PERSONALIZED MEDICINE

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ABSTRACT

Since ancient era, the approach for the diagnosing and treating the patient is evidence mostly evidence based. To elaborate we can say that for diagnosing and managing the patient, physicians use to focus on individual’s signs and symptoms followed by going through the series of data from the lab and imaging. Then the final treatment for the disease starts. In short we can say today it’s a population based- combined with evidence along with individual’s clinical expertise is the approach in prescription writing. But the same won’t be tomorrow, thanks to the novel concept of Personalized Medicine.

WHAT IS PERSONALIZED MEDICINE?

According to various papers and articles, Personalized Medicine is defined in different way:

“...personalized medicine uses new methods of molecular analysis [and predictive modelling] to better manage a patient's disease or predisposition toward a disease. It aims to achieve optimal medical outcomes by helping physicians and patients choose the disease management approaches likely to work best in the context of a patient’s genetic and environmental profile…”[1]

According to me, personalized medicine is a concept of “we are treating the patient, not the disease” where medications are tailored according to an individual response and need.

CONCEPT OF PERSONALIZED MEDICINE:

We are all different and so is our behavior whether it is to anyone or to anything like drug. That is why different people react differently to same drug. Apart from this if we know the patient’s entire genome then we can very efficiently tell that which medication will suite to an individual. So in late 1990’s with the evolution of molecular biology, genetics and molecular medicine, came the concept of “tailored medical caring according to individual’s need”. This concept is based on the following backbone:

Human Genome Project is a joint project done by US Department of Energy and National Institute of Health which completed in 2003. The goal was to learn the order of 3 billion units of DNA making human genome. Currently it is indicated that 22000 to 23000 genes are contained in human genome. Personalized Medicine Research Project is one of the largest population based genetic study project running in United States, which studies the genetic pattern of about 20,000 participants forming a database which enables scientist to know which gene is responsible for causing the disease and which one for the reaction to a drug (Pharmacogenomics). This will help physicians to select correct drug or the treatment processes thus lowering down the side effects with a more successful outcome.

In the form of diagram personalized medicine can be described by this simple diagram.

Diagram to show how personalized medicine concept works. [2]
HOW THE SYSTEM WORKS:

Human Genome project have identified that human genome is made up of about 22000-23000 genes. Scientists compare genes behavior in normal individual to those in the diseased individuals. One of the real world examples is the genetically linked variability response in patients on Warfarin. Warfarin is prescribed to >2 million patients a year. Common reasons for inpatient treatment are the diagnosis of clots (DVT or PE), clot prevention after heart attack. Out of these patients 21% of patients (400,000/year) experience adverse bleeding events during their warfarin therapy. According to a multi-centre, randomised, blinded, parallel group study design of genomics CYP2C9/VKORC1 combined with other clinical factors, accounts for up to 60% of variation in Warfarin response. Results of this trial showed that dosing just on basic of clinical factors it took 32 days to achieve stable anticoagulation whereas dosing with pharmacogenetic support it took just 14 days to achieve stable anticoagulation [3]. Another example is its use in the cancer management like breast cancer. The Breast Bio-classifier, used by a private company, is a 55-gene-qRT-PCR assay which classifies ER-positive and ER-negative breast cancers into expression based subtypes that can predict the patient’s outcome very efficiently so that they can undergo surgical interventions before they actually develop those cancer.

TECHNIQUES USED:

The various techniques used for genome sequencing are:

1. **Microarray Technique:** It is a powerful genomics technology which allows quick expression profiling of millions of genes in parallel. “A microarray is a tool for analyzing gene expression that consists of a small membrane or glass slide containing samples of many genes arranged in a regular pattern” [4]. Various microarrays used nowadays are Affymetrix, Agilent, Illumina and Nimblegen. This technology is based on the principle of hybridisation of DNA/RNA (mRNA) strand. In the figure below we are seeing that mRNA has been exploited to hybridize to the DNA template from where it originated. By the use of this technology we can precisely measure the gene expression in the cell.

There are various applications of this technology like in gene discovery, diagnosing a disease, discovering new drugs and in toxicological research. The amount of data used in this analysis is so vast that to ease its access National Centre for Biotechnology Information has formulated Gene expression Omnibus or GEO where gene expression from varied sources is stored.
2. **Genome Wide Association Study:** The GWAS is the concept to study the genes involved/responsible/associated with the development of the disease. It involves comparing the DNA of two groups of individuals, one with the disease and other similar people without the disease. Basically there is a very small variation in the genome of the diseased individual known as Single Nucleotide Polymorphism (SNP’s), where a single nucleotide like G gets replaced with one of the other 3 nucleotide letters – A, C or T - thus producing variation and this study searches for these SNP’s. With this study we can scan a large number of dataset, of many individuals and identify the genetic variation associated with particular disease. Further to this it can also help the scientists in identifying and locating the gene responsible for person’s risk in developing the disease. In order to do a study scientists collect the blood samples from the diseased individuals and study their DNA for SNP patterns, after this they compare these patterns to the DNA patterns of the unaffected individuals. In this pattern scientists can detect and locate the disease causing gene. This is known as Genome Wide Association Study. The first GWAS was used to confirm the involvement of VKORC1 and CYP2C9 as the principal genetic determinant of warfarin dose[^6].

3. **Next-Generation Sequencing:** Next Generation Sequencing (NGS) also known as high-throughput sequencing principle is based on the Capillary Electrophoresis (CE) based Sanger sequencing method. In this method the analysis of complimentary DNA was purely fractionation base for all the varieties of DNA fragment by using electrophoresis on high resolution
denaturing polyacrylamide gels [7]. Although NGS is based on the Sanger Method but it is different from it in many matters like it has the ability to generate millions of sequence at a time, entire bacterial genome can be sequenced within a matter of hours which generally took days, weeks or months. Furthermore in Sanger method vector based cloning was done whereas in NGS direct fragmented and amplified DNA is kept for sequencing [8]. The two most common amplification template used are Emulsion PCR [9] (EmPCR) and Solid Phase Amplification [10]. EmPCR is used to prepare sequencing templates in a cell-free system, thus avoiding the arbitrary loss of genomic sequences which is generally present in bacterial cloning methods. After successful amplification, these fragments can be attached to individual plates where NGS can be performed. Solid Phase Amplification is used to produce randomly distributed clonally amplified clusters from fragment on a glass slide. Thus providing free ends to 100 – 200 million spatially separated template clusters to which universal sequencing primer can be hybridised to initiate Next Generation Sequencing.

WHAT IS IN OFFER?

It is clear that personalized medicine can offer three key things:

a. Better diagnosis with early intervention;
b. Effective Cures; and
c. Efficient Drug Improvement.

a. Better Diagnosis and early intervention:

In reference to the early intervention, there has been a recent technical breakthrough where sequencing of the foetal genome from the DNA of mother’s blood has been done. Cell-free foetal DNA (cffDNA), which comprises of 5-10% of total free DNA in mother’s blood during early pregnancy, can be used to diagnose many diseases like trisomy 21, β thalassemia, early detection of cystic fibrosis and to know the Rh factor of the foetus and can be treated in-utero. In one of the first GWAS, two genes were detected VKORC1(vitamin K epoxide reductase complex, subunit 1), CYP2C9(cytochrome P450, family 2, subfamily C, polypeptide 9) which were causing≈40% of the variability in warfarin dose and simultaneously discovered a new gene (CYP4F2) contributing only 1–2% of the variability [6].

b. Efficient Cure:

The other aspect of the personalized medicine is the correct drug delivery. Personalized medicine increases the diagnostic precision of a disease and its
therapeutic implication. For example, testing the tumour biopsies for significant gene signatures so that correct chemotherapy can be given. In the field of cancer, personalised medicine has a special place because here specific therapeutics which suits best to an individual and the type of tumour is given.

c. Efficient Drug improvement:

The third most important aspect of the personalized medicine is the tailored medicine according to an individual’s need. This allows treatment only to the likely responders and avoids adverse reactions and expensive treatments in non-responders. This approach has formed the basis on how the prospective future clinical trials will be designed. For example, to predict the dose of warfarin in an individual, multiple algorithms like genotypes for 4 genes, 6 host factors and 6 clinical or environmental factors are used. On combining these parameters can predict for approximately 50 to 60% of an individual dose, thus improving the trial and error approach\textsuperscript{[11]}. Some of the other examples of the personalised drugs are Herceptin for breast cancer (target Her2/neu), Erbitux for colorectal cancer (target EGFR), 6-MP for leukaemia (target TPMT), Tarceva for lung cancer (target EGFR) and etcetera.

ISSUES:

Some of the issues generally get raised for personalized medicine:

a. \textit{Patient’s Privacy and confidentiality and right’s}: The top most issue in personalised medicine is about the patient’s privacy and confidentiality. The psychological and social impact of genetic testing on the tested individuals and their family and informing that you are at high risk.

b. \textit{Insurers}: It has raised some issues that who will pay for these costly diagnostic tests along with appropriate medications. As of now the insurance premiums are based on the statistics of a large population whereas at present the personalised medicine population is very less. Apart from this the other aspect is its commercialization that is the test really necessary.

c. \textit{Physicians}: in order to not to lose the clientele, physicians have to build a strong background in genomics so as to make the best use of the data and provide wellness.
FUTURE OUTCOME:

The future outcome of personalised medicine mainly depends on the evidence from the clinical trials showing its effectiveness and value for money. Secondly, adopting the method of genomic study to diagnose and treat the cause should be well designed with clinical proof. It may seem to be a more cumbersome and expensive process at present but in a near future it will provide benefit to patients (almost 100%), payers and the pharmaceutical industries. By knowing the sequence of their patient’s doctors can prescribe more suitable and safer medication thus avoiding any adverse effects. Payers can choose their treatment with higher successful rates thus higher economic return. And for the pharma industries personalised medicine provide a better benefit: risk ratio thus increasing the successful market access.

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