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Review Article

Application of precision medicine in medical conditions

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ABSTRACT

The idea of precision medicine came into existence that all patients who received the same therapy do not respond in the same manner and there exists an inter-individual variation. Researchers then found that precision medicine plays a vital role which may lead to treatment failure or toxicity. Precision medicine will provide the right medicine at the right time to the right patients with specific characteristics for a better clinical outcome. It utilizes the information related to a person's genes, proteins and environment to cure disease. This breaks the model of "one fits for all" and it helps us to sequence DNA which is unique for everyone and to decide therapy based on the genetic information. The difference between the terms "precision medicine" and "personalized medicine" is to be understood since the former will classify people into subpopulations that have difference in their susceptibility to disease and the latter refers to a single drug for a single individual. It has its applications to detect any genetic alterations starting before birth and till old age. Due to this reason, precision medicine has taken over the personalized medicine and the word "precision" means accurate and precise.

Keywords: Precision medicine, Umbrella trial, Targeted therapies

INTRODUCTION

The idea of precision medicine came into existence that all patients who received the same therapy do not respond in the same manner and there exists an inter-individual variation. Researchers then found that precision medicine plays a vital role which may lead totreatment failure or toxicity. Precision medicine will provide the right medicine at the right time to the right patients with specific characteristics for a better clinical outcome. It utilizes the information related to a person's genes, proteins and environment to cure disease. This breaks the model of "one fits for all" and it helps us to sequence DNA which is unique for everyone and to decide therapy based on the genetic information. It has its applications to detect any genetic alterations starting before birth and till old age. There is a difference between the terms "precision medicine" and "personalized medicine". The former will classify people into subpopulations that have difference in their susceptibility to disease. Thelatter refers to a single drug for a single individual. However, precision medicine has taken over the personalized medicine and the word "precision" means accurate and precise.

Precision medicine is defined by the national institutes of health as, "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person".[1]

Integration of clinical phenotypes and biological information including-omics data is done in precision medicine. There are many precisions medicine driven studies like basket or umbrella trials which have a role in oncology cancer studies.

PRECISION MEDICINE TRIALS

Stakeholders involved in precision medicine include participants, providers, patients, payers and regulators. If successful evidence of value is found, there will be a treatment shiftfrom disease treatment to prevention since prior genetic testing will make us aware of the condition

and avoid giving drugs to the patient.

Precision medicine trials include basket trials, umbrella trials, adaptive trials and n-of-1 trials. In basket trials, drug is tested against a single mutation which is responsible for multiple conditions. Based on the basket trial, Vemurafenib was approved in the year 2017 and given to patients having BRAF V600 mutation for a rare hematological cancer named "Erdheim-Chester disease (ECD)".[2]

In umbrella trials, "Umbrella" means the separation of one cancer into many subclasses based on their molecular features.[3] These trials will help us to discover new effective drugs faster. The combination of both basket and umbrella trials refer to Super umbrella trials. N-of-1 trials involve a single individual who is given the treatment which is repeated over many crossover periods. It is done till conclusive conclusion comes for that particular individual. Adaptive trial design is used to evaluate targeted therapies.

In this design, interim analyses are done and trial is altered based on the results obtained. An example for adaptive trial is BATTLE (Biomarker-integrated approaches of targeted therapy for lung cancer elimination).[4] The main issue with adaptive design is pre-specified adaptations should be formed before starting the trial and confidentiality should be maintained in the patient getting allotted to one arm in order to maintain the integrity of the study.

DOMAINS OF PRECISION MEDICINE

There are various domains in precision medicine which contribute for the unique phenotypic profile. The word "omics" refer to study relating to information of an individual based on the protein structure, genome, metabolite and they will help to rationalize and guide the dosing of the patient at the time of prescribing. They include genomics, metabolomics, proteomics, epigenomics and micro-biomics. They help to optimize the need for precision medicine.

Proteomics refers to the analysis of protein expression profile and to study the causality in the presence of protein abnormality. Mass spectrometry, western blot is employed as the analytical methods in proteomics. They also compare the protein expressionprofiles. Issues faced with proteomics are that protein expression alters with time and this becomes complicated. They have application in oncology, agriculture and food technology.

Metabolomics refers to the study of metabolites that occur in biological samples and the collection of metabolites is called "metabolome". They can identify the phenotypic changes which tend to occur due to genetic manipulations like deletions, insertion, substitution and their application lies in the prediction of the function of unknown genes.

Epigenomics refers to the modifications by which cells "read" genes get affected leaving the sequence of DNA intact. This will lead to the occurrence of cancer by increasing the damage to DNA. DNA methylation and histone modification are the mechanisms behind the role of epigenetics leading to cancer. Blocking DNA methylation (e.g., Azacytidine and decitabine) and histone deacetylation inhibitors (vorinostat and romidepsin) are employed for the treatment of myelodysplasia and cutaneous T-cell lymphoma respectively.[5]

The human microbiome project (HMP) deals with study of gut microbiome which also affect not only in gut but also in other parts of the body because of microbiota-gut- brain axis. This study is referred to as microbiomics.

Pharmacogenomics refers to analysing the entire genome to assess multigenic determinants of response of the drug which helps to guide the dose on an individual basis. E.g., Warfarin is metabolized by the CYP2C9 gene. If there is any polymorphism in the gene,it will lead to a decrease in requirement of dose. Pharmacogenetics means studying of differences in drug metabolism mediated by genes in humans. Main role of genomics lies in the field of oncology.

Implementation of precision medicine is to identify the right patient who should receive the right dose. The variation in treatment response is to be considered.[6]

Pharmacokinetic variability includes change in subject phenotype, weight, organ status, age, ethnicity, gender. Subject genotype: Any genetic change (Polymorphisms) in metabolizing enzymes or transporters. Progression of the disease with time. Treatment compliance, route of drug administration, dosing regimen and formulation of the drug. Pharmacodynamic variability: Polymorphism in drug target or downstream pathway.

DISEASE HETEROGENEITY

The important source of response variability in terms of selecting the right treatment is disease heterogeneity. e.g., Vemurafenib (Acts by targeting mutated b-raf in tumors having V600E mutation in b-raf gene). This drug is used for melanoma but not effective for colorectal carcinoma with the same mutation.[7] The additional factors accounting for this heterogeneity should also be borne in mind.

ROLE OF THERAPEUTIC DRUG MONITORING IN PRECISION MEDICINE

Therapeutic drug monitoring (TDM) has an important role in the execution of precision medicine as doses can be adjusted in individual patients in order to achieve a predetermined target exposure. Drug dosage adjustment is done based on plasma drug concentration. e.g., Drugs used in seizures as well as biologic agents in the rheumatoid arthritis.[8]

ROLE IN ONCOLOGY

Precision medicine in the field of oncology (precision oncology) is to identify which therapies will be effective for a patient based on genetic makeup in cancer. By precision medicine, targeted therapy is given and so all the cells which are dividing are not affected unlike in conventional chemotherapy (Table 1). The biomarker is divided into 4 categories which include diagnostic, prognostic, predictive and pharmacodynamic biomarker. The biomarker is measured and evaluated to detect physiological or pathological process e.g., In breast cancer, Her2 + cancer is treated by targeted therapy like trastuzumab.[9] Biomarker assay is done to detect the staging of cancer. Targeted therapy works by decreasing the spread of cancer.

Table 1: Targeted therapies.

Drugs	Mechanism of action	Condition
Geftinib, erlotinib, afatinib, osimertinib	Tyrosine kinase inhibitors	Non-small cell lung carcinoma
Nivolumab, pembrolizumab	Immune check point inhibitors	Non-small cell lung carcinoma
Dabrafenib, vemurafenib	BRAF V600E inhibitor	Melanoma
Imatinib	Tyrosine kinase inhibitor	Melanoma
Trastuzumab	Monoclonal antibody against HER-2	Breast carcinoma
Everolimus	PI3K-mTOR inhibitor	Breast carcinoma
Palbociclib	CDK 4/6 inhibitor	Breast carcinoma

Liquid biopsy is another new method to detect biomarker. It is used for treatment selection especially used in non-small cell lung cancer. It is useful when not enough tissue is present in the sample and hard to reach the tumor. Unlike tissue biopsy, liquid biopsy is non-invasive. It is also used to monitor various tumors at an early stage.

Examples

The mechanism of action of Imatinib is to target BCR-ABL fusion gene and it is used in chronic myelogenous leukemia (CML).[10] In patients where there is presence of overexpression of tyrosine-protein kinase erbB-2 (HER2) indicating the tumor's aggressiveness with poor prognosis, trastuzumab is given to prolong the survival and benefit the patients. Trastuzumab is a monoclonal antibody against HER2.[11] Around 40% of patients with metastatic colon cancer do not respond to cetuximab and panitumumab due to the KRAS gene mutation. This is the reason why patients without mutation in KRAS gene should be treated with cetuximab and panitumumab.[12]

ROLE IN ASTHMA

When an underlying etiology for persistent hyper-eosinophilia is not found despite thorough diagnostic evaluation, clinicians should consider the diagnosis of hyper-eosinophilic syndromes (HES).[13] Mepolizumab, an IL-5 antibody, was not found to be effective in patients with moderate asthma. It was later shown that it is effective in patients having hyper-eosinophilic syndrome.[14,15]It was later found that there is role of disease heterogeneity in selecting the right drug for the right patient. Efficacy of omalizumab depends on free IgE levels to be<50 µg/mL.[16]

ROLE IN METABOLIC CONDITIONS

Diabetes mellitus

Sulfonylurea is a first-line treatment in neonatal diabetes with KCNJ11 and ABCC8 gene mutation.[17-20] Permanent diabetes is developed in half the people who develop neonatal diabetes. The mutation in genes which encode ATP-sensitive K+ channel (KCNJ11 and ABCC8) is present in 70% of population. The result is the closure of K+ATP channels is blocked preventing insulin secretion and beta-cell depolarization. Treatment with sulfonylurea corrects this defect allowing to discontinuing giving exogenous insulin.[21]

Dyslipidemia

PCSK9 [Proprotein convertase subtilisin/kexin type 9 (PCSK9)] is a hepatic secretory protein that binds to low-density lipoproteins (LDL) receptors (The role of LDL receptors is in the clearance of circulating cholesterol) and is considered to be the drug target in hypercholesterolemia.[22] PCSK9 inhibitors like alirocumab and evolocumab are used in the treatment of hypercholesterolemia. Loss of function mutation of ANGPTL4 gene is related with better lipid profile and decreased risk of heart disease and this makes ANGPTL4 a drug target in coronary artery disease.[23]

ROLE IN PREVENTIVE MEDICINE

Precision medicine has a vital role in reducing ADRs of a drug thereby facilitating compliance. Many ADRs result due to variation in genes that code for drug-metabolizing enzymes like CYP450. The result will be that the drug will be metabolized at a faster or slower rate.[24,25]

Pharmacogenetics of an individual has a great deal to play in prediction of the risk of adverse events and it will identify the patients who should receive a particular drug.

Genetic testing is required for all patients who take abacavir due to multi-organ system hypersensitivity associated with HLA-B*5701 gene.[26]

Biomarkers like HLA-B*1502 and SLCO1B1 are useful in

patients with Steven-Johnson syndrome and Simvastatin-induced myopathy respectively and this shows there is presence of pharmacodynamic variability on selection of the drugs.[27]

The effects of warfarin are altered in genetic polymorphisms of vitamin K epoxide reductase convertase 1.[28]

Identification of genetic aberrations related with familial cancer syndromes has paved the way for therapeutic options to reduce risk of cancer occurrence.

Tamoxifen has been found to be beneficial among women with BRCA2 mutations and it is one of the preventive measures to prevent cancer.[29,30]

Aspirin is also found to reduce the risk of colorectal cancer in Lynch syndrome.[8]

HOW TO CONVERT PRECISION MEDICINE IN CLINICAL CARE?

Implementing GeNomics in Practice (IGNITE) is a network established in the year 2013 and is consisting of six projects with a coordinating center. The aim is to translate available genomic information obtained from precision medicine and translate into clinical scenarios.

POLICY AGENDA FOR PRECISION MEDICINE

The main thing is to generate evidence and share the data at the point of care. Precision medicine tests are mainly laboratory-developed tests (LDTs) and they don't require the approval from FDA. The study as such involves a lot of questions regarding the patient engagement and trust and the emphasis should involve populations rather than individuals referring to the term "Precision public health".

CONCLUSION

The development of a precision medicine approach minimizes the time to diagnose and makes an accurate diagnosis at early stage. In India, precision medicine is utilized mainly for oncology purposes by targeted therapy based on the detected mutations. Even though the genomics is supported by evidence, their evidence is not converted into actions in our country. Excluding some drugs like carbamazepine and abacavir where HLA testing is done to detect HLA-B*1502 and HLA-B*5701 respectively, clinicians mostly don't convert this evidence into their clinical practice. Apart from the cost, lack of proper awareness and poor family conditions make the patients refuse such novel methods. This is a stumbling block for medical practitioners. If only precision medicine is implemented at the early stage, the success rate of treatments of most of the genetic diseases will be very high and it will be agreat service to the society.

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