EDITORIAL

Precision Medicine: From Concept to Clinical Practice – A Promising Challenge!!

INTRODUCTION

In 2011, the US National Research Council initiated a holistic concept of precision medicine (PM), based on the assumption that an individual’s variations in genomic and epigenomic determinants will enable personalization of appropriate prevention and treatment interventions. This in contrast to the “one size fits all” strategy for the management of diseases which has got a laid down standard of care. The concept supposedly can predict which treatment to initiate and at what point of time in the natural course of a disease focused on an individual [Figure 1]. It has been gaining ground in the last decade, and its application is being discussed. Currently, the National Institute of Health (NIH) has initiated a project on PM where they plan to recruit a cohort of one million volunteer who will provide genetic data, biological samples, and other health information to generate a big data for precise and targeted diagnosis and treatment options for a variety of diseases.

PM focuses primarily on oncology because of the existing understanding of the unique genomic signatures of increasing number of cancers and their genetically targeted therapies. However, deep data analysis of “individual variations” in genetic predisposition, reaction to food, nutritional deficiencies, dysfunctional hormonal response, variable inflammatory, or immune response to an infectious agent, and microbiome imbalances are found to be influencing common complex diseases such as autoimmune diseases, malnutrition, hypertension, heart disease, type 2 diabetes mellitus. In these diseases, the genomic variations are usually small, but other individual variations are large. In this article, we have discussed the potential involvement of both noncommunicable and communicable diseases in PM and its impact on clinical practice of medicine.

PRECISION MEDICINE IN ONCOLOGY

Cancer is a complex condition which manifests as uncontrolled growth of tissues. There are almost 100 different types of cancers located in different organs and tissues originating from different cell types. It is becoming increasingly clear that cancers and its treatment are not the same in two patients. Hence, traditional treatments, such as chemotherapy and radiation, are not always effective. PM model is widely used in this approach and is different from the traditional clinical approach [Figures 2 and 3]. This concept has encouraged the development of specialized treatments of each specific subtype of cancer based on measurement and manipulation of key patients’ genetic and omic data (transcriptomics, metabolomics, proteomics, etc.). “Omic” technologies have a broad range of applications and are aimed at the detection of genes (genomic), mRNA (transcriptomic), proteins (proteomics), and metabolites (metabolomics) in a specific biological sample.

Some promising examples of PM in oncology are the use of anaplastic lymphoma kinase (ALK) blockers such as “crizotinib” and “ceritinib” for non-small lung cancer patients positive for ALK mutation and use of the poly ADP ribose polymerase inhibitor “olaparib” in the treatment of BRCA-mutant ovarian cancer. In the diagnosis front, companion diagnostics, an in vitro device, can help in identifying which treatment will be most effective for a specific cancer (pharmacogenomics), causing minimal damage to healthy tissues, making the PM model more effective and safe in the practice of oncology.

IT IS NOT ALL CANCER-PRECISION MEDICINE IN DIABETES, HYPERTENSION, AND MENTAL HEALTH

PM has embarked on the clinical practice of lifestyle diseases to predict the onset and prognosis of these complex diseases based on individual patient’s age, family history, ethnicity, mental health, medications, biochemical profile, lifestyle, and body weight. For example, in diabetes mellitus, the etiology, clinical presentation, and consequences vary greatly from one patient to the next, but the management is directed only toward the biochemical consequence of the disease, i.e., elevated blood sugar levels. Recent studies have found individuals’ genotypes to be associated with variable responses to lifestyle interventions in individuals with prediabetes and women at risk with gestational diabetes mellitus. Advances in pharmacogenomics have been used to predict individual response to drugs in diabetes. Patients with genetic variants associated with increased response to metformin and sulfonylurea as a result of reduced renal clearance might also be at risk of side-effects with deteriorating renal function, whereas patients with variants associated with increased responsiveness to thiazolidinediones might benefit from the drug. With big data analysis, PM can recommend personalized treatment of diabetes and match the right drug with the right patient at the right time to obtain the best clinical outcome.

Advanced research on hypertension has found that almost half of all patients being treated for the condition are taking...
more than one drug and that high blood pressure remains uncontrolled in 40% of patients despite treatment.\[^{10}\] Although many reasons exist for poor blood pressure control, a likely contributor is the inability to predict to which antihypertensive drug an individual is most likely to respond. Hypertension PM has the potential to identify genetic signals that are predictive of response or adverse outcome to a particular drug, and guide selection of hypertension treatment for a given individual.

PM in psychiatry is a new field\[^{11}\] and is greatly needed given the huge societal costs and a prolonged time needed for an observed benefit from treatments and their response variability. Although over 50% of response variance of antidepressants are genetically controlled, at present, only a few genetic and nongenetic targets are known and their predictive power is still to be fully understood for routine use in clinical practice. Similarly, evidence from family, twin, and adoption studies show that bipolar disorder is highly heritable, with genetic variables estimated to account for 60%–85% of the risk.\[^{12}\] Wang et al., in an open-label randomized controlled trial observed that genetic variation in glutamatergic or NMDA neurotransmission to be implicated in short-term antipsychotic treatment efficacy in schizophrenia.\[^{13}\]

**Microbiomes in precision medicine**

Advances in microbiomes, the genetic material present in microbes, have revolutionized the application of PM in infectious diseases. Genome sequencing and molecular tests have enhanced patient care by delivering precise and timely identification of pathogens as well as susceptibility to antibiotics. We are currently trapped in the biological arms race between emerging resistance and novel antibiotics. Human trials of nonlethal precision drugs which disrupt this cycle by inactivating the pathogen without killing them are in vogue. A recent trial by Laterre et al. found positive results of CAL2, a novel antitoxin liposomal agent administered as an adjunct to antibiotic therapy in severe community-acquired pneumococcal pneumonia with success.\[^{14}\]

There is an inherent lack of understanding in pathogen detection and treatment effect size for the same antibiotic agent in individuals suffering from sepsis. The variability depends upon the microbial load, site of infection, presence of comorbidities, duration of sepsis, age, gender, and functional immune status of the patient. Increasing the use of rapid nucleic acid sequencing, along with epigenomic-, metabolomic-, and proteomic-based tools with big data analysis to determine the molecular basis of variability in host response have been showing great promise for addressing early diagnosis and personalized antibiotic treatment and stewardship in sepsis.\[^{15}\] PM has been studied in the poorly understood multidrug-resistant tuberculosis. Whole genome sequencing data of *Mycobacterium tuberculosis* along with individual clinical case histories

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**Figure 1:** The precision-medicine ecosystem contains building blocks that link patients, clinicians, researchers, and clinical laboratories to one another.\[^{4}\]

**Figure 2:** Traditional model of diagnosis and treatment of cancer

**Figure 3:** Precision medicine model of diagnosis and treatment of cancer. Adapted from Krzyszczyk et al.\[^{8}\] Traditional versus precision medicine model for cancer treatment. Traditionally, cancer has been treated using chemotherapy, immunotherapy, radiation, and surgical excision of tumors. These treatments vary widely in efficacy across individuals and also often cause harm to healthy, noncancerous organs and tissues. The precision medicine approach is characterized by individualized treatments tailored to specific tissues, gene mutations, and personal factors relevant to each unique case of cancer and symptoms, may address the complicated nature of the epidemiology of resistant tuberculosis and allow for tracing...
Figure 4: Domains of precision medicine in diseases. Diverse approaches and techniques converge to a unique phenotypic profile. These domains when analyzed with big data so generated will produce a better diagnosis and targeted therapy. 

its transmission in the community taking into account the individual variability in genetic, environmental, and lifestyle of each person. 

**Precision Nutrition**

Increasingly, it is being understood that an individual’s diet and environment may impact disease susceptibility. The genetics and omic driven precision nutrition deal with the variability of nutritional metabolism among individuals in response to dietary interventions. Large scale trials have not specifically concluded the beneficial effects of foods rich in omega-3 on cardiovascular disease. Omega-3 index, which ranges from 2% to 20% and depends on race, with Japanese and South Koreans having a high omega-3 index, has been found to be a promising novel biomarker for the prediction of cardiovascular disease. Precision nutrition trials promise to consider big data analysis taking an individual’s phenotype, metabolic profile, nutritional biomarkers and environmental factors to prescribe specific, individualized, actionable dietary therapy for nutritional disorders such as obesity, diabetes, and cardiovascular diseases.

**Conclusion**

Precision Medicine intends to offer to clinicians the possibility to tailor the diagnosis and treatment of cancer, lifestyle diseases, psychiatry diseases, and infectious diseases according to the best possible evidence of effectiveness and tolerability for each subject. However, implementation of PM may be challenging. A genetic test is usually 100% sensitive and 100% specific for identifying a genetic disorder. However, the test result is associated with only a risk of the development of a disease or a differential response to drugs. It is necessary to collate specific biological data of different diseases and population wide data of individuals’ behavior, lifestyle and environmental effects to make clinically actionable decisions. The generation of big data will need large scale PM trials. The implementation of PM will require collaboration across the fields of research and healthcare, funding agencies, academic institutes, private hospitals and omics providers, and most importantly, proactive involvement of the physicians.

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