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A Review on Determination and Future of the Predictive and Personalized Medicine

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Abstract

Medicine contents' have extended to predictive, personalized, preventive and participatory medicine (P4). 'Personalized medicine' focuses on the prediction of potential benefits or risks for individuals as possible as in detailed. Biomarker discovery, biocomputing and nanotechnology have opened a new horizon on 'personalized medicine' (including disease detection, diagnosis and therapy by using individual's molecular profile) and 'predictive medicine' (to predict disease development, progression and clinical outcome, by using the genetic and molecular information).

Personalized medicine can be applied to a lot of different areas. P4 medicine, based on use of marker-assisted diagnosis and targeted therapies, comes from an individual's molecular profile, will form a new way on drugs development and medicine administration. Genetic screening aimed to identify carrier and affected individuals in a particular population. Molecular diagnostic test, including genome-derived tests are getting more attention within the medicine with genotyping, RNA expression analyses, metabolic profiling, and other biomarkers. Genomics research has getting more attention on the biomedical research, translational science, and personalized medicine; divided into 3 main parts: 1) genomics to biology, 2) genomics to health, and 3) genomics to society.

We conducted a literature search via PubMed databases with using "personalized medicine", and "application areas of P4" keywords, and summarized some of new studies.

Personalized medicine is described as an individualized treatment based on the individual's genetic variants. In other words, "for predicting health, preventing and preempting disease, and personalizing treatment depending on the each person' unique biology", has a speedy improvement.

Keywords: participatory medicine, personalized, predictive, preventive, (P4)

1. Introduction

The genomic and personalized medicine, concern the government officials, industry leadership, health care providers, and the public especially in the last 10 years. Genomes information, including RNA, proteins, and metabolites can be used by genomic medicine within the personalized medicine, to decide health care of each person's based on their unique clinical, genetic, genomic, and environmental information. By using these genomic information, including "whole genome" interrogation of sequence variation, transcription, proteins, and metabolites, it is possible **to do** more precise prediction and treatment in every kind of disease. But the fundamentals of genomic and personalized medicine, need the development, standardization, and integration of several important tools into health systems **especially in clinical levels.** Health risk assessment, family health history, and clinical decision are the main of these tools. Molecular signatures for cancer diagnosis, DNA-based risk assessment for common complex disease, genome-guided therapy and dose selection are some information within the genome information, that will be used by the personalized medicine. The using of these information by genomic and personalized medicine in health care, needs changing in regulatory and reimbursement policies for privacy (Gingsburg &Willard, 2009). The capasity of sequence the entire human genome, lead to using of individual's complete genomic blueprint to understand disease risk and predicting therapy outcomes, in other saying, optimizing drug therapy. **The suspicion is still present about the reliability of predictive biomarker tests and the size of required genetic/genomic factors, on the basis of influence to disease and treatment outcomes.** The genomics definition is now extent to DNA sequences plus transcriptomics, proteomics,

metabolomics, and epigenomics, with integration of genomic and environmental factors, in shortly, systems biology (Sadee, 2011). Especially increasing in a number of diseases and health conditions, including patient's therapy or drug response, have epigenetic or epigenomic etiology (Stambuck, Sundow, Kuret, Beljan, & Andelinovic, 2010).

Medicine content's extended to predictive, personalized, preventive and participatory medicine (P4). To complete the expectation of P4 medicine, a "fifth P" must be integrated-the population perspective-into each of the other four components. A population approach applies principles of population screening to preventive medicine; integrates predictive medicine into the ecologic model of health; uses evidence-based practice to personalize medicine; and support participatory medicine on the three core functions of public health: assessment, policy development, and assurance. Population sciences-on the basis of the epidemiology; behavioral, social, and communication sciences; and health economics, implementation science, and outcomes research-are needed to indicate the worth of P4 medicine (Khoury, Guinn, Glasgow, & Kramer, 2012). P4 medicine success based on the two major challenges; technical and societal barriers (Hood & Friends, 2011). Personalized predictive medicine (PPM) covers the genetic passport and its methodological basis, which is genetic testing (GT) (Baranov, 2011). 'Personalized medicine' focuses on the prediction of potential benefits or risks for individuals as possible as in detailed (Arnold & Bokemeyer, 2010). Improvement in molecular profiling technologies and molecular target agents allow the development of personalized medicine. Biomarkers have a critical role in drug discovery, development, and prediction of treatment response and safety, and cause to improve disease understanding, and extent to utility and reduce the toxicity (Saito & Yoshino, 2010).

2. Application Areas of P4 Medicine

P4 medicine, in other words predictive, preventive, personalized and participatory medicine, is a new concept in medical care. Also, people can adjust their lifestyles to prevent disease. P4 medicine can be fed from personalized genome sequencing and new computational techniques with using huge amounts of data, comes from a variety of OMICs (Bengoechea, 2012). The predictive, preventive, personalized, and participatory (P4) medicine provide new approach to the healthcare (Hood & Flores, 2012). Personalized medicine, in other words"for predicting health, for preventing and preempting disease, and for personalizing treatment depending on the each person's unique biology", focusing especially on genomics, has an slowly improvement (Burns & Blaxall, 2008). P4 medicine apply to patient and consumer has an **two** side effect; first, developing technologies and strategies within the P4 medicine and second, the effect of P4 medicine on society with ethical, social, legal, regulatory, and economic issues (Hood & Flores, 2012).

Personalized medicine can be used and applied to different areas of medicine. A lot different studies were evaluated and summmarized in these subdividing. Such as:

2.1 Personalized Medicine in Genetic Test

Molecular diagnostic test, including genome-derived tests are getting more attention within the medicine with genotyping, RNA expression analyses, multiplex protein and metabolic profiling, and other biomarkers. Medical therapies are considered based on their effectiveness—whether or not positively effect (with for example; drug, device, or procedure) in reducing mortality, morbidity, or some positive possibilities— with a reasonable cost. But, diagnostic tests are not independent and shows effect indirectly (i.e., by influencing the choice of therapy or treatment strategy), which means they can't be evaluated in a same way. Actually, the beter improvement can be obtained from diagnostic tests for health-related patient outcomes. The high risk possibility, in most diagnostic test, is the inaccuracy of the tests including genomic tests as well. In clinical practise there are six assessment levels for genomic tests: 1). Technical capability and operational excellence. 2). Diagnostic capability. 3). Impact on diagnostic and/or prognostic thinking. 4). Impact on therapeutic strategy. 5). Cost effectiveness 6). Health outcomes (Douglas & Gingsburg, 2008).

2.2 Personalized Medicine in Biomarkers

New developing technologies, in biomarker discovery, biocomputing and nanotechnology have composed and developed a new era 'personalized medicine' (including disease detection, diagnosis and therapy by using individual's molecular profile) and 'predictive medicine' (to predict disease development, progression and clinical outcome, the genetic and molecular information is used). Biomolecular markers contains; RNA, proteins, lipids, carbohydrates, small metabolite molecules, changed or mutant genes, and changed position with the effect of biological behavior or a clinical outcome of that markers. Biomarkers are divided into prognostic, predictive and therapeutic response markers. Prognostic biomarkers can be used to determine the metastasis of the tumor within the individual cancer. Predictive biomarkers can be used to determine the effectiveness of particular treatment to the patient.

Pharmacodynamic biomarkers can be used to determine the effect of a drug onto tumor and to give suggestion in dose selection in early stages of treatment for new drugs (Phan et al., 2009).

The benefits of predictive markers based on three parameters, sensitivity, specificity and positive predictive value. Specificity is important, especially biomarker will be going to use to identify individuals for counseling or for preventive therapy. Also there is a mutual relationship between sensitivity and specificity which means, successful biomarkers should be highly specific and have sensitivity. But most of the biomarkers don't have a enough specificity and sensitivity together for many diseases. For this problem, the solution is to use large number of biomarkers together. The new technological progress in genetics, genomics, proteomics, and bioinformatics support the biomarker developments and cause to identification of new biomarkers, that are more accurate in disease diagnosis, classification and therapeutic monitoring as well (Collins et al., 2006).

Biomarkers are marker of normal or abnormal biological processes that could be used to display or diagnose disease, monitor its activity, predict its progress, or assesment of response to treatment. Based on the information type, that biomarkers provide, biomarkers seperated into 5 groups as: 1) antecedent biomarkers, evaluate the risk of developing disease; 2) screening biomarkers, determine individuals with subclinical disease; 3) diagnostic biomarkers, provide contribution in diagnosis of explicit disease; 4) staging biomarkers, estimate disease intensity; and 5) prognostic biomarkers, provide information on the progress of a disease, predict response to therapy, or monitor benefit of a therapeutic strategy. There are a lot of characteristics of biomarkers, used in clinical studies successfully. First, the clinical importance of a biomarker is based on the stability of the association between the marker and the result or disease of interest. This formation needs to be confirmed with several population studies. Second, a transformative biomarker supply important new information for improving current tests. Third, attain to the assesment, simplicity of analysis, basic interpretation, and acceptable cost increase the value of biomarker. Fourth, a biomarker can be used effectively only when it helps the clinician to achieve patients. So that, a biomarker-guided approach provide improved patient outcome if its' clinical value is recruited. If biomarkers don't have a guidance into medical procedure, may also be useful in some situations by providing psychological benefits to patients. Biomarkers used to screen serious illnesses (such as cancer), have to be more sensitive, **but the ones used to monitor** disease progression or response to treatment, don't need to be higly specific because serial other examination also would be conducted at the same time (Frangogiannis, 2012).

Personalized medicine includes biomarkers with applications into diagnosis, prognosis, and selection of targeted therapies. Biomarkers are used by pharmacodynamics for treatment monitoring. Three broad categories of biomarkers which are DNA biomarkers, DNA tumor biomarkers, and other general biomarkers, can be used as a diagnostic and prognostic biomarkers. Predictive biomarkers with the help of diagnostic tests predict treatment response (Ziegler, Koch, Krockenberger, & Grosshenning, 2012). Environmental, behavioural, and genetic factors effect patient' decision and disease period (Salari, Watkins, & Ashley, 2012).

Biomarkers form a base for the development of individualized treatment strategies. With the improving in the pathophysiological processes of the disease, novel biomarkers can be used more efficiently. Also, novel markers are being examined and more frequently used in personalized medicine, causing to increase efficacy and safety for patients and potentially the cost-effectiveness (Scherer, Burmester, & Häupl, 2012).

The main issue in personalized medicine is the introduction of target specificity to diagnostic tools and therapeutic agents. For this aim developing of aptamers, sequences of nucleic acids that are able to recognize and bind to a specific target, getting more attention and taking interest in this technology. Big improvement has been made in developing DNA apta-mer-based techniques for diagnosis and therapy of cancers as well as other diseases including influenza, Hepatitis C, and thrombosis. The combination of diagnosis and therapy in one system (theranostics) holds the key to the future success of personal medicine. To achieve this goal, first of all, identification of disease markers from an individual patient, then in vitro selection of DNA aptamers for these markers and finally the production of theranostic tools specifically designed for that patient has to be done (Xing, Huang, Li, Torabi, & Lu, 2014). The adaptation of molecular imaging into therapy, theranostic approach could be usefull in therapy selection, treatment planning, objective response monitoring and follow-up therapy planning based on the molecular characteristics of a disease (Ryu et al., 2014).

2.3 Personalized Medicine in Pharmacogenomics

Personalized medicine is described as individualized treatment based on the individual's genetic variants. This treatment with the application in pharmacogenetics, have a role on the prevention of 100,000 deaths per year in the USA because of drug reactions or inadequate treatment in some disease. The use of the multimillion single nucleotide polymorphism (SNP) array effects positively genotyping studies (Roberts, 2008).

Pharmacogenomics is a forerunner of personalized medicine, indicating 'the right drug for the right patient at the right dose and time' instead of former 'one-drug-fits-all' idea, which means, patients will be grouped based on their genetic and other markers that estimate disease progression and treatment outcome. Also, numerous factors such as age, sex, body weight, nutrition, organ function, infections, comedications and genetic factors asistant to variable drug response (Sadee & Dai, 2005). Determination of genetic polymorphisms because of SNP is the most common dealing, but the potential relevance of copy number variants, gene-gene and gene-interactions, noncoding RNA gene regulation, and epigenetic modifications, cause an increae in the complexity of pharmacogenomics research (Howland, 2012). Pharmacogenetic includes widespread effects of genetic polymorphisms on drug response. Convenience of SNP maps and increase probability on functional polymorphisms, together built high level hope for applying pharmacogenetics to the adjustment of individual patients' therapies via new drug discovery, development and therapy.

Because of the disease processes and drug therapies are complex systems, pharmacogenomics as one of many approaches in personalized medicine, have limited predictive power (Sadee & Dai, 2005).

2.4 Personalized Medicine in Genomic Research

Genomics research has been getting more attention on the central part of biomedical research, translational science, and personalized medicine (10). Especially, these applications are divided into 3 main parts: 1) genomics to biology, 2) genomics to health, and 3) genomics to society. The first part focused on the clarification of the structure and function of the human genome and other biological systems. The second one, focused development of the human haplotype map, inspire to the gene discovery for complex human disease. The last one encourages the benefits of all implications to all society, especially by using genetic data to ethical and social implications, and to behavior, and by reducing the possible genetic discrimination. Additionally, the genomic information could be used to develop improved diagnostic methods for disease prediction, genetic characterization of the disease process, and the determination of response to treatment, especially in early phase. The future genomics can't be determined with 'biomarker' term. The use of biomarkers in the determination of complex human disease via genomics need detected genes' modifying risk. Especially using biomarkers in the single-gene (or oligogenic) disorders can be very effective and the boosting of marker density from 400 microsatellite polymorphisms to thousands of single nucleotide polymorphisms (SNPs), including whole genome lead to increase on information content. Also if extra information added from family, it causes an increase in the information, that could be helpful and used as a positive control in determining of unrecognized population structure or stratification via marker alleles' transmission within families (Rich, 2008).

Genomic variation indicates the differences in an individual's response to drug treatments. Genomic medicine concentrates to the identification of genetic polymorphisms and gene mutations involved in the development and progression of disease. The genetic tests developed to predict how certain patients respond to therapy with a given pharmacological agent. The field of predicting responses to drugs include different areas, which are; the use of liver microsomes, cell models, monitoring of probe drugs, assays with recombinant proteins and recently the use of microarray platforms or DNA chips (Leon-Cachon, Ascacio-Martinez, & Barrera-Saldana, 2012).

2.5 Personalized Medicine in Genetic Profiling (GWA)

Over 200 loci influencing a wide range of complex phenotypes have now been identified via genome-wide association (GWA) technology. Within this technology, genome-wide data on sequence variation and global transcript profiling information could bring together and use in understanding of the genetic basis of variation in expression levels named as genetic profiling' which several companies have already made high-profile entries into this market (Mccarthy & Hirschhom, 2008).

Personalized medicine, based on use of marker-assisted diagnosis and targeted therapies, comes from an individual's molecular profile, will form a new way on drugs development and medicine administration. The information of the molecular basis of disease will lead to change in the pharmaceutical industry. The integrated and heuristic approach will come to front in drug development instead of traditional applications. Also, the reform will come to the patient care with using of novel molecular predisposition, screening, diagnostic, prognostic, pharmacogenomic and monitoring markers (Gingsburg & Mccarthy, 2001).

The personalized medicine and the accompany of diagnostics, high-throughput screening in clinical diagnostics and point-of-care testing (POCT), need more biological information, especially the samples are in low concentrations and volumes. Optical biosensors can be an answers to this problem with their unique photophysical properties, which can be used successfully in sensitive multiplexed detection (Jin & Hildebrandt, 2012).

Genetic screening aimed to identify carrier and affected individuals in a particular population. Currently, genetic screening include carrier screening, prenatal screening, and newborn screening (Mccabe & Mccabe, 2004).

Molecular imaging aims at detection of processes at the cellular level by probes binding to specific structures. This extra diagnostic information will provide more effective, less invasive therapy for the patient with fewer side effects. This indicates that, the imaging is more specific for the mechanism of the disease and the target of the therapy leading to personalized medicine (Schönberg & Wangler, 2013).

Complex diseases eventuate from the together effects of multiple genetic and environmental causes, with each factor having small contribution to the formation of disease. For complex diseases, genome-based prediction needs the simultaneous testing at multiple genetic loci, known as genetic profiling. Personalized medicine demands more accurately tests that, predicts disease risk, especially when interventions are incursive, expensive or have major side effects. New gene identification with genome-wide association studies will help to improve the prediction of common diseases, but the question is whether this improvement is enough to facilitate personalized medicine (Jansens, Cecile, & Duijn, 2008).

2.6 Personalized Medicine in Nutrigenomics

The Human Genome Project and the identification of single nucleotide polymorphisms (SNPs) within populations have played an important role in pharmacogenetics, predicting individual response to drugs, leading to the "personalized medicine." The subsidiary product, 'Nutritional genomics' includes 1) nutrigenomics: based on the interaction of dietary components with the genome and the resulting proteonomic and metabolomic changes; and 2) nutrigenetics: rely on the gene-based differences reaction to dietary components and developing nutraceuticals. Nutrigenomics showed that, nutrients and botanicals can interact with the genome and modify gene expression, which has provided motivation for nutrigenetic research and nutraceutical development based on nutrigenetics. More research on individual differences in genetic profiles and nutrient requirements will provide a lot of support on formation of nutrigenetics as a necessary discipline for nutrition and dietetics practice (Subbiah, 2007).

Nutrigenomics introduce the expectation of personalizing nutrition to the genotype of the consumer, based on variations in the genes of nutrient metabolism and in downstream genes and proteins that have related to nutrients (Ghosh, Skinner, & Laing, 2007).

2.7 Personalized Medicine in Regenerative Medicine (RM)

The regenerative medicine (RM) area, covers stem cell (SC) technologies, therapeutics, tissue engineering (TE), biomaterials, scaffolds and other enabling technologies provides a wide range of tools and tracks to battle, manage and hopefully cure serious human and animal problems, injuries, dysfunctions and diseases. The advances and contribution of RM translational research are expected to be practised for personalized repair and curative outcomes (Mhashilkar & Atala, 2012).

By using modern molecular, genetic and biochemical methodologies it is possible to identify individual gene or gene expression profile ('signature'). By using this data it is possible to define the individual disposition for a given disease and to predict disease prognosis as well as the efficacy of therapeutic strategies in the individual patient ('individualized medicine'). These findings affect the regenerative medicine moving to the center of biomedical research worldwide with a major translational impact on tissue engineering as well as transplantation medicine (Blum, 2014).

2.8 Personalized Medicine in System Biology and Omics

Systems biology transforms the modern health care area from symptom-based disease diagnosis and treatment to absolute medicine in which patients are treated based on their individual characteristics. Development on the technologies such as high-throughout sequencing and mass spectrometry has given scientists and clinicians to examine genomes, transcriptomes, proteomes, metabolomes, and other omics information in matchless detail.

The joint 'omics' information provides new approaches for personalized health monitoring and protective medicine (Chen & Snyder, 2012). The ability to study biological events at omics levels will provide significant advances to personalized and precision medicine. Patients can be treated on the basis of their own molecular characteristics. Individual and whole omes such as the genome, the epigenome, the proteome, the transcriptome, the metabolome, the antibodyome, and other omics information are expected to be precious for health monitoring, preventative measures, and precision medicine. Also, omics technologies have a talent to convert medicine from traditional symptom-based diagnosis and treatment of diseases toward early diagnostics and disease prevention (Chen & Snyder, 2012).

It is clear that the systems biology area and proteomics, will have an important role in predictive, preventative, and personalized approach to medicine (Weston & Hood, 2004).

Predictive, preventive, personalized and participatory (P4) medicine is based on the adaptation of all medical aspects (i.e. practices, drugs, decisions) of the individual patient. P4 medicine lean on the using of omic datas with molecular profiling of patients, supposing these informations may explain differences of patients on the basis of disease prevention, diagnosis and therapies (Guzzi, Agapito, Milano, & Cannataro, 2015). Large number of molecular informations in other words omics data provide prediction in prognosis and in prediction related to patient and treatment. This huge amount of data is the hope for the personalized therapy and as a result improving health outcomes (Sachs, 2015).

P4 medicine, is a new aspect to medical care; instead of acting and determining the signal when the patient is sick. Also, people might even be able to adjust their lifestyles to prevent disease. P4 medicine can be supported by methods, based on personalized genome sequencing and new computational techniques for building disease predictive networks from huge amounts of data, comes from a variety of OMICs. For example new P4 medicine, can create new approach to the cancer treatments. In particular, focus on early detection, followed by genotyping of the patient to find most convenient treatment according to the genetic background (Bergoechea, 2012).

The systems biology approach will help transforming of diagnostic and therapeutic strategies with the novel biomarkers to predictive and preventive medicine leading to personalized medicine (Pesce, Pathan, & Schena, 2013).

2.9 Personalized Medicine in Epigenetic and Tailoring Therapy

Tailoring therapy has giving opportunity in maximizing efficacy and minimizing drug toxicity to the individual patient. Personalized medicine has advantages in the identification of predictive biomarkers that can help in treatment decisions and, ultimately, improve treatment outcomes. With the help of genomics and proteomics, molecular profiling provides datas to tailoring of therapy (Jiang & Wang, 2010).

Epigenetics can be used as a coordinator between environmental/exogenous factors, cellular responses, and pathological processes. Epigenetic indicators (DNA methylation, mRNA and microRNA expression, etc) may consider as biomarkers in risk steps, early detection, and disease classification, as well as aims for therapy and chemoprevention. For example, DNA methylation assays are widely administrated to formalin-fixed, paraffin-embedded archival tissue specimens as clinical pathology tests (Ogino et al., 2013).

Personalized medicine is the tailoring of therapies to determine the patients based on their respond to therapy or risks, comes from treatment. The progress on the genomic tools gave a acceleration to the understanding of the molecular pathology of diseases at molecular level. ‘Personalized medicine’ state to the tailoring of medical treatment with individual characteristics of each patient, on the basis of their susceptibility to a particular disease or their response to a specific treatment (Bates, 2010).

2.10 Personalized Medicine in MPE (Molecular+Pathological+Epidemiological)

The 'molecular pathological epidemiology (MPE)' has appeared as transdisciplinary of 'molecular pathology' and 'epidemiology' to understand the interaction between etiological factors, cellular molecular characteristics, and disease evolution. In MPE, each disease process results from aspect of exposomes, proteomes, epigenomes, transcriptomes, metabolomes, microbiomes, and interactomes in relation to the macroenvironment and tissue microenvironment. MPE science is in its way of personalized medicine and prevention (Ogino et al., 2013).

2.11 Personalized Medicine in Cancer and in Oncology

Cancer is one of the most important diseases with no cure presently. Best strategy to struggle with oncological diseases based on early detection and prevention. The existing methods are vaccines to target specific viruses (primary prevention), in combination with screening (secondary prevention), administration of adjuvant therapy (tertiary prevention), and use of biomarkers. Vaccination has been determined to be highly effective against targeted diseases, especially, vaccination is given in the early years of life. Regular screening (for breast cancer, cervical cancer, etc.) is very important to detect unusual changes or abnormalities in the body. Adjuvant treatment is getting more attention in tertiary prevention for remedy of the disease. The discovery of biomarkers and latter targeted therapies has led to personalized medicine which is getting more popular treatment in cancer care (Chow, Yip, & Ng, 2012).

The oncogenomics, include the determination and implementation of clinically actionable targets tailored to an individual patient's cancer genomic information. The screening of tumors via DNA sequencing and the assessment ability of these large data sets from well-organized tissue banks can be used in definition of molecular subtypes of cancer. These new genomic informations bring new approach to perspectives on cancer diagnosis and treatment,

offering insight into prognosis, progression, and susceptibility or resistance to known therapeutic agents. By using these informations it is possible to form treatments tailored to patients that can greatly improve their chances of survival. The connection between tissue banking and genomic sequencing datas can be used as a new force in precision medicine. (Miles, Rae, Ramalingam, & Pfeifer, 2015).

Personalized oncology within the individualized medicine, provide right care to the right cancer patient at the right time and results in measurable improvements in outcomes and a reduction on health care costs. Molecular individualized medicine and biomarkers are replacing the conventional "one size fits all" medicine. The principle of personalized oncology based on the use of biomarkers. These biomarkers can be from serum, tissue, urine or imaging and must be accebtable. There are three different types of biomarkers which are important of particular importance: predictive, prognostic and early response biomarkers. Tools for implementing preemptive medicine based on genetic and molecular diagnostic and interventions will improve cancer prevention. Imaging technologies such as Computed Tomography (CT) and Positron Emitted Tomography (PET) are already influencing the early detection and management of the cancer patient. Future advances in imaging are expected to be in the field of integrated diagnostics, molecular imaging, biology driven interventional radiology and theranostics. Molecular diagnostics include testing for genes, gene expression, proteins and metabolites. The molecular diagnostics will apply into new cancer therapies in future with greater efficiency, value and cost savings. This approach will provide a unique opportunity in personalized oncology (Kalia, 2013).

2.12 Personalized Medicine in System Pharmacology

The predictive, preventive, personalized, and participatory (P4) medicine provide new approach to the healthcare (Hood & Flores, 2012). Transformative changes, related to P4 medicine, have connection with a new discipline, called systems pharmacology. Systems pharmacology assembles genome-wide experiments with advanced computation and modeling to understand drug activity in the cell related to the human phenotype. Systems pharmacology includes systems biology with pharmacology and also involves genetics, genomics and computer science. It tries to find a connection of drug perturbations of the molecular networks of cells to the human phenotype. For example, whole-genome sequencing of individuals could be used to detect mutations that can be used to identify genetic disorders and novel drug targets (Baranov, 2011). In addition, gene expression, metabolomics or proteomics of cells from the blood (Sadee, 2011), or sequencing of the microbiome from mouth or skin (Laing, Hess, Shen, Wang, & Hu, 2011), can be used to monitor the health status of an individual (Sadee, 2011). These data can be interprets with drugs taken by individuals and the adverse events of it (Jenkins & Ma'ayan, 2013).

2.13 Personalized Medicine in Pluripotent Stem (iPS) Cells

Pluripotent stem (iPS) cells, have become the most important tool in improvement of personalized medicine. The capasitiy of pluripotent stem cells to self-renew and differentiate into all somatic cell types created big oppurtunity and expectations in regenerative medicine and human health (Ferreira & Mastajo-Radji, 2013). There is a possibility of reprogrammed somatic cells can be used in personalized medicine as an autologous cell therapy. Actuated pluripotent stem cells display several genetic and epigenetic abnormalities which cause to tumorigenicity and immunogenicity in vivo. Understanding of these effects in abnormalities by actuated pluripotent stem cell derivatives, provide a possibility in taking measures to prevent immune rejection (de Almeida, Ransohoft, Nahid, & Wu, 2013).

The discovery and characterization of stem cells, with self-renewal and differentiation capacities, also accelerated this field, making regenerative medicine a new independent discipline (26). The recent discovery of induced pluripotent stem cell technology, which eventually turn into a pluripotent stem cell; with potential of differentiation to any cell type, provide a big opportunities in cytotherapeutics. The applications in pluripotent stem cell technology such as; to derive, repair, propagate, and transplant cells specifically for individual patient provide new route to personalized medicine (Janowski, Bulte, & Walczak, 2012).

Addition to these subject also:

Relatively few data also started to use personalized medicine in physical exercise (Buford, Roberts, & Church, 2013) and in the psychiatry. Genotyping-based personalized psychiatry is getting popular in near future as well (Costa e Silva, 2013). Cardiovascular diseases and neurodegenerative disorders and perhaps infectious diseases will be the next targets of P4 medicine as well (Bergoechea, 2012).

3. Conclusion

All these research and studies indicate that medicine contents' have extended to predictive, personalized, preventive and participatory medicine (P4). 'Personalized medicine' focuses on the prediction of potential benefits or risks for individuals as possible as in detailed.

The worth of health care can be increased by individualized medicine. Personalized medicine include right drug for the right individual for the specific disease affecting particular individual. Using of personalized medicine will effect more efficiently the clinical trials via lowering the costs. The genotypic experiments have added significant values into genetic background of diseases (Gupta, 2015). Molecular diagnostic tests are subject to the predictive, preventive, and personalized medicine for clinical and socioeconomic benefits to the patients. (Akhmetov & Bubnow, 2015).

Genomic and personalized medicine include the use of traditional genetic information, as well as modern pangenomic information, aiming personalized risk assessment, prevention, diagnosis, and treatment of cancers and other diseases. This genetic information has been used for several decades. However, the rapid improvement in techniques provided us to perform high-throughput, high-density molecular analyses to describe the genomic, proteinomic, and epigenomic make-up at individual bases. Personalized medicine, in other words, "for predicting health, preventing and preempting disease, and for personalizing treatment depending on the each person' unique biology", focusing especially on genomics, has a speed improvement and application in different subject and area of medicine such as; oncology and cancer; **biomarkers**; genetict test; pharmacogenomics; nutrigenomics; system biology and omics; genomic research; genetic profiling; epigenetics and tailoring therapy; molecular, patological and epidemiological studies; regenerative medicine; and pluripotent stem cell studies. The personalized medicine applications' in all these areas are giving promise in more effective treatment of disease and illness.

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