PERSONALIZED MEDICINE- A MODEL FOR CUSTOMIZATION OF HEALTHCARE

Anindya Bose[1]*, Somnath Mukherjee[2]

[1]Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Dr. Meghnad Saha Sarani, Durgapur-713 206, India.

[2]Laboratory Automation Services, HCL Technologies Ltd, New Town, Rajarhat, Dist North 24 Parganas, Kolkata - 700 156.

***Corresponding author:**

E-mail: anindyabose_in@yahoo.com , Tel: +91 343 2532678; Fax: +91 343 2532679.

ABSTRACT

There is an urgent demand for rectification of the “one-size-fits-all” method of treatment using personalized medicine model. Personalized medicine involves the determination of an individual’s unique genetic profile with respect to disease risk and drug response to optimize preventive health care strategies while people are still well or at the earliest stages of disease. Personalized medicine also helps to address the serious adverse drug reactions (ADRs) that not only are very costly but are responsible for thousands of deaths each year. However, the potential benefits of personalized medicine cannot be realized until certain obstacles in its adoption in its adoption are removed. These obstacles include uncertain regulatory requirements, insufficient insurance reimbursement for diagnostic tests linked to pre-emptive care, incomplete legal protections to prevent genetic discrimination, the lack of a comprehensive healthcare information technology system, and the present “one-size-fits-all” medical education system.

Keywords: Personalized medicine, adverse drug reactions (ADRs), patent, single nucleotide polymorphisms (SNPs).

INTRODUCTION

There are different levels of variation among individuals that could account for the varying outcomes of drug therapy, such as patients’ different drug absorption, distribution, metabolism, and excretion (ADME) profiles measurable at organ, tissue, or cellular levels and more fundamental differences at molecular levels. In current drug therapeutics world, it is widely observed that a drug doesn’t work for all the patients all of the time. Drugs do not have the desired outcome in 30%–40% of patients on an average, even the blockbuster drugs are often efficacious in 40%–60% of the patients, and it is not unusual to see chemotherapy working for only 30% of cancer patients[1, 2]. In addition, drugs can at times cause adverse drug reactions (ADRs), with some more severe than others. Moreover, the traditional clinical diagnosis and management focuses on the individual patient’s clinical signs and symptoms, medical and family history, and data from laboratory and imaging evaluation to diagnose and treat illnesses. This is often a reactive approach to treatment, i.e., treatment starts after the signs and symptoms appear.

It is obvious that there is an urgent demand for personalization of healthcare for individual patient to rectify the “one-size-fits-all” method of treatment. Personalized medicine involves the determination of an individual’s unique genetic profile with respect to disease risk and drug response. It also involves classifying patients with the same phenotypic disease

profile into smaller subpopulations, as defined by genetic variations associated with disease, drug response or both. In simple terms, it means knowing what works, knowing why it works, knowing who it works for, and applying that knowledge for patients. The assumption underlying this approach is that drug therapy in genetically defined subpopulations can be more efficacious and less toxic than in a broad population. The goals of personalize medicine are to take advantage of a molecular understanding of disease, combined with other individual factors, to optimize preventive health care strategies while people are still well or at the earliest stages of disease. In addition, this knowledge might prevent the negative side effects of the "one-size-fits-all" method of prescribing drugs that most often is used today.

Although, personalized medicine has always been at the heart of the doctor-patient relationship, with doctors considering such factors as family history and lifestyle when recommending treatment. Now there is hope that a more sophisticated version of personalized medicine will emerge from recent findings in genetic and molecular biology and from advances in imaging that are opening the door to new knowledge of the causes of disease and new treatment strategies. This new science of personalized medicine has the potential to eliminate unnecessary treatments, reduce the incidence of adverse reactions to drugs, increase the efficacy of treatments and ultimately, improve health outcomes. This new approach in the science of medicine is embodied with four attributes:

1. It is personalized; it is based on an understanding of how genetic variation drives individual treatment.
2. It is predictive; it is able to identify what conditions a person might contract in the future and how the person will respond to a given treatment, enabling the development of a tailored health strategy.
3. It is preventive; it facilitates a proactive approach to health and medicine, which shifts the focus from illness to wellness.
4. It is participatory; it empowers patients to make informed choices and take responsibility for their own health.

PERSONALIZED MEDICINE MARKET POTENTIAL

Pharmaceutical industry view the prospect of smaller markets and shrinking revenues as the greatest challenge they will face over the next decade, as blockbuster drug patents continue to expire (Figure 1). Hence the big pharmaceutical companies are trying to discover and develop tailored therapies for smaller markets. The concept of tailoring is not new to the industry; for years, companies have segmented customers by type of disease and used biomarkers such as cholesterol levels to guide treatment decisions. However, the development of new therapeutics based on genomics and proteomics will require an entirely new level of tailoring. John Lechleiter, chairman and chief executive officer of Eli Lilly and Company commented in this context that "our business model will accommodate personalized medicine—in fact, it may depend on it." Lechleiter acknowledges his peers' concern over replacing the revenues lost from blockbuster drugs, but he sees a viable new revenue model emerging: "Instead of getting a relatively small share of a really large pie—the traditional blockbuster model—a tailored therapy could expect to claim a relatively large share of a more segmented pie." [3]

Personalized medicine market is growing rapidly while still in the early stages, personalized medicine is steadily emerging as the new healthcare paradigm. According to PricewaterhouseCoopers' estimates, the US core diagnostic and therapeutic segment of the market—comprised primarily of pharmaceutical, medical device and diagnostics companies—is estimated at $24 billion, and is expected to grow by

10% annually, reaching $42 billion by 2015[4]. The personalized medical care portion of the market—including telemedicine, health information technology, and disease management services offered by traditional health and technology companies—is estimated at $4-12 billion and could grow tenfold to over $100 billion by 2015. And the related nutrition and wellness market—including retail, complementary and alternative medicine offered by consumer products, food and beverage, leisure and retail companies—is estimated at $196 billion and projected to grow by 7% annually to over $290 billion by (Figure 2) .

While the market for personalized medicine diagnostics and therapeutics shows great potential, the biggest opportunities exist beyond these core products and services— particularly in less traditional, more consumer-oriented areas. The nutrition and wellness market— including retail health, complementary and alternative medicine, nutraceuticals and organic care, and health clubs and spas—is estimated at $196 billion and projected to grow by 7% annually to $292 billion by 2015. The personalized medical care portion of the market—including telemedicine, electronic medical records, and disease management services—is estimated at $4 billion to $12 billion and could grow tenfold to over $100 billion by 2015. This segment is largely comprised of a range of healthcare players, as well as information technology companies that are starting to enter the space.

Such robust market size and growth potential will continue to attract many new players and require the development of new business models. A wide variety of organizations are entering this space, including consumer products, food and beverage, leisure and retail companies, as well as more traditional health companies that are successful in marketing directly to consumers. There are other products and services related to the field of necessary that the responses obtained are well fitted to the following equation:

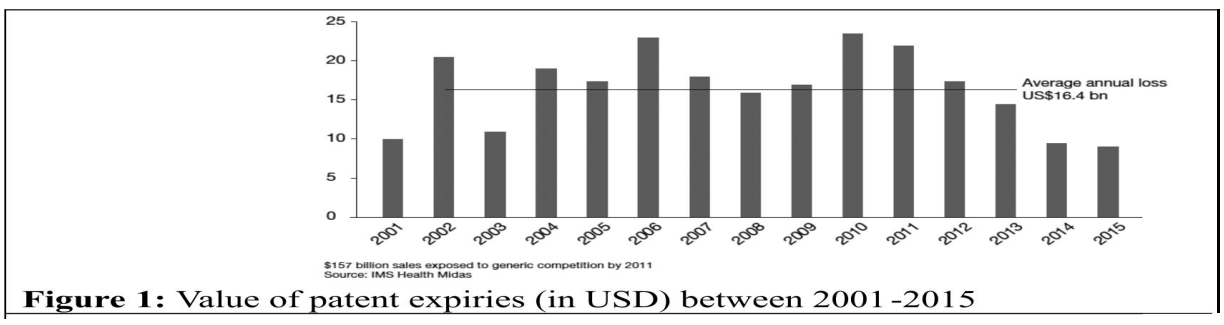

Figure 1: Value of patent expiries (in USD) between 2001 -2015

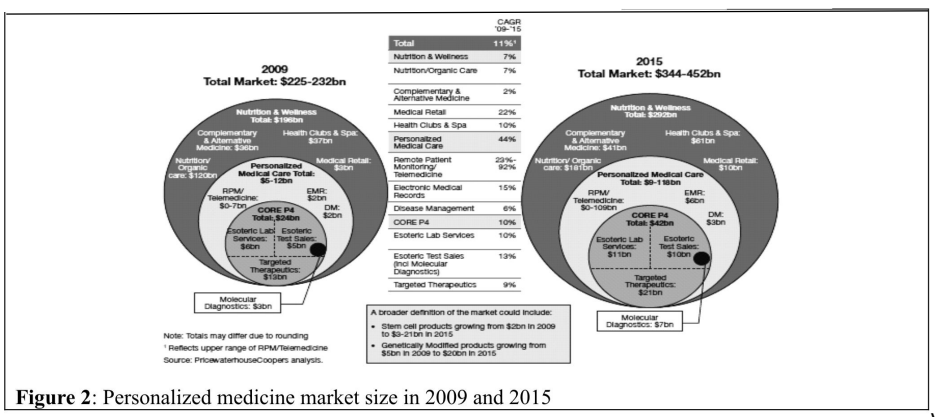

Figure 2: Personalized medicine market size in 2009 and 2015

THE SCIENCE OF PERSONALIZED MEDICINE

An individual's reaction to a particular drug depends, in large part, upon whether the drug's target cells have the proper receptors for the chemical compound being delivered and on how the individual metabolizes the drug. Ultra rapid metabolism of a drug can cause it to be ineffective and slow or non-metabolism can result in the accumulation of toxic amounts of the drug in the body. Genes control both these factors, the receptor binding sites and the enzymes involved in metabolism. Scientists believe there are 20,000 to 25,000 genes in the human body. About 99.9% of the DNA sequence is identical in all people, according to the National Human Genome Research Institute. But the 0.1 percent difference is critical because it represents the genetic variations that determine a person's risk for getting a disease, how mild or severe the disease will be and how the individual will respond to treatment.

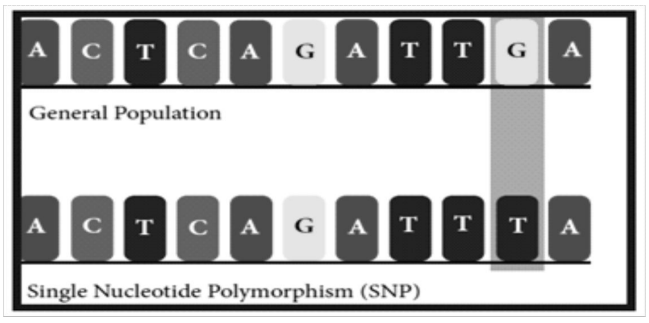

Figure 3: Single Nucleotide Polymorphism (SNP) showing a base pair differs from what is expected

Single nucleotide polymorphisms (SNPs)

In a human genome sequence of three billion base pairs, there are instances where one member of the base pair differed from what they expected. Of the four bases that DNA comprises adenine (A), cytosine (C), guanine (G) and thymine (T). Adenine generally bonds with Thymine, and Cytosine generally binds with Guanine. But about every 1,000 or so base pairs, scientists observed a mistaken pairing: a Guanine paired with a Thymine, for example, instead of with a Cytosine. These single departures are known as single nucleotide polymorphisms, or SNPs[5] (Figure 3). What makes SNPs helpful is that certain SNPs are found scattered throughout the population, so by looking at the DNA of individuals, who share a certain inherited condition, drug reaction or susceptibility, a shared SNP can be correlated with the drug toxicity and ineffectiveness. In the next stage, genetic tests can identify individuals who would have serious adverse drug reactions (ADRs) before they receive the drug. Finally, drugs can be designed to work effectively but non-toxically on those who have ADRs instead of the "one-formula-fits-all" blockbuster drugs. For example, a set of enzymes called CYP34 metabolizes about 50 percent of all common drug compounds. While searching for SNPs that control these enzymes, pharmacologists at St. Jude Children's Hospital in Memphis, Tenn., discovered two SNPs that suppress production of active enzymes. People who carry either one of the culprit SNPs metabolize drugs more slowly than the people who possess the other versions of the gene[6]. Scientists in the field predict that testing for most enzyme-related drug reactions and resistance will be available within the next five years.

Future prospect

The results of research into personalized medicine could benefit patients and health care providers in several ways. Identification of susceptibility genes related to specific diseases will allow health care providers to predict more accurately an individual's risk of developing a specific disease. With this information, it might be possible to prevent or to delay the onset of the disease or to diagnose it and begin treatment more promptly if it were to occur. Increased understanding of the underlying genetic and biochemical causes of disease could lead to the

development of more accurate ways of diagnosing disease to discover several distinct subtypes of a particular disease, stemming from different specific causes. Better diagnosis will contribute to more effective treatment.

The use of genomic techniques in target identification and progression might result in the more rapid and efficient discovery and development of new medicines that are safe, effective and aimed at the underlying mechanisms of disease. Medicine response tests could increase the confidence of health care providers in writing prescriptions, especially for medicines that are known to cause serious side effects in a significant number of people. Screening for known gene differences that affect drug metabolism might give health care providers the ability to adjust the dose of a medicine before prescribing it so patients safely receive the optimum benefit from the medicines they use. In some cases it might be possible for a medicine that would have been withdrawn from the marketplace because of a serious side effect in a small number of people to stay on the market, thus benefitting the majority of people who can take it safely.

APPLICATIONS OF PERSONALIZED MEDICINE

Discovery of a disease-causing mutation in a family can inform "at-risk" individuals as to whether they are at higher risk for cancer and may prompt individualized prophylactic therapy including mastectomy and removal of the ovaries. This testing involves complicated personal decisions and is undertaken in the context of detailed genetic counseling. Using the drug tamoxifen, for example, might prevent breast cancer among women with BRCA1 and BRCA2 gene mutations[7].

Tyrosine kinase inhibitors such as imatinib have been developed to treat chronic myeloid leukemia (CML), in which the BCR-ABL fusion gene, the product of a reciprocal translocation between chromosome 9 and 22, is present and produces hyperactivated ABL-driven protein signaling[8].

BENEFITS OF PERSONALIZED MEDICINE

Researchers predict many benefits will result from the science of personalized medicine. Among these are:

More Powerful Medicine: Accurate analysis of the proteins, enzymes and RNA molecules associated with genes and diseases will facilitate drug discovery and drug therapies targeted to specific diseases. Accuracy not only will maximize therapeutic effects but also will decrease damage to nearby healthy cells.

Safer Drugs: Instead of the standard trial-and-error method of matching patients with the right drugs, doctors will be able to analyze a patient's genetic profile and prescribe the best available drug therapy immediately. Not only will this take the guesswork out of finding the right drug, it will speed recovery time and increase safety, as the likelihood of adverse reactions is eliminated.

More Accurate Drug Dosages: Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics — how well the body processes the medicine and the time it takes to metabolize it. This will maximize the therapy's value and decrease the likelihood of overdose.

Screening for Disease: Knowing one's genetic code will allow a person to make lifestyle and environmental changes at an early age in order to avoid or to lessen the severity of a genetic disease. Advance knowledge of particular disease susceptibility also will allow careful monitoring, with treatments being introduced at the most appropriate stage to maximize their therapeutic value.

Better Vaccines: Vaccines made of genetic material, either DNA or RNA, promise all the benefits of existing vaccines without all the risks. They will activate the immune system but will be unable to cause infections.

Decrease in the Overall Cost of Health Care: Decreases in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the length of time patients are on medication, the number of medications patients must take to find an effective therapy, the effects of a disease on the body (through early detection) and an increase in the range of possible drug targets might promote a net decrease in the cost of health care. While the potential of personalized medicine is enormous as gene discovery accelerates, some people believe it will be important to assess the relative benefit of targeted intervention strategies based on personalized medicine. They argue that the medical and economic benefits offered by targeted interventions should be weighed against the cost of genotyping all individuals in order to direct an intervention to only a few.

CHALLENGES and POTENTIAL FUTURE RISKS

Personalized medicine is a developing research field that is still in its infancy. However, several of the following barriers will have to be overcome before many of its benefits can be realized:

Complexity of finding gene variations that affect drug response

Millions of SNPs must be identified and analyzed to determine their involvement (if any) in drug response. Further complicating the process is our limited knowledge of which genes are involved with each drug response. Because many genes are likely to influence responses, obtaining the big picture on the impact of gene variations is highly time consuming and complicated.

Limited drug alternatives

Only one or two approved drugs might be available for treatment of a particular condition. If patients have gene variations that prevent them using these drugs, they could be left without any alternatives for treatment.

Disincentives for drug companies to make multiple personalized products

Most pharmaceutical companies have been successful with their “one-size-fits-all” approach to drug development. Because it costs hundreds of millions of dollars to bring a drug to market, these companies may not be willing to develop alternative drugs that serve only a small portion of the population.

Educating Health Care Providers

Introducing multiple personalized products to treat the same condition for different population subsets undoubtedly will complicate the process of prescribing and dispensing drugs. Physicians must execute an extra diagnostic step to determine which drug is best suited to each patient. To interpret the diagnostic accurately and to recommend the best course of treatment for each patient, all prescribing physicians, regardless of specialty, will need a better understanding of genetics.

Ethical considerations

Because it promises to reveal previously unknown facts about an individual, personalized medicine also poses challenges to the current procedures that protect the confidentiality of information. From an individual perspective, concerns have been expressed about the negative impact of genetic information on potential

employment and on the ability to acquire disability, life and long-term care insurance. From a physician's perspective, concerns revolve around communication issues as well as around a new definition of "standard practice of care." Most people agree that the social justice and policy issues suggested by these outcomes are significant.

CONCLUSION

Personalized medicine offers a new paradigm for the development of drugs and the practice of medicine. Applying knowledge about an individual's inherited response to commercial pharmaceuticals holds the promise that drugs might one day be tailor made to each person's genetic makeup, replacing the one-formula-fits-all model that is intended to serve an entire patient population. Personalized medicine also might address the serious adverse drug reactions (ADRs) that not only are very costly but are responsible for thousands of deaths each year. Personalized medicine promises to take the guesswork out of developing and prescribing safe and effective drugs.

While the potential benefits of personalized medicine include development of drugs that are safer and more effective for specific disease populations, such benefits cannot be realized until certain obstacles to adoption are removed. Obstacles in public policy include uncertain regulatory requirements, insufficient insurance reimbursement for diagnostic tests linked to pre-emptive care, incomplete legal protections to prevent genetic discrimination, the lack of a comprehensive healthcare information technology system, and a medical education system that has not taught physicians how to incorporate personalized medicine diagnostics or personalized medicine into their practices. A supportive public policy environment would address each of these issues, and provide incentives to reinforce emerging business models that accelerate the co-development of drugs and diagnostic tests. Understanding all of these key factors – from obstacles to incentives – is a necessary step in determining how to apply resources to influence the direction of personalized medicine and its progress.

REFERENCES

1. Industry expert interviews, the American Medical Association (retrieved from www.ama-assn.org/ama/pub/category/7459.html).
2. S. X. Hu, T. Foster, A. Kieffaber, Pharmacogenomics and personalized medicine: mapping of future value creation, Biotechniques 39 (2005) S1-S6.
3. John C. Lechleiter. Markets of One: The Pharmaceutical Industry and the Pursuit of Personalized Medicine. Presentation at the Conference on Personalized Medicine: A Call to Action, Boston, Massachusetts, November 29, 2007.
4. PricewaterhouseCoopers. The new science of personalized medicine: Translating the promise into practice, 2009.
5. L. B. Barreiro, G. Laval, H. Quach, et al., Natural selection has driven population differentiation in modern humans. Nature Genetics 40 (2008) 340-345.
6. T. Gura, Can SNPs deliver on susceptibility genes? Science, 293 (2001) 597.
7. J. Gronwald, N. Tung, W. D. Foulkes, K. Offit, et al., Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update, Int. J Cancer. 118 (2006) 2281-2284.
8. G. Saglio, A. Morotti, G. Mattioli, et al., Rational approaches to the design of therapeutics targeting molecular markers: the case of chronic myelogenous leukemia, Ann. N. Y. Acad. Sci. 1028 (2004) 423-31.