individuals respond to drugs and nutrients in foods. The overall goals of the DPNM are to develop and implement research strategies that will be able to account for genetic, environmental, and cultural factors that influence the expression of genetic makeups and