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PERSONALIZED MEDICINE: FUTURISTIC PREDICTIVE NANOMEDICINES FOR DIAGNOSIS AND THERAPEUTICS

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ABSTRACT

The concept of personalized medicine has got its credential due to the development of molecular techniques. It involves right drug & dose, right patient and with right time administration of a medication. By averting the knowledge of gene sequence and their functions, biomedical researches are diversified towards inter-individual variations that are expected to become an eminent part of treatment planning in terms of efficacy and toxic side effects of drugs. The clairvoyance of the future health care adjudicate a system in which patient care is consistently belay by captivating information on the individual patient's genomes and their downstream products. By combining the credentials of various disciplines such as life sciences, mathematics, physics, chemistry, and information and communication technology ameliorated this concept. These have been well addressed by the so called '-omics' technology. However, assimilation of genomic data to its risk-benefit analyses and the adaptability of the patient population with certain ethical issue becomes one pillar for this and the view of the pharmaceutical industry towards this discipline.

Keywords: Pharmacogenomics, SNPs, FDA, Proteomics, Cancer, Ethical issues, Legal issues, Social issues.

Contribution/ Originality

This study contributes in the existing literature with a view to provide the reader the potential avenues that can be grafted using gene delivery particularly by “-omics” technology. It can be studied under two subheadings 1. Biomarker and 2. Therapeutics; which were cogently cited with example in this manuscript.

1. INTRODUCTION

If we look back in 70's researchers sought to fit one drug to as large a population of patients as possible, and identify the opportunities of using it to treat several different illnesses. Snyderman and Yoediono [1] have done studies for the same. The ultimate aim of their work is the broadest possible application for each drug. On another side large inter-subject variation is one of the major problem in drug development and in clinical practice results in to therapeutic

failure or adverse effects of drugs (ADRs). Milne [2] reported that either a positive or negative reactions have seen by a person that is influenced by many different genes. To develop a genetic test for particular patient the scientist should acquaint information of all the genes involved in the drug response. Ginsburg [3] quoted in his prophecy patient specific drug and setting an optimal dose for him/her anticipate the future therapy. It does not provide more specific information rather it is utilizing the readily available and routinely used biochemical methods for precise diagnosis; only help in establishing the patient's susceptibility to certain illnesses.

Selecting and administering a precise medication at a right time to right patient is the doctrine of personalized medicine. This is becoming possible thanks to the latest diagnostic tools that utilize molecular biology techniques to analyze genomes of bacteria or human being. Since last few years our knowledge on the genetic background of individual receptiveness toward drugs has progressed efficiently. Once drug effect on people's genes which shows small variations or changes in their nucleotide (DNA base) content, can be ascertained by genetic testing the way become more easy. Rosenberg [4] robust evaluation and sensible regulation of genetic tests are necessary to realize the promise of personalized medicine. This includes consideration of a drug and/or treatment's efficacy, and genetic test's analytical and clinical validity, in order to ensure that the test is safe, and performs as intended.

Pharmacogenomics (PG) studies exhibit how genotypic variation is responsible for variability in drug response and applies concepts about variations in hepatic drug metabolism enzymes to the rest of genome. Although environment, diet, age, lifestyle, and state of health all can influence a person's response to drugs, understanding an individual's genetic profile is thought to be the key to creating personalized drugs with greater efficacy and safety. The terms pharmacogenetics and pharmacogenomics are often used interchangeably, which causes some confusion. However, the term pharmacogenomics is preferred when referring to clinical practice [5].

2. HISTORICAL ASPECTS AND “-OMICS” TECHNOLOGY

Genomics is a discipline in genetics concerning the study of the genomes of organisms. It mainly determine the entire DNA sequence of organisms (genetic mapping). Fred Sanger and co-workers (in 1970-1980s) have first sequenced a genome of virus. They also invented the techniques of sequencing, genome mapping, data storage, and bioinformatic analyses. Chavda and Gohil [6] quoted that the genetic variations were first studied in relation to ABO blood group frequencies at the end of First World War by two Polish scientists Ludwik and HankaHirszfeld. Polymorphisms or SNPs (pronounced "snips") are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) is altered in the genomic DNA sequence. Two of every three SNPs involve the replacement of cytosine (C) with thymine (T). SNPs can occur in both coding (exons) and non-coding (introns) regions of the genome. Although many SNPs have no effect on cell function, certain others could predispose people to disease or influence their response to a drug. [7]

Microarrays and bioinformatics based technology known as *proteomics* is achieving much attention now days. *Study of the full set of proteins in a cell type or tissue, and the changes during various conditions, is called proteomics*. On the other hand *materiomics* is defined as the study of the material properties of biological materials. It also considers their effect on the macroscopic function and failure in their biological context, linking processes, structure and properties at multiple scales through a materials science approach. Each cell of our body is capable of making complete human being. However, not all the genes are expressed in all the cells. That's why proteomic is very much specific in its finding either a bio-marker or in functional therapeutics. PROTEOMEX is representing a combination of proteomics and serology which is most widely used in the bio-marker's discovery. The proteome is dynamic in nature unlike genome which depends on the tissue, cell type and environmental factors. Thus, genomic approaches alone are insufficient to investigate the causative mechanism underlying disease. Chavda and Gohil [6] cited that the current version of human gene catalogue contains 22,287 gene loci with a total of 34,214 transcripts. Over 1.4 million SNPs have been identified so far and the number is increasing every day as more humans are being studied.

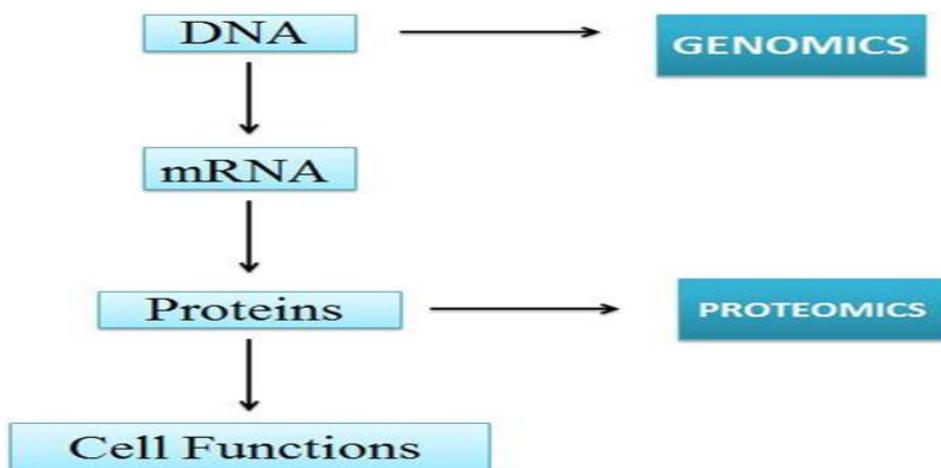


Figure-1. Biochemical context of genomics and proteomics

The “responders” are those who respond well to the particular drug in question while “non-responders” showing no response to drug at all. Another group of patients are “toxic responders” where the drug causes toxicity leading to SARs. In short for scientific, economic, and social point of view suggest that “tailor-made” medicine is future medicine for diagnosis and therapeutics. Personalised medicine is defined as: ‘the capacity to predict disease development and influence decisions about lifestyle choices or to tailor medical practice to an individual’ [8].

3. BIOMARKERS

For predicting likely course of illness and to check any progress of an illness in a given patient biomarkers are used which also sense individual response to treatment. In medical

terminology, a biomarker can be a traceable substance that is introduced into an organism as a means to examine organ function or other aspects of health. Małyska and Twardowski [9] reported a useful way of finding genetic causes for diseases such as schizophrenia has been the use of a special kind of biomarker called an endopheno type. The genomic biomarkers (GBMs) for diagnosis of specific diseases have showing steep growth since last few year. Slamon [10] and co-workers defined them as to be diagnostic, prognostic or predictive markers. The enzymes and hormones linked with tumors are of prior importance as biomarkers when it comes to oncology as routine biochemical techniques detect them easily. Their presence is not always indicative of the presence of a specific tumor. For example, an increase in the levels of the prostate-specific antigen (PSA) indicates a high likelihood of a prostate tumor being present, but it can also be a result of a mild hyperplasia. Similarly, raised levels of the carcinoembryonic antigen (CEA) are characteristic in between 60–90% of colon cancer cases and 50–80% of pancreatic cancers. A *prognostic marker* can be defined as either a single trait or signature of traits that separates different populations with respect to the risk of an outcome of interest in absence of treatment, or despite non-targeted 'standard' treatment. Prognostic markers are useful to assess the risk of disease recurrence, by comparing the outcome for marker-positive and marker-negative patients, regardless of the treatment, where intervention (e.g., drug therapy) is not a variable. Predictive markers can be defined as a single trait or signature of traits that separate different populations with respect to the outcome of interest in response to a particular targeted treatment. According to Kondratovich and Mansfield [11] genomics, Transcriptomics, Proteomics and Metabolomics are some of the techniques which are utilized in the screening of biomarkers. The biomarkers are classified in to three classes:

1. DNA Biomarker

Mutations in oncogenes, tumor suppressor genes, and mismatch-repair genes can serve as DNA biomarkers. Promoter region methylation of MGMT, an enzyme that reverses 5'-guanine alkylation, predicts the response or resistance of tumors to nitrosourea alkylating agents. [12]

2. RNA Biomarker

RNA biomarkers include differences in the transcription levels, or RNA molecules that take part in regulation. Pattern based RNA expression analysis of clinical breast cancers has identified previously unknown molecular subtypes. [12, 13].

3. Protein Biomarker

Not protein quantity, but its function can be utilized as a marker. Single RNA markers in tumor classification, prognosis or prediction of response to therapy, protein-based 'fingerprints' may outperform individual protein markers. [12, 13]

Table-1. DNA based biomarkers of enzyme [14]

Model drug	Enzyme	Remark	Reference
Proton pump inhibitors	CYP2C19	Higher dose (40 mg) showed no difference	[15]
Irinotecan	UGT1A1	UGT1A1 7/7 and 6/7 more frequent than 6/6	[16]
Atomoxetine	CYP2D6	PM higher AUC (10-fold)	FDA labeling
Pravastatin	Organic anion transporting peptide-C	Lower clearance	[17]
Statins	ATP-binding cassette family (ABC) B1,	LDL-cholesterol Lowering	[18]
Testosterone	CYP3A4	<i>In vitro</i> metabolism rate	[19]
Cyclosporine	CYP3A5	Non-expressers associated with higher trough plasma	[20]
Efavirenz	CYP2B6	Homozygous associated with higher plasma concentrations	[21]
Repaglinide	CYP2C8	Lower plasma Concentrations	[22]
Nicotine	CYP2A6	Higher nicotine and lower cotinine plasma concentrations	[23]

4. THERAPEUTICS

Genetic susceptibility to complex diseases and genetic variability in drug responses were comprehensively studied particular after the completion of the Human Genome Project. Lander, et al. [24] reported that pharmacogenomics findings in last decades or so allow bold steps to be taken toward personalized medicine. Genomics has become an integral part of modern drug development, and a large number of pharmaceutical companies are using this information to identify novel drug targets, identify patient subpopulations that are likely to benefit from the therapy under development, or for other screening purposes. Hong-Guang and Felix [25] reported that the safety and efficacy of a drug is evaluated according to strict regulatory guidelines before the drug is marketed. However, it is impossible for an approved drug to be safe or effective for everyone. Genetic and environmental factors, including their interactions, result in substantial variability among individuals. Drug safety varies from drug to drug, from person to person, and even from disease to disease. The costs of drug-related morbidity and mortality are expected to exceed US\$177 billion annually in the USA alone. As per Ernst and Grizzle [26] many drugs have been withdrawn from the major markets only because they cause severe toxicity in a small number of people. The thiopurine drugs, azathioprine (AZA), 6-mercaptopurine (6-MP), and thioguanine (TG), are widely used for childhood acute lymphoblastic leukemia (ALL), organ transplant rejection, and rheumatic diseases. Prospective genotyping or phenotyping is able to improve thiopurine *S*-methyltransferase associated drug therapy and avoid drug toxicity. Gardiner [27] quoted that the US Food & Drug Administration (FDA) has updated the labels of 6-MP and AZA to inform consumers about the risk of toxicity, and recommends genotyping before the initiation of treatment with these drugs. An individual patient's genetic factors, including gene-gene and allele-allele interactions are responsible for wide variation in warfarin

dose requirements, accounting for approximately 75–85% of the overall variability. Veenstra, et al. [28] studied SCN1A IVS5–91 G allele and IVS5–91G allele were linked to significantly reduced maximum carbamazepine and phenytoin doses respectively. Tate, et al. [29] studied that in CYP2D6 poor metabolizers shows reduced analgesics activity of codeine where in ultra-rapid metabolizer increased response to normal doses, or, in some cases, severe toxicity as per Gasche, et al. [30]. Tyrosine kinase inhibitors; Gefitinib (Iressa®) and erlotinib (Tarceva®) were successfully utilized in the treatment of adenocarcinomas of the bronchioloalveolar carcinoma (BAC) subtype. The human epidermal growth factor receptor (HER)2 (ErbB2) gene is amplified in up to 30% of patients with breast cancer, resulting in the overexpression of the HER2 receptor protein that serves as the target for the anti-HER2 antibody trastuzumab (Herceptin®), a humanized monoclonal antibody while cetuximab (Erbixux®) binds to the extracellular domain of EGFR. Slamon, et al. [31] studied that chronic myeloid leukemia has been a target for Imatinib (Gleevec®) is a competitive inhibitor of ATP binding to the ABL kinase. Druker, et al. [32] reported that if we talk about recent progress, Vemurafenib is a B-Raf enzyme inhibitor developed by Plexxikon and Genentech for the treatment of late-stage melanoma [33].

5. ISSUES AND CHALLENGES

On paper the concept of personalized medicine seems admirable which turns ambiguous in reality. Identifying each individual's reaction for absolute personalized medicine is neither easy and straightforward from a research perspective nor practical from a pharmaceutical, diagnostic, or prognostic perspective. According to Bansal, et al. [34] a cogent Agenda has to be prepared to anticipate regulatory requirement and its pharmaceutical clairvoyance. Several initiatives in Europe including the UK's Stratified Medicine Innovation Platform, Sweden's Biobank Program, BIOMEDREG in Czech Republic, and the Munich Biotech Cluster are already working toward this goal. The US Food and Drug Administration is in the process of evaluating medical products and integrating the various medical product regulatory authorities provided by Congress in the Federal Food, Drug and Cosmetic Act to develop effective mechanisms for successful implementation of personalized medicine in the USA. There are certain questions raised which will be solved and acceded; what about privacy issues? As an adult, that child might not want to know what awaits him/her in the future. This raises another question – how do we interpret prognostic information and what do we actually want to predict and where to intervene? Are we going to end up with a health care system that will not be accessible to everybody? Will the patient gain from the new approach when clinically beneficial new products and procedures are translated into affordable clinical practice?

5.1. Ethical Issues

Privacy of the study subjects is one of the most cardinal issue when one talks about personalized care. Lindpainter [35] mentioned in their work that each participants should be

adequately informed that how their genetic material will be handled, what all tests may be done, how and by whom the data will be utilized, where the genetic material be stored and how secure the DNA blanks are? As per Bansal, et al. [34] DNA may be required for future use and how that data will be maintained. Informed consent for future use should also be taken before hand. Patent's family should be informed or not, is one point to be addressed further [36].

5.2. Legal Issues

Before full implementations of any diagnostic or therapeutic intervention being made for personalized care this surely be addressed cogently; Bansal, et al. [34]. Lindpainter [35] quoted some important questions regarding personalized care. What is the legal liability if that data if stolen or lost or made public? Who is responsible for the damages? What is the compensation? What is legal issue if discrimination is made by job providers or insurance firms? In case the job providers know the person's gene data and avoids job which is good for company as only best fitted individuals will be there to improve success but a loss for person who may have to face unemployment and switch over to malpractices, or insurance cover is avoided [36].

5.3. Social Issues

It is well castigated if any new diagnostic method or therapy invented using the -omics technology leads to increase in therapeutics cost. Bansal, et al. [34] have well defined this problem in their work. Patient becomes the main aim but of course! This leads to breach in privacy of whole community whose consent is not taken. This may also lead to formation of a group susceptible to a particular drug, having a possibility of a particular disease in future or having a predisposition to something not curable as per current standard [35, 36].

6. PHARMACOGENOMICS TESTING IN CHILDREN

It is quiet tough to conquer such issues especially ethical one however it may be done for conditions where immediate therapeutic outcome may be feasible as per current levels of advances in pharmacology. Etical issues needs consideration of complete genome matching even though the final decision will be made by the patient only. Anticancer therapy to a patient deficient to Thiopurine S Methyl Transferase after math in myelosuppression. Such patients can be advised to undergo pharmacogenomics testing so as to predict outcome and alternatives [34].

7. BARRIERS TO PROGRESS IN PERSONALIZED CARE

As mentioned earlier in this manuscript that the -omics technologies are in emerging phase and have to pass many barrier before it actually commercialized.

1. Complexity of finding gene variations that affect drug response: SNPs occur every 100 to 300 bases along the 3- billion-base human genome, there for millions of SNPs must be

identified and analyzed to determine their involvement (if any) in drug response. In simple term it requires huge amount of efforts, time and money.

2. Limited drug alternatives: There are only few alternatives as approved drugs may be available for treatment of a particular condition leads to treatment failure if patients gene variation surpass it.
3. For making such medicines drug companies have to suffer from large financial loss
4. Educating Healthcare Providers: It surely requires that physician should be through with gene knowledge so as to tackle any problem during therapy as it is patient specific.

Table-2.Recent patent on personalized medicines

Patent no.	Inventor	Title	Reference
EP 1842909 A1	Hiroyuki c/o Institute for Frontier Med MATSUMURA, Norio c/o Institute for Frontier Medica NAKATSUJI, Masako Tada, Takashi c/o Institute for Frontier Medical TADA	Method for removing desired chromosome and tailor-made medical treatment utilizing the same	[37]
WO 2012170422 A1	Subinoy DAS, Lauren O. Bakaletz	Proteomics based diagnostic detection method for chronic sinusitis	[38]
EP 2045332 A1	Michaela Bairlein, Henrik Daub, Klaus Godl, Kirti Sharma, Andreas Tebbe, Christoph Weber	Proteome-wide quantification of small molecule binding to cellular target proteins	[39]
EP 1618388 A2 and WO2004088324A2	Mike Gravett, Sri Nagalla, Ron Rosenfeld	Proteomic analysis of biological fluids	[40]
WO 2008063928 A2	Ron Rosenfeld, SrinivasaNagalla, Mike Gravett	Proteomic analysis of cervical-vaginal fluids for detecting intra-uterine infection or determining pre-term delivery risk in a pregnant female	[41]
WO 2001084148 A2	Trevor Collingwood, Dmitry Guschin, Brian Johnstone, Xiao-Yong Li, Fyodor Urnov, Alan Wolffe,	Pharmacogenomics and identification of drug targets by reconstruction of signal transduction pathways based on sequences of accessible regions	[42]
WO 2004091794 A1	Gary R. Epler	System and method for pharmacogenomic testing	[43]
WO 2003039234 A2	Elizabeth Gray, Jack D. Hidary, David Pickar	Pharmacogenomics-based system for clinical applications	[44]
WO 2005077974 A1	Christian Ehnholm, PaiviPajukanta, LeenaPeltonen-Palotie, Marja-RiitaTaskinen	Identification of SNPs associated with hyperlipidemia, dyslipidemia and defective carbohydrate metabolism	[45]
EP 2490694 A2	Giuseppe Bianchi, Patrizia Ferrari, Fabio Macciardi	Methods and systems for pharmacogenomic treatment of cardiovascular conditions	[46]
WO 2006089185 A2	Michael E. Burczynski, Andrew J. Dorner, Frederick Immermann, Donna Slonim, Andrew Strahs, William L. Trepicchio, Natalie C. Twine	Pharmacogenomic markers for prognosis of solid tumors	[47]

8. CONCLUSION

Due to the advancement in so called “-omics” technology the concept of personalized medicine has become reality. The identification of SNPs from almost three billion base long

human genome is a complex and costly process though it looks simple on paper. Nobody is interested in investing huge money, time and efforts for only single fit medicine. At this stage, without government support in terms of subsidies and exemptions, it seems unclear. Apart from this there are certain ethical and social issues which need consideration. One should also not forget patient's affordability! When it comes to diagnostic marker role of physician has to be discussed because physicians are the one show will diagnose the disease and prescribe medicines accordingly. Before full application of this branch, various issues and technical difficulties have to be critically analyzed with suitable aftermath. It is worth to say here that still it is in its infancy a lot of nutrition it requires for proper growth!

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