

Precision medicine, pharmaco-genomics and neutro-genomics and genomic medicine: A newer approach for patient management from clinic to basic

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Introduction

What is precision medicine, pharmacogenomics and neutron genomics?

Precision medicine refers to the adapting medical treatment to the individual characteristics of each patient. According to the Precision Medicine Initiative, precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. In this field, the individuals are classified into subpopulation that differ in their susceptibility to a particular disease or in prognosis of those diseases they develop, or in their responses to the specific treatment, in terms of their uniqueness in genome and targeting therapeutic and preventive intervention according to it. This approach allows doctors and researchers to foresee more accurately which treatment and prevention strategies for a particular disease work for the individual or groups of people.

Although the term "precision medicine" is relatively new, the idea has been a part of healthcare for many years. For example, a person who needs a blood transfusion is not given blood from selected donor directly; instead, the donor's blood type is matched to the recipient to reduce the risk of complications. Only thing is that the new domains are added to it in diagnostic testing based on molecular diagnostic, imaging and analytics for selection of appropriate and optimal therapies in perspective of patients' genome. Pharmacogenomics is a part of precision medicine. Pharmacogenomics is the study of how genes affect a person's response to particular drugs. This relatively new field combines pharmacology and the functions of gene to develop effective, safe medications and doses customized to variations in a person's genes.

Neuro-genomics is the study of how diet and our dietary habits affect our genes. DNA and RNA analysis employed to see how the mutations happen in the subject population pertaining to diseases and how the nutrients we consume affect them. The difference in the nutrients our body absorbs is due to genetic differences that affect absorption of carbohydrate, proteins as well as vitamins and minerals and other nutrients.¹

Inter-personal difference of molecular pathology is distinct, so as inter-personal difference in the exposome, (environmental exposures) which influence disease processes through the interactome (whole set of interactions in particular cell) within the tissue microenvironment, differentially from person to person, so as different nutrient affect each person differently.

Origin of the Disease Principle

Long back, human genomic project confirms such variations exist among ourselves and influences the choice of drugs, food exercise and tendency towards disease, where the 1.42 million variation /mutations (SNPs: single nucleotide proteins) are identified associated with the lifestyle diseases. Though the disease principal was first describe in neoplastic pathogenesis as unique tumor principle and named as "unique disease principle" in precision medicine and now began to hold the universal phenomenon of heterogeneity of disease pathology and etiology and capable of identifying potential biomarkers for precision medicine.

Role of Pharmaco-genomics and Neutron-Genomic in Modern Era

According to the neutron-genomic link study² Liver X Receptor (LXR)- α , a key transcription factors, related with the several chronic diseases including coronary heart disease and neurodegenerative diseases (Alzheimer) have found to be regulated by the dietary components. It regulates array of genes involved in lipid metabolism, Inflammation, glucose homeostasis and innate immunity and highly expressed in normolipidemic and hyperlipidemic coronary heart diseases patients. But this protective role of it is challenged owing to inherent genetic aberration in such subjects.³

The various other study on LXR- α also found Vit. D3 as alternative ligand for the aberrant form of LXR- α which maintains functional normality also statins which said to best drug of choice for CVD and Vit. C increases expression of LXR⁴ and Withaferin A, isolated from *Withania somnifera* a plant product used to promote mental and physical health and also act as a ligand⁵ suggesting dietary component plays major role in activation of LXR-alpha and regresses CVD, also study suggestive of association of CVD with low serum Vit. D3⁶ confirms it.

We can quote many such examples,⁷ where various genes affect obesity management which are associated with type of food (carbs vs Fats) meal plan, type of exercise (power vs endurance), time of exercise (CLOCK gene), so prescribing similar diet plan to all didn't help. Likewise, various cardiac governing genes alter outcome in cardiac and vascular health in different subject individually. These governing genes can give insight and revolutionized treatment modality and individualize the treatment plan according to genetic specificity under genomic medicine. Genomic medicine uses individual genetic information of an

individual clinical care and applied effectively in treating the conditions. The era has begun where it has been efficiently used in cancer genomics, Pharmacogenomics and rare and undiagnosed diseases and shall be used for many common diseases like diabetes, tuberculosis, obesity, insomnia and depression. The ministry has to take more researches in this field of pharmacogenomics and neutrogenomics to explore all the common diseases in India considering all to different ethnicity, cultural habits in interest of public health.

Who will be benefitted?

Considering the high treatment cost of this modality, doctors should wisely choose the cases which are stubborn and fails to show response to standard regime to this personalized medicine. It also can help clinicians/practitioners in many ways such as:

1. In assessing risk: few individuals are more susceptible to particular disease like CVD, Stroke cancer and their genetic responses associated to various risk factors like atherosclerosis, hyperlipidemia, smoking habits due to certain genetic makeup. Awareness of it about the non-responders help in managing the risk through tailored medicine, medical intervention and positive lifestyle.
2. Diagnosis: In diagnosis of diseases, where the cause of range of symptom cannot be identified by any other resources.
3. Marital genetic counseling and prenatal counseling, where there is family history of any disease to help in persons and parents to make informed choices and plans the future.
4. In developing national and international health scheme: developing strategies to take care for rising trends and particular community and giving platform to doctors and the parents of the children having rare diseases to learn about it from open-access database of all genetic condition.
5. Role in epigenetic: It is based on the concept that each gene has chemical tag which determine how it has to act, which makes that gene dormant or active, keeping the genetic code same but the way it expresses it change. These chemical modifications can also be passed on to the next generation, creating a more variable level to genetic inheritance. This knowledge will give opportunity to researchers and scientists to bring changes, positive and negative way in the future generations in basic biological level to create super humans free from all diseases.

ClinGen a Specific Program of NHGRI (National Human Genome Research Institute, USA) in Implementation of Genomics

NHGRI has developed program ClinGen (clinical genomic resource) to bridge the gap between practitioners, clinicians and researchers and policy makers based on depth characterization of the patients and breadth of implementation under NIH undiagnosed disease program (UND). The UND was assessing undiagnosed diseases by

several advance method where phenotypic and genotypic data of individual patients were shared across clinical site and laboratories and compared for exome and genome in undiagnosed disease. Then CSER (Clinical Sequencing Exploratory Research) utilizes this data to explore the prospective of clinicians to use the genome sequence in diagnosis and management for various clinical prospective like screening, preconception, cancer, healthy subject. It also analyzes and generate an evidence of clinical utility. EMR and eMERGE (Electronic Medical Records and Genomics) network establishes the research values of collected biorepositories particularly in rationality of electronic phenotyping and generate the evidences of impact of genomic medicine implementation at hospital level and academic healthcare system along with IGNITE (Implementing Genomics in Practice). This network assesses and disseminate successful genomic medicine practice models that integrate genomic data effortlessly into the EMR and implement clinical decision support tools for decision making for early adopter institutions; and transporting that to diverse set of partners sites with less expertise genomics practitioners to expand, link genomic medicine efforts and bring evidence generation for assessment of impact beyond the level of individual institutions.⁸

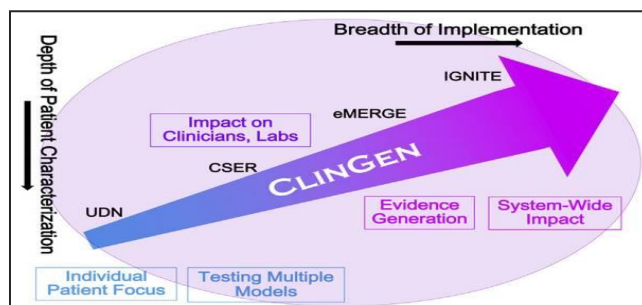


Fig. 1: NHGRI genomic medicine implementation programs by depth of patient characterization and breadth of implementation

Present Scenario and Future Prospects of Genomics in India

Since last 2 -3 decades India has progressed in molecular diagnostics and develop excellent skills in medical genetics for metabolic disorders, cancer genetics and bringing the benefits to the patients. Though journey has begin, the research in genetic disorders still far away in the areas of understanding pathogenesis and pharmacogenomics in developing new drug molecule.⁹ Notwithstanding numerous reports of new syndromes from India, there has been no impact in the area of gene mapping. However, the input by Indian scientists to gene mapping is limited, these scientific group had achieved a landmark by sequencing the first Indian genome and establishing the Indian Genome Variation Consortium which doing further research in MENDELIAN Genetics.¹⁰ Also we are failing in inclusion of medical genetics in medical curriculum,

bridging gap between practitioners, and sensitizing them about recent advances in this field.

To cater a demand of huge population in India, we need to expand the more number of genetic laboratories, improved health budget allocation, sensitization of health authorities and policy makers toward burden of diseases with its genetic makeup. The proactive involvement of policy maker in appropriate screening management of rare diseases, registration of common diseases and implementation of specific designed program like ClinGen must be developed, so as the clinical scientist will not underutilize voluminous clinical data available in India. Medical council of India should develop medical curricula to take molecular medicine at every level of medical practice. As we are far away in gene therapy and stem cell therapy and recombinant products research, development in this area will go long way to provide genomic medicine at affordable cost in India.

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