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Chapter 1

IMPACT OF PERSONALIZED MEDICINE IN CANCER

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ABSTRACT

Personalized medicine aims to customize therapeutic care based on a person's unique genetic profile. Physicians have tailored care based on individual's health history and the environment. However, the decoding of the human genome in 2003 was an important step towards breakthroughs in personalized medicine, as a clinical care that takes benefits of molecular tools to facilitate highly specific health care based on individual's unique genomic and molecular characteristics. Pharmacogenetics refers to a single gene that influences drug metabolism. However, pharmacogenomics encompasses all genes in the genome that may determine the drug response. Pharmacogenomics enables the improved understanding of disease pathogenesis through genomics research, via identification of new biomarkers for cancer diagnosis. Pharmacogenetics and pharmacogenomics are around to revolutionize the aspect of medicine; yet, many challenges stand in the way. Hike in the cost of genotyping make genetic profiling less attractive and its clinical implementation is also lagging far behind. This book chapter presents an overview of the opportunities and challenges that influence the

participation of personalized approach of giving the right drug at the right dose to the right patient.

Keywords: personalized medicine, cancer, pharmacoproteomics and metabonomics, pharmacogenomics

INTRODUCTION

Personalized medicine approaches to provide excellent health services by using advanced genomics technologies and family histories to more efficient therapeutics for individual patients. The primary objective of personalized medicine is translating the core science into clinical practice. Advancement of pharmacogenomic technologies provide better prescriptions to distinct sub-populations and possibly individuals, based upon genetic make-up that led to improving the effectiveness and safety of drugs.Although Watson and Crick explained the structure of double helix of DNA in 1953, still it took more than 50 years to complete the human genome project. It is among the grand discoveries which disclose the lots of unanswered question; this is international demand for the study of human genetics. Human genetics have two main objectives, 1) Mapping of the human genome sequence. 2) Use of new information generated from genomics for diagnosing, preventing and treating disease.

Progress toward personalized medicine, even after 10 years following the sequencing of the human genome remains slower than expected. Two potential factors that might be responsible for limited progress 1) the restrictions of genetic prediction and 2) the shortage of appropriate financial incentives. The theory behind the personalized medicine is that everyone should get the same care based on clinical trials. A prospective application of personalized medicine is to recognize individuals at elevated risk for diseases such as cancer by using Pharmacogenetics, pharmacogenomics, and pharmacoproteomics. Earlier physicians used family history to decide the individuals at augmented risk and to recommend preventive measures. Scientific advancements augmented the perception to define an individual's risk for particular disease based on their genetic make-up. Various fields of translational research such as "*omics*"(genomics, proteomics, and metabolomics) aims to study the contribution of genes, proteins, and metabolic pathways that can lead to disease susceptibility. It is predictable that advances

in these fields will facilitate to develop new diagnostic approaches, drug development, and individualized therapy.

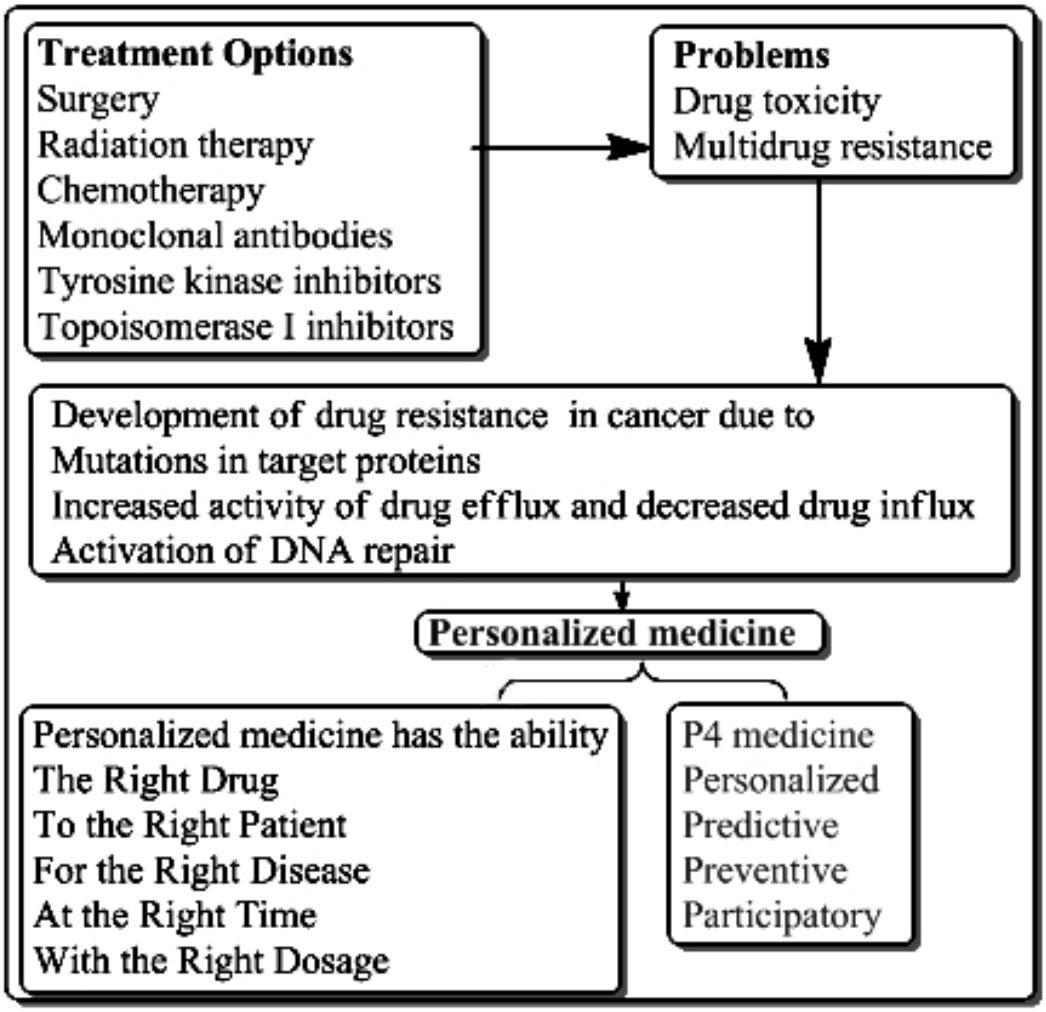

Figure 1. Short map of origin of personalized medicine.

Today personalized medicine is defined as the right treatment for the right person at the right time. Moreover, genomics is the study of individual's genes while proteomics is the study of the proteins that genes express for the character. Genomic testing helps in identifying an individual's susceptibility towards disease, predicting patient's response to a particular drug, and corresponding patients with the right therapeutics.Personalized medicine is referred to as P4 medicines because of its four characteristics are shown in figure 1. Genotype of each is unique and differs in closest relatives. These differences are extremely significant in determining the individual's medical course through life and their response to the environment. Preferably, in the

future, a comprehensive, unique genetic profile of each patient's will be available to physician's best diagnostic and therapeutic for treating that individual. The term "personalized medicine" is now being used to describe the concept of tailoring medical care by detectable genetic differences between patients. In the genomics era, the nature and treatment of different disease are redefined at a molecular and genetic level that is unique to each patient. Genetic differences may never manifest during times of wellness but can be of critical importance in the face of disease.

FOUNDATION OF PERSONALIZED MEDICINE

Pharmacogenetics, pharmacogenomics, toxicogenomics, metabonomics, and pharmacoproteomics are the basic foundation of personalized medicine.

Pharmacogenetics

Pharmacogenetics is the study of the genetic variation in response to drug and used as a predictors of drug efficacy and toxicity. More than 1 million genetic markers recognized as single nucleotide polymorphisms (SNPs) have become accessible for genotyping and phenotyping studies. There are many techniques for the genotyping and phenotyping; these are oligonucleotide genomic arrays, gel electrophoresis and flow cytometry, classic gene sequencing, mass spectroscopy, and microarray or gene chips. Single nucleotide polymorphisms play a significant role in the study of complex diseases such as asthma, diabetes mellitus, atherosclerosis, and psychiatric disorders. SNP map will elaborate the identification of genes for such complex diseases. To date, more than 3 million SNPs have deposited into the SNP consortium's public database (http://www.snp.cshl.org). Pharmacogenetics focuses on two key principles: pharmacodynamics and pharmacokinetics.

Pharmacodynamics

It describes the pharmacological effects of a drug on the target biologic pathway. How a drug effect the body, its biochemical and physiological effects on body, mode of action and the relationship between drug concentration and its effect on the body.

Pharmacokinetics

It describes the course of drug and metabolite levels in different tissues and incorporates drug absorption, distribution, metabolism, and elimination.Thus, pharmacodynamics can be viewed as what the drug does to the patient, whereas pharmacokinetics is what the patient does to a drug. It is widely accepted difference.

Pharmacokinetics or Pharmacodynamics

Pharmacokinetics or pharmacodynamics can lead to variable drug efficacy or risk of toxic effects. Thus, the goals for the clinical application of pharmacogenetics are to predict patients who are most likely to obtain the desired therapeutic effect from the drug and to predict patients at high risk of toxic effects (and to whom a lower dose or a different drug would be administered).

Pharmacogenomics

Pharmacogenomics is the study of the application of genomics to the study of human variability in drug response. Pharmacogenomics illustrate the task of the whole genome in the both condition disease susceptibility and drug response. Pharmacogenetic variations classified into three main types 1) pharmacokinetic 2) pharmacodynamic3) idiosyncratic. The term, "pharmacogenomics" is more encompassing as it describes the impact of genomic information on the drug discovery process. Therefore, pharmacogenomics includes identifying the individual's genes and polymorphisms, correlating polymorphisms with therapies, predicting the drug response, clinical outcomes, reduction in adverse events, and selecting the dose of medicines based on genotype. Thus, the prediction of polymorphisms results in reducing the adverse reactions, enhancing the design of rational drug development, and ultimately drug prescription. Some of the expected long-term benefits of pharmacogenomics include the potential for "personalized" prescriptions, improved patient compliance, reduction or elimination of certain adverse events and the decline in the cost of disease management.

Toxicogenomics

Toxicogenomics is the study of gene expression patterns using high-throughput microarrays, automated reverse transcription– polymerase chain reaction, nuclear magnetic resonance, and proteomic strategies designed to detect up-regulation and down-regulation of genes associated with risk for toxic drug effects. Toxicogenomic markers for adverse side effects might influence selection and optimization of lead compounds before human studies.

Metabonomics

Metabonomics combines the study of individual genetic variation (pharmacogenetics) and diseased tissue gene expression (pharmacogenomics) with systems biology to predict the potential impact on drug metabolism. The relationships between "endogenous" metabolic processes (coded in the genome and intrinsic to cellular function) and "xenobiotic" (foreign compound) metabolism are poorly understood. This led to the consideration of the ability of a variety of mathematical models to predict the metabolic fate in humans of newly discovered candidate compounds.

Pharmacoproteomics

Pharmacoproteomics has been defined as a subdiscipline of functional genomics that computed the qualitative and quantitative changes in the disease markers in response to the drug. Pharmacoproteomics is a paired approach to pharmacogenomics that applied gradually for better drug treatment. Currently, unlike DNA or RNA, the magnitude of proteins in a clinical sample cannot be augmented by an amplification step. Thus, proteomic analysis often is sample limited, thus a fact that drives the development of ever increasing sensitivity for the new analytic technologies. The primary methods of proteomics include 2-dimensional gel electrophoresis (2DGE) and both matrix-assisted (MALDI) and surface-enhanced (SELDI) mass spectroscopy approaches. 2DGE, MALDI, and SELDI have been used to predict the toxic effects of several drugs, including cyclosporine, statins, and anticancer drugs. Proteomics also has been used to extend circulating biomarker profiles that can constantly predict the safety profile of a various medicine. The mass spectroscopy approach also has been sophisticated by the use of radioactive isotope–coded

affinity tagging of novel compounds, a practice that increases the sensitivity and improves the categorization of proteins involved in drug metabolism.

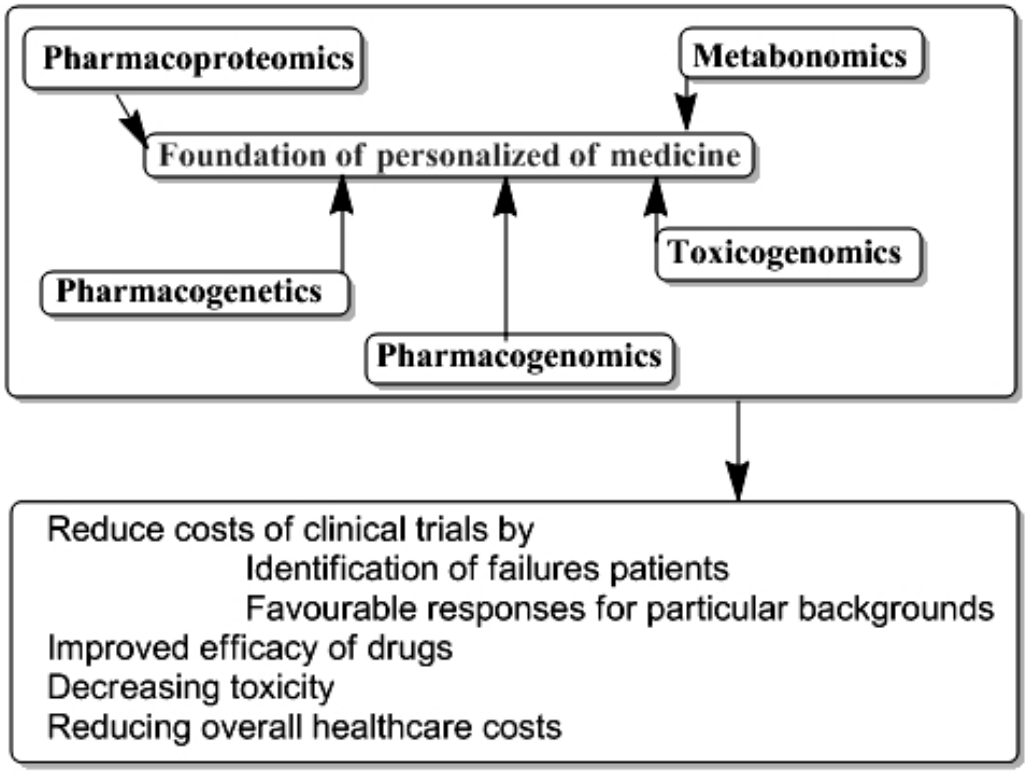

Figure 2. Foundation of personalized medicine.

Personalized Medicine in Cancer

The present approach to cancer treatment referred to as rational drug design or combinatorial drug design. This practice is ineffective and led to drug toxicity. In contrast, personalized treatment has the proper perspective to boost efficacy and diminish toxicity. To attain personalized treatment for cancer patients, we require markers to determine prognosis, predict response to therapy and severe toxicity related to treatment. Pharmacogenomics is a fast growing field that aims to illuminate the genetic basis of drug response that led to the prediction of the toxicity. Pharmacogenomic approaches have been applied to the existing chemotherapy agents, to identify important inherited variations that effectively predict patient's response to chemotherapy. These inherited variations include insertions, deletions, and RNA splicing. Such genetic polymorphisms in drug-metabolizing enzymes, molecular targets and transporters have been actively explored concerning functional changes in

phenotype and their contribution to variable drug response.The major objective of the budding disciplines of pharmacogenetics and pharmacogenomics is to personalize therapy based on an individual's genotype. To date, the success of pharmacogenetics and pharmacogenomics has spread across all fields of medicine. Genetic information is crucial for chemotherapeutic agents, which affect both tumor and nontumor cells and thus have a thin therapeutic option, and increase toxicity. Medical oncologists and hematologists are making efforts to individualize cancer treatment which would maximize efficacy and minimize toxicity in patients. Identification of host genetic variations may contribute to amplify the drug effectiveness and reduce the risk of toxicity; this would provide a means to tailor therapy.

CONCLUSION

The present approach to complex disease (diabetes and cancer) treatment often referred to as "trial and error" or "one size fits all." This is an unproductive practice, which led to toxicity. In contrast, personalized treatment has potentially augmented efficacy and decreased toxicity. Completion of human genome project discloses many clues for the treatment of complex disease by the genomics. Now pharmacogenetics converts to pharmacogenomics. The understanding of disease pathogenesis improved through genomics research, via identification of new biomarkers for cancer diagnosis. However, such interventions will more likely be made available to individuals who are eligible by novel biomarkers rather than on genetic risk profiles. Instead of all these technological advancements sometimes people encounter such situations where genome-based prediction becomes more or less as good as the prediction based on traditional risk factors. To popularize these techniques, it is essential to reduce the cost of genotyping so that genetic profiling may become more economical than disease prediction based on traditional risk factors.

Although pharmacogenomics improves our understanding of drug response still, the progress in this field is gradual, and its clinical implementation is also lagging far behind. For strong implication of pharmacogenomics to drug therapy, many hindrances needed to overcome. Multiple processes contribute to the response of patient towards drugs and drug combinations, such drug–drug interactions leads to unexpected outcomes associated with polymorphic genes. We are entering in an era of genomic medicine, where genetic tools are available to improve the care of patients and

make the best use of health care expenditures. Physicians who understand genetic risk can develop a personalized prescription of care targeting at-risk individuals and tailoring their care towards the efficacy of interventions while minimizing adverse reactions to treatments. Pharmacogenomic investigations of the disease yielded variations at genomic loci containing common variants with translational consequences of altering susceptibility disease risk, clinical course, and response to standard therapy. Discoveries of gene polymorphisms in drug transporter, targets, effector proteins, and metabolizing enzymes have clues for the treatment discoveries of possible causal genes. Therefore, it is necessary to keep advancing the pharmacogenomic approach to improving our knowledge in preventing the disease state and managing to attain optimal health outcomes. There are many problems including ethical, legislative, political, economic, and technological issues that delayed the widespread acceptance of pharmacogenomics within the clinical practice. However, such matters would resolve at a relatively rapid pace, which puts pharmacogenomics at the forefront of future medicine in clinical practice.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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