A Review on Personalized Therapies

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Authors’ contributions

This work was carried out in collaboration among all authors. We confirm that all listed authors meet the authorship criteria, and all authors are in agreement with the content of the manuscript. Authors AS, and DS had the original idea for the study and proposed the study design. Authors NP, DS and AS conducted the literature search, screened and selected the studies initially identified. Author DS wrote the initial manuscript and serves as guarantor. Author NP revised the manuscript. All authors contributed to interpreting the study findings and to the final manuscript.

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ABSTRACT

Aims: Healthcare and pharmaceutical research are incessantly reaching to new zeniths which is substantiated by the increasing numbers of diagnostic and therapeutic options available to healthcare professionals for treating patients but a major impediment to this growth has been the evolution of genetic mutation that makes diagnosis and treatment an enigmatic job. Unfortunately, the study of etiology of mutations is still a very neonatal area of research due to the high number of different factors involved in cellular signal trafficking, several metabolic pathways and their simultaneous effects. Owing to these reasons it has been very difficult to select an appropriate treatment modality based on the manifestations of certain common mutations in a pack of symptoms especially in patients who are resistant to treatment. This has led to the development of personalized therapy which can be delineated as acclimatizing of medical treatment based on the characteristics of the individual being treated. This development leans on our understanding of how
an individual ingrained molecular and genetic profile makes them prone to certain diseases. To discover a right target for personalized therapies a long screening process along with in vivo analysis are needed. To begin with this review is an attempt to summarize the information available for personalized therapies.

Keywords: Personalized therapies; genome sequencing; pharmacogenomics; biomarkers, ayurveda etc.

1. INTRODUCTION

A personalized medicine is an evolving medical practice that uses an individual’s genetic profile to guide decisions made about the overall diagnosis, treatment along with prevention of diseases. The patient's unique profile of genetics aids doctors to choose right medication/treatment and treat it using the right dose or type of medication. Customized medicines are developed with information from the patient's genetic data. The concept of personalized medicine offers the benefit of being treated with the best treatment tailored for each individual based on their genetic profile and environmental information, including new integration and translation expertise in patient clinical care. [1] All of this is based on the study of the human genome. The genome plays the pivotal role in formulating the personalized therapy as it provides information about how the patient can react to certain diseases as well as drugs. [1-2]

Customized treatment also provides an advantage in the economic sector because it helps in the cost management of drug production and in addition to this the inclusion of pharmacogenomics in clinical trials also reduces the chances of failed clinical trials and therefore increases the chances of safe and efficient treatment in certain groups of patients. [3] Therefore, it is safe to say that personalized therapies is a broad field in health care and it is yet in its germinal stage. Health care professionals are rooting for new advancements and innovations in this field as it looks to meander away from the pedestrian one-size-fits-all-approach to giving better clinical outcomes which will likely be beneficial to a majority of patients. Hence, several benefits, as well as challenges in developing a custom-made medicine, are being explored.

Fig.1. Clinical trials of drug
Fig. 2. A personalized approach that examines patients with the nature of medical history, Environment and genomic mutations

LITERATURE SURVEY:

- Neuner et al. (2019) the authors have mentioned about the genetic diversity greatly alters human influence Alzheimer's disease mutations in both genetic phenotype genes. They have confirmed this complex AD model by showing elevated levels of genetic variation, transcriptomic, and tool for studying methods AD is basic and come up with evidence that pre-implant models include genetic variation it can better interpret/translate into personalized treatments for human AD.

- McLaren et al. (2015) It was found in the study the levels of amino acids found in the HLA (HLA-A and B) binding proteins and SNPs in genetic chemokine (CC motif) receptor 5 which together represent 14.5% of significant differences in the -HIV. To control these symptoms, they estimate that an additional 5.5% can described in general, genetically augmented variety. Therefore, they show that the general variance of the main outcome describes the majority of the manager part of the genetic makeup of HIV. This is a lesson suggests that the analysis of various classes were not examined GWAS should be at the forefront of this movement forward.
2. GENERAL METHODOLOGY OF PERSONALIZED MEDICINE

Personalized therapy works by analysis of a patient’s genome and their derivatives which are RNA, Proteins and metabolites. The process starts by identification of biomarkers of an individual. Biomarkers can be delineated as innately occurring gene, molecule or characteristic which are used for the identification of particular physiological or pathological processes as well as diseases. The identification of these biomarkers is then used to study DNA and RNA differences related to drug responses. By evaluating these genomic differences there is a preclinical modeling of treatment strategies. Once the treatment is devised the patient is prudently monitored for parameters like treatment response, quality of care and life and depending on this monitoring the personalized therapy is continued or rejected.[4-5]

3. THE 4P’s OF PERSONALIZED MEDICINE

P4 medicine describes a focus on programs that include prescribed, customized, preventative and participatory activities. It releases a combination of multiple biological data points, including molecular, cellular and phenotypical measurements, as well as individual gene sequences, in order to better define individual health or well-being, predict disease progression and direct medical interventions. The introduction of P4 drug from a clinical perspective will create predictable and personal models that reflect the well-being of all patients or diseases, facilitating the development of new clinical trials that address differences in treatment responses and disease formation. [6]

![Fig. 3. Methodology of Personalized Medicine](image)

<table>
<thead>
<tr>
<th>Predictive</th>
<th>Predictive of risk, treatment, or outcome and Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized</td>
<td>It is customized in the genetic makeup and composition of the patient and his disease</td>
</tr>
<tr>
<td>Protective</td>
<td>Prevention, early intervention to prevent diseases from appearing completely</td>
</tr>
<tr>
<td>Participatory</td>
<td>Participatory, involvement of the patient or his or her community and clinical care team in prevention or treatment decisions</td>
</tr>
</tbody>
</table>
4. GENOME SEQUENCING

Genome sequencing is one of the tools having paramount importance for guiding therapeutic intervention in personalized medicine. Genome sequencing process identifies almost the complete sequence of bases present in DNA also expressed as nucleotide, in the genome - the series of As, Gs, Cs, and Ts forming the body’s DNA. The genome of the human contains more than three billion genes.

Today, large-scale DNA sequencing - needed for prominence plans such as genetic sequencing - is largely driven by advance technology. As your eye scans the alphabet to know a sentence and read them, in a similar fashion these machines “learn” the sequence of bases present in DNA. [7]

Fig 3A: The sequence of DNA translated from the alphabetical chemical alphabet to our written alphabet may appear.

Therefore, in this sector of DNA, adenine (A) is followed by guanine (G), guanine (G) is followed by thymine (T), which is followed by cytosine (C) and so on continuously.

The gene sequence involves revealing the order of the foundations that exist throughout the body’s genetics. Genome sequencing is supported by default DNA sequencing methods and computer software to compile large sequence data.

It can be divided into four categories:

1. The preparation of clones containing all genetic compounds
2. DNA sequencing of clones
3. Contig assembly of the DNA sequencing;
4. Database development.

Benefits of genome sequencing include detecting presence of mutations or changes (single or multiple) and whether the effects of these mutations can be reduced. It also helps in investigating if the onset of the disease symptoms can be delayed. Additionally, it allows the appropriate drugs and doses to be used for their maximum performance. Other Benefits of Genome sequencing also include the ability to quickly question multiple regions of genomic, to identify its different kind. Genomic methods can be used in a directed or non-hypothesis way, and data can be held for the changes regarding future. [8]

There are also certain drawbacks of genome sequencing. Genome sequencing is able to lead the more potent details, and tools should be applied to assist better management of the data obtained. Genome sequencing sometimes lead to false and misleading data, and analysis should address these and other related issues.

5. PHARMACOGENOMICS

Pharmacogenomics can be delineated as response given by genes present in our body to drugs administered. This contains pharmacology (science of drug) and genomics. This new field contains pharmacology (drug science) and genomics (study of genes as well as their roles) to modify effective and safe, drugs and dosages that will suit the human genetic makeup. In the pharmaceutical industry it is a vast tool, which is expected to be used to great advantage. It represents the greatest advances in medical history. [5, 9]

Its main objectives are; customized treatment, improvement in safety and efficacy as well as reduction of resistance to drug, gene interactions etc.

Future of pharmacogenomics looks promising as novel developments will have an impact on drug development at three major levels:

1. Drug interactions with its binding receptor;
2. Absorption and distribution of the drug;

Pharmacogenomics Benefits:

- Pharmacogenomics refers to the use of genes follow-up of genomics information in the patient executive to be able to make treatment resolution.
• Genetic sequence and genomic data can be genetically modified (common or disease) or pathogen.
• Pharmacogenomics affects the entire process of drug development- in every stage of drug discovery and also clinical trials. Thus therapies are also subject to the challenges as well as difficulties created by diversity among individual.[10,11]

6. ROLE OF BIOMARKERS FOR TARGETED TREATMENT

6.1 Following are Some Major Roles of Biomarkers

Biomarkers are targeted medical indicators (unlike patient-reported symptoms) used to measure the presence or progression of a disease, or treatment outcomes. Biomarkers can have cellular, histologic, radiographic, or physiological features.

These biomarkers are used for cell diagnostics, patient prediction and to determine the outcome of targeted treatment. Therefore, it is very important to understand the changing nature of genetic cancer and to combine biological disorders with targeted biomarker-based treatment.

7. AYURVEDA AS A PERSONALIZED HEALTH CARE SYSTEM

In addition to the holistic approach to treatment of diseases, therapies are designed for the constitution of human needs (Prakruti) - such an ancient counter part of kind. Ayurgenomics is a combination of Ayurveda goals and genomics. A major challenge for Ayurgenomics is to establish a link between DNA and 'Prakruti'. The basis for individual diversity in Ayurveda indicates that people with Pitta Prakriti are the fastest metabolism and the Kapha Prakriti the fastest metabolism. Different strains may have different drug metabolism levels related to the polymorphism of the drug metabolizing enzyme (DME). The relationship between the CYP2C19 enzymes involved in the body's metabolism of many genotypes and prakruti drugs has been studied. Ayurgenomics therefore appears to be similar to pharmacogenetics and has the potential to be the platform for achieving drug treatment tailored to you. Ayurveda provides the following guidelines for personal testing:

# Identification of the physiology prior before illness.
# Tenfold of a test (Dashavidha-pariksha).
# Dashavidhapatiksha: Acharya Vagbhata described 10 things to consider such as Dushya (seven muscle elements and three metabolic reductions)

7.1 The Importance of Dasha Vidha Pariksha in Clinical Practice

The prakriti pariksha has significant characteristics for achieving care in health and treatment of this disease, which is the main the purpose of Ayurveda. Diagnosis, treatment, prognosis and Pathya, ahara and Vihara based on Prakriti for example, when Pitta Prakriti person is suffering with vata Vyadhi then enhanced vayu Prakriti increases Pitta Prakriti. Snigdha and Guru Items are used in the treatment of it, Vata is silenced and Pitta is unopposed. That is the right Management which also helps to predict disease. Practical information for children may result inculcating in and embracing the new-born's lifestyle it will lead to the prevention of chronic diseases and higher quality of life for one person.

# Vikriti Pariksha helps with the size and prediction of Disease.
# Sara Pariksha helps to test the colour (strength) of a person.
# Pramana Pariksha helps with testing and admission various diseases.
# Satmaya Pariksha - it is important to be diagnosed again for different types of the disease.
# Satva Pariksha - necessary for ruling the mental state of person.
# Ahara Shakti Pariksha - helpful in checking the ability to digest food because all the distractions are caused Mandagni. It is therefore helpful to diagnose and treat disease, helps Pathya-vyavastha (food created and everything management) as it depends on the digestive capacity. Dosage of the drug and various actions of the drug depends on the child's Agni. Therefore, the testing will help in determining and selecting drugs in One Prakriti disease.
# Vyayama Shakti is useful for physical examination Power.
# Vaya Pariksha provides information on the status of Dosha and body and mind condition.
1. Establish standard evidence criteria for clinical

2. Establish an orderly and transparent structure for biomarker testing of Cellular-directed therapies

3. Improve communication with patients and providers

4. Revitalize and strengthen the oversight and accreditation of biomarker

5. Ensure continuous clinical evaluation

6. Ensuring the development and implementation

7. To develop and maintain a national state molecular biomarker testing database

8. Improve balance in access to biomarker testing

9. Develop various management and documentation

10. Improving development processes as well update clinical practice guidelines

Fig. 4. Flow chart
It is necessary to demonstrate the effectiveness of ancient research methods in modern times in the various fields of research held in Ayurveda such as basic research, literature, medicine and medicine. Traditionally established facts need to be scientifically proven. Confirmation of ancient methods of investigation or research will eventually lead to the establishment of Ayurveda as a science that offers a broader field of Indian research methodology.

Dashavidha Pariksha Bhava (ten times research) not only helps to organize research in all fields, but any organized work will benefit from it. The desired goals can be achieved if planning is to be done ahead of time with the help of ten times the investigation (Dashavidha Pariksha Bhava). [12]

8. PERSONALIZED BIOLOGICAL THERAPIES

Historically, blood transfusions and organ transplants have become frost-based therapies as they were matched to the human species. A specific cell molecular therapies are customized drugs, especially targeted drugs from individual patient cells. A lot freshly processed human proteins can provide a different treatment.

8.1 Cell Therapy

8.1.1 Stem cells

# Correspondent Tissue and Cell Transplants
# Personalized Chemical Therapy

8.1.2 Gene therapy

# Personalized Genetic Cancer Treatment
# Chromosome Modification by CRISPR / Cas9 System

8.1.3 Customized vaccines

# Vaccines for Viral Diseases
# Vaccines for cancer
8.2 Antisense Therapy

8.2.1 Cell therapy

The prohibition of disorder of the human by cell management selected, repeated and treated with drugs or modified externally (ex vivo). The source of the cells that is been used would be a patient or donor. Other sources are maybe the cells line and patient tissues for preparing the vaccines for cancer. Cells can be inserted into the selected membrane that prevents the entry of the immune system they do not interfere but allow external extensions to operate molecules are produced by cells. The ex vivo gene therapy is a portion of Genetic engineering. Cells are introduced in a variety of ways in the body and then selectively placed on site of action.

8.2.2 Gene therapy

Genetic therapy is defined as transferring the specific genes to the specific patient’s tissues or cells for the purpose of maintaining or preventing specific disease specificity. Wide range of the genetic therapies including cell and tissues that can be modified extracting some substances like neurotropic properties. Ex vivo gene therapy includes genetic modification of the patient's in vitro cells, especially through the vectors of the virus, before re-transplanting these cells into the patient's body tissues. This is a type of personalized treatment.

8.2.3 Personal protective drugs

Identifying genes that are directly or indirectly involved in the production of antibodies in vaccines is important. Such data may provide additional insights into genetic predisposition to defective immune response to vaccines, and ultimately the development of new vaccines.

8.3 Antisense Treatment

Antisense molecules are nothing but the synthetic segments of DNA or RNA, modified to demonstrate the specificity of specific mRNA and to inhibit protein production. The use of antimicrobials to block proteins that are rarely referred to as antiviral drugs. The synthetic fragments of DNA or RNA are called oligonucleotides. Occasionally RNA or DNA oligonucleotides rarely have antibodies these therapies vary in genetic function for therapeutic purposes hence called as genetic therapies. However, oligonucleotides are different from conventional genetic therapies in that they do not produce protein but can only inhibit existing genetic expression. Several antisense methods use genetic therapeutic technology.

9. PERSONALIZED THERAPY OF NEUROLOGICAL DISORDERS

Neuroinformatics is a compilation of computational biology or bioinformatics with neurosciences.

Large number of details from neuroimaging and structure and function brain studies habituated to create a portfolio “Visual brain” as the basis of the particular disease replica, which can be used to customize treatment of neurologic diseases in the specific extent.

Components of a wide range of treatments are Neurosurgery, Pharmacotherapy, and Psychotherapy, drug delivery devices, automated neuromodulator by bioelectronics hyperbaric oxygenation, Physiotherapy and physiotherapy.

E.g... Atremorine as a Personalized Dopaminergic Treatment of PD

E-PodoFavallin-15999 (Atremorine®) is a potent dopamine (DA) supplement obtained by biotechnological processes such as non-denaturing from the Vicia faba gene. Atremorine affects the neuronal dopaminergic system by acting as a neuroprotective agent against Parkinson's disease (PD).

10. DEVELOPMENT OF PERSONALIZED CANCER THERAPY

Decades ago, the literature emerged as one of the most powerful forms of oncology, providing both the anticipated use and speculation of cancer management. Advances in novel technology, such as the succession of future generations, led to the discovery of cancer biomarkers, genetic signatures, and their distinct meanings affecting ontogenesis, as well as the discovery of anticancer therapeutic targets.

Transcriptomics contributes to the transformation of the full understanding of cancer, from histopathological and organic to cell, opening up a unique concept of tumor diagnosis and treatment. Advances in print printing could allow for standardization and cost reduction in its analysis, which would be the next step in transcriptomics becoming a modern cancer treatment list.[13]
Fig. 6. Atremorine-induced dopamine (DA) response in patients with Parkinsonia. DAb: Basal dopamine levels; DAT: Plasma dopamine levels one hour after administration of Atremorine (5 g, p.o.). Modified with permission from Cacabelos et al. [14]

Table 2. Personalized drug approvals – New Drug [15]

<table>
<thead>
<tr>
<th>Approval Date</th>
<th>Drug</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/10/18</td>
<td>Galafold (migalastat)</td>
<td>Amicus Therapeutics</td>
<td>Fabry disease w/GLA variant</td>
</tr>
<tr>
<td>28/11/18</td>
<td>Xospata (gilteritinib)</td>
<td>Astellas pharma</td>
<td>Relapsed/refractory AML w/FLT3 mutation</td>
</tr>
<tr>
<td>28/09/18</td>
<td>Vizimpro (dacomtinib)</td>
<td>Pfizer</td>
<td>First-line NSCLC w/EGFR mutations</td>
</tr>
<tr>
<td>13/02/18</td>
<td>Symdeko (tezacaftor/ivacaftor)</td>
<td>Vertex</td>
<td>Cystic Fibrosis w/ two copies of F508del</td>
</tr>
<tr>
<td>26/11/18</td>
<td>Vitrakvi (larotrectinib)</td>
<td>Loxo Oncology</td>
<td>Solid tumors W/ NTRK fusion (absent resistance mutation)</td>
</tr>
<tr>
<td>11/02/18</td>
<td>Lorbrena (lorotanib)</td>
<td>Pfizer</td>
<td>ALK-positive Mnsclc progressed on xalkori + another inhibitor or zykadia as the first treatment</td>
</tr>
</tbody>
</table>

Cancer treatment has not been satisfactory in the last decades but the reorganization of cells, genetics, & type of cancer accelerates the growth in the treatment of cancer. Custom-made compounds are needed, as no two boils are exactly alike and therefore no two forms are alike.

10.1 Role of Molecular Diagnostics in the Management of Cancer

Molecular testing invades the treatment of cancer in a number of ways that lend to the human genome. These technologies enable cancer cell classification according to cell profiles as the basis for more effective personalized therapies.
Various tests have been used to predict response to treatment and prediction [16-18]  

Factors that drive personalized cancer treatment:

1. Search for the best treatment options due to the limited effectiveness and toxicity of chemotherapy
2. Advances in the application of omics to cancer technology.
3. Diagnosis and sequence of cells are increasingly used in cancer
4. Cancer biomarkers can be used to diagnose and manage drugs and monitor treatment outcomes
5. Advances in understanding the pathophysiology of cancer
6. Regeneration of cancer
7. Advances in the immune system of cancer
8. Availability of cancer treatment
9. Advances in cancer vaccination technology
10. Examples of personal cancer treatment are already working
11. Increasing the burden of cancer on US older people is a driving force for development.
12. Developmental encouragement from motivational physicians, patients and payers of external companies
13. At the current incidence rate, the total number of cancer cases is expected to increase by 2050 (1.3-2.6 million) [19,20]

11. CONCLUSION

In the rapidly evolving era of Genomic and Molecular Medicine, patients' satisfaction with disease management is top priority along with the need for therapies to work better with a reduced incidence of side effects to ensure better health. Physicians are required to adopt treatment options that will lead to more accurate treatment and reduce the risk of diagnostic errors. Pharmaceutical and biotechnology companies are also making progress in drug development with the aid of genomic and molecular medicine which is more efficient and saving them time and money. In addition, medical science has adopted a molecular and genetic basis for diagnosing risk factors and preventive measures. In conclusion, personalized medicine is establishing its presence in healthcare and slowly taking the place of conventional therapy and even though conventional therapy is still the sought-after way for treatment advances in personalized therapy is attracting more and more interest from healthcare professionals as it provides better
disease management along with patient satisfaction.

CONSENT
It is not applicable.

ETHICS APPROVAL
It is not applicable.

AVAILABILITY OF DATA AND MATERIALS
All data are fully available without restriction.

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COMPETING INTERESTS
Authors have declared that no competing interests exist.

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