One Size Does Not Fit All: An Overview of Personalized Treatment in Cancer

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Authors’ contributions

This work was carried out in collaboration among all authors. Authors SK and SC conceptualized the study. Authors SK, CG, and MS managed the literature searches, performed the analysis, and wrote the first draft of the manuscript. Authors SK, and CG sketched the figures. Author SC critically reviewed, edited and finalized the article. All authors read and approved the final manuscript.

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ABSTRACT

The last few decades have witnessed ‘one size fits all’ kind of conventional treatment strategy i.e. a similar line of treatment or usage of the same drug to treat a particular disease. This approach is not associated with specific personal characteristics but with individual genetic constitutions. Precision oncology holds great opportunities to improve prediction, treatment and follow-up care for the benefit of cancer patients. In this study, many pieces of literature and various clinical data have been surveyed to understand how multiple genes are responsible for a particular cancer type and tabulate them. Having the genetic information of a patient and knowing the genes that are susceptible to mutation can help in the diagnosis. That in turn help to get the most tailored medicines, which will decrease the chances of treatment failure, which is quite common in cancer therapies. This review focuses on providing an idea of the genes whose mutation directly or indirectly can lead to cancer and other diseases also, and hence might be helpful to design separate treatment strategies for each individual in future.

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1. INTRODUCTION

One size doesn't fit all; that is, a particular drug might not suit all as every individual is unique in their genetic constitution. The term 'personalized medicine' or 'precision medicine' refers to the medicines designed based on these unique genetic constitutions. It is not a new concept as it first appeared in the works published in 1999, though some of the field's core concepts have been present since the early 1960s. Personalized medicine is a more tangible reality due to the advent of new technologies. It has also enabled researchers to provide a connecting link between an individual's molecular and clinical profiles. In the field of personalized medicine, the vital discoveries that have allowed significant progress are — single nucleotide polymorphism (SNP) genotyping and microarray/biochips. SNPs are changes in a single nucleotide of the DNA sequence that are predominantly frequent in the population and account for most known polymorphisms. The classification of these polymorphisms is crucial, as SNPs are linked to the susceptibility of patients to various disease processes and their responsiveness to drug therapy. SNPs are also being established to be an important tool in segregating patients based on multiple studies and clinical trials. The microarray biochip invention revolutionized the field of personalized medicine, specifically by creating its ability to stock and rapidly analyze a patient's genome as a whole. This technology has enabled researchers and clinicians to conduct SNP genotyping efficiently and eventually allows for the rapid development of diagnostics and therapeutics based on proteins [1]. There are different proposed approaches to personalized treatment Fig. 1.

2. LITERATURE REVIEW

2.1 Emergence of the Concept of Personalized Medicine

Personalized medicine has been an emerging field for research for quite a few years now. Precision medicine, or prevention and recovery methods that differs for each individuals, is not a new strategy. For example, blood typing, has been used to control blood transfusions for over a century. However, the rapid emergence of large-scale biologic databases (such as the human genome sequence), effective techniques for characterizing patients (such as proteomics, metabolomics, genomics, complex cellular assays, and even mobile health technology), and analytical resources for processing large collections of data have significantly increased the prospects of extending this principle widely. [2]. It has the intention to prevent and treat diseases based on the analysis made on the variables that make each of us a unique individual. As we know, each individual's genetic makeup is unique; what is successful for one person may not work for another individual, existing in a different environment and following a different lifestyle.

Fig. 1. Proposed types of approaches of personalised medicine
Frequently, we see examples of this approach in action, whenever a medication label containing warnings regarding risks for pregnant women, or even when a commercial advertisement quickly announces that the product or medicine must not be used by patients suffering from heart disease. There is a basic difference between the approaches made towards conventional treatment methods and personalized medicine. Unlike conventional treatment methods, instead of following a single line of treatment for all except a select few, personalized medicine tries to consider each person separately and determine the best-suited treatment specifically for him or her.

Our antecedents realized the importance of personalized medicine through the history of using arsenic to treat leukaemia. Although being very poisonous, arsenic was considered effective in treating leukaemia and its administration caused a few patients' conditions to improve during the mid-1800s. The future goal of personalized medicine is to revolutionize patient care in many ways [3].

Patient data is the lifeblood of precision medicine. Patients' and good volunteers' health histories and genetic codes are crucial, as they enable individuals to have a say in their health care and science. [4]. There will undoubtedly be major obstacles ahead, but none are insurmountable. Nevertheless, aspirations must be realistic; precision medicine will not happen immediately or instantly. International consortia representatives from education, health care, finance, and industry should guide the transition and draft recommendations for public feedback. The World Economic Forum’s Health Council is currently building organized consultation on the main issues raised related to precision medicine. It recommends that multi-stakeholder adaptation be crucial to the precision-medicine enterprise. [5]. The lack of supporting IT infrastructure, lack of data standards and system interoperability, inadequate decision support technology, and insufficient resources for translational health science are major obstacles to incorporating and adapting precision medicine advances into health care practice. The introduction and incorporation of precision medicine technology into health care around the world and the collaborative mechanisms to promote it globally would be dependent on policies that support development in these fields [6].

3. CANCER

Cancer is the most common disease that is, dealt with using personalized medication. Cancer, as we know, is the uncontrolled growth of abnormal cells anywhere in a body. More than two hundred types of cancer is known till date. Anything that may lead a normal body cell to divide abnormally has the potential to cause cancer; general categories of causative agents of cancer are as follows: exposure to chemical or toxic compounds, radiation, some pathogens, and human genetics. Symptoms and signs of cancer are signified by the specific type and stage of cancer. However, general signs and symptoms like fatigue, weight loss, pain, skin problems, disturbance in bowel or bladder function, abnormal bleeding, persistent cough, fever, lumps, or tissue masses are not very specific. Although there are many ways to screen and diagnose cancer at an early stage, a definite diagnosis can be made by examining a biopsy sample of suspected cancer tissue. Biopsy results help to determine the stage of cancer and also help determine the cancer type and the extent of cancer spread; this staging, in turn, allows caregivers to determine treatment protocols. In almost all staging methods (usually between-0 to 4), the higher the number assigned, the more advanced the cancer type. Staging method is crucial, because it differs from cancer to cancer and need to be individually discussed with respective health care providers. Treatment that is to be undertaken varies according to the type and stage of cancer. Most treatment practices are designed to fit the individual patient's disease. Most treatments include at least one of the following or may include all: surgery, chemotherapy, and radiation therapy. There are many home remedies and alternative treatments for cancers, but patients are strongly encouraged to discuss with an oncologist before using those. The cancer type and its staging determine the prognosis of the disease. Those cancers staged with higher numbers (3 to 4) often known to be progressive, and their prognosis ranges more toward poor [7].

4. TRADITIONAL TREATMENT VS PERSONALIZED TREATMENT

Traditionally, radiation, chemotherapy and surgery are the only means by which doctors treat cancer. Problems associated with this kind of treatment are huge. Few are serious and few not so, serious as given in Table 1.
On the other hand, in personalized treatment, doctors use a patient's gene to uncover the clues for treating the disease. Doctors usually use the Gene sequencing technique to locate the cancer-causing genes. The ways to attack those cancer-causing genes are identified, hence overall turning it into targeted therapy.

Table 1. Severe and not so severe drawbacks of the traditional treatment

| Serious                      | Not so Serious               |
|------------------------------|-------------------------------|
| Bleeding or bruising         | Fatigue                      |
| Low blood cell counts        | Hair loss                    |
| Infection                    | Loss of appetite             |
|                              | Mouth sores                  |
|                              | Nausea                       |
|                              | Vomiting                     |
|                              | Skin changes                 |

Source: https://www.cancer.gov/about-cancer/treatment/side-effects [8]

5. TRANSITION OF THE TREATMENT METHODS

The transition from the 'one size fits all' to 'precision medicine' took place with multilevel patient stratification, and it has been clearly illustrated in Fig. 2.

6. MATERIALS AND METHODS

In the present course of study, various platforms like PubMed, Google Scholar, NCBI and various clinical data have been used to understand how multiple genes are responsible for a particular cancer type and tabulated in an organized manner. All the other approaches towards the designing of personalized treatment have also been mentioned in the review.

7. DISCUSSION

7.1 RESEARCH DONE TILL DATE (2016-2020)

There have been many studies done on Personalized medicine and treatment techniques associated with it for a long time. This approach to treatment gives the researchers an idea regarding the challenges that are faced already and predicts the ones that might come up in the research path in this field soon. In this section, some of the research breakthroughs are mentioned during four years, from 2016-2019.

In 2016, a versatile data fusion (integration) framework, based on graph-regularised non-negative matrix tri-factorization, a machine learning technique for the co-clustering heterogeneous dataset, was introduced, which could effectively assimilate somatic mutation data, molecular interactions and drug chemical data to address three main challenges in cancer research, i.e.;

- stratification of patients into groups based on clinical outcomes,
- prediction of the genes whose mutations lead to the onset and development of cancers, and
- identifying the drugs treating particular cancer patient groups.

Fig. 2. New paradigm shift in treatment
The new framework was applied to ovarian cancer data to simultaneously cluster patients, genes and drugs by utilizing all datasets. The top-scoring genes identified as new drivers through database search and biomedical literature curation was confirmed. Finally, the potential candidate drugs that could be used to treat the identified patient subgroups by targeting their mutated gene products were validated. A large percentage of our drug-target predictions by using other databases and through literature curation was identified [9].

The year 2017 revealed that the use of rapid, high throughput genomic sequencing could provide insights into the unique mutational landscape of each tumour (in real-time), stratifying patients and identifying potential therapeutic targets, which when combined with key techniques like data analysis, mutational profiling, PDXs, metabolic profiling, circulating biomarkers offers a powerful toolbox for the advancement of personalized therapies. In addition, these techniques helped reveal the fundamental mechanisms of cancer pathway or treatment resistance, which in turn increase the options for patient treatment and ultimately the chances of survival. The annual meet of IACR in 2017 highlighted the advancement in individualized precision medicine due to the application of improved individualized real-time tumour profiling. Especially, combining these approaches was demonstrated to be a powerful method for the standardization and monitoring of treatments that can have real-time impacts on patient outcomes and is seen to be the future of medicine [10].

One of the first historic FDA approvals in 2017 marks a milestone in precision oncology; that is, the immune checkpoint inhibitor pembrolizumab became the first to receive a tumour-agnostic indication for cancer treatment. It got accelerated approval to treat any type of tumour that is solid and has mismatch repair deficiency, a defect that challenges the cell’s DNA damage repairability. This approval allowed patients with a wide range of different cancers to receive an effective way to control the disease.

Another promising treatment, which homes a different, rare genomic abnormality in the tumour, is larotrectinib, a tropomyosin receptor kinase (TRK) gene fusion, which also seems to work across different tumour types and in both adults and children. Larotrectinib also can develop as the first tumour-agnostic targeted cancer therapy [11].

In 2018, a review published revealed that several genetic alterations/mutations have been discovered in gliomas which seem to be new potential predictive and prognostic biomarkers. Alterations in BRAF, H3-K27M and EGFRvIII and fusion of FGFR-TACC will allow developing better therapeutic approaches to cure the disease. Recently, WHO 2016 classification of gliomas has shown new possibilities in personalized treatments enabling a better understanding of pathogenesis and mechanisms of drug resistance [12].

2019 is the most active year for research in precision oncology. In the case of bladder carcinoma, it was found that in the context of routine diagnostics, only 20 bladder carcinoma cases were sequenced using NGS, whereby in 10 of the cases, there is scope for targeted therapy [13].

Molecular analysis of circulating tumour DNAs is an alternative approach that can be used to characterize the molecular heterogeneity of tumour and their evolution. Hence, ctDNA testing may guide us to get important clues to investigate dedicated predictive biomarkers for new drugs since a wide range of agents are being established for metastatic breast cancer [14]. It is also found that radiomics-based assays derived from large databases of breast MRIs could lead to available ductal carcinoma in situ imaging test to assist precision therapy [15].

Moreover, the combination of genetic characteristics and clinicopathologic has eventually progressed toward individualization of breast cancer therapy. With an appropriate design and conduction of a new generation of spatiotemporal genomic trials in a medium-term perspective, the challenges of early and late acquired resistance and relapse could be outdone. However, personalized therapy optimization for women with breast cancer will require the valid identification and information of comprehensive intraindividual coding and noncoding mutational landscape. Both bulk NGS and single-cell RNA sequencing and a combination of single-cell RNA sequencing with CRISPR-CAS9 systems could be used [16].

It is recently revealed that particular osteopontin (SPP1) prognostic is not relevant to most previous studies on colorectal cancer. Saudi Arabia has got both a specific genomic constitution and a certain environment that could lead to roots of cancer which have distinctive
molecular basis. Several isoforms of SPP1 are present along with tissue localizations and molecular functions, signalling pathways, and downstream molecular functions. Thus, individualized approach for studies related to colorectal cancer and especially SPP1 prognosis results evaluation is highly suggested for precision oncology [17]. The presence of distinct molecular biomarkers in metastatic colorectal cancer influences clinical presentation and guide to make decisions for the treatment, which directly impacts patient outcomes. Identifying such established molecular subtype like BRAFV600E, MSI-H, RAS, and HER2 amplification in colorectal cancer shows the heterogeneity of this disease. It confirms the need to use precision oncology for the sophisticated management of the disease [18]. Moreover, the FDA approved immune checkpoint inhibitors for advanced stage MSI-H/MMR-D colorectal cancer patients and larotrectinib for metastatic CRC patients with NTRK fusion genes recently [19].

The upfront molecular classification; using MMR and p53 IHC and targeted NGS panel tests of primary endometrial cancer (EC), done on the biopsy specimen, which is achievable for approximately $500, was proposed to be a better investment of resources for health care than isolated and expensive tests only for recurring ECs. This upfront molecular sorting provides information for both prognosis and prediction to patients and clinicians, helping to identify one of the most common FDA-approved targeted therapeutic approaches for women with MMRd ECs. We have a high scope to study the efficacy of molecular classification-driven treatment algorithms compared to the currently available high variable standard of care. It is expected to have more impact if the clinical outcomes and treatment efficacy using EC molecular subtypes could be determined to guide management of the disease at an early stage [20].

Dynamic monitoring of genomic profiles of tumour can help detect the driving genes and get information regarding the drug resistance mechanisms and thus guide cancer treatment. This study revealed that the total survival time of non-small cell lung cancer (NSCLC) patients in stage IVA after radiotherapy and targeted therapy was found to be above three years, indicating the importance of dynamic monitoring of gene profiles for the study of the mutations for cancer treatment [21]. Another study revealed that the phospholipids signature enables the classification of the status of EGFR mutation accurately. Rendering to phospholipids imaging, it was not difficult to generate the EGFR mutation spatial distribution map, with which the EGFR mutations spatial distribution features could be observed. It was also revealed that phospholipids imaging could reveal EGFR mutations spatial distribution heterogeneity. The mass spectrometry imaging (MSI) method may provide a new viewpoint to understand and monitor the EGFR mutation status in vivo, which is expected to potentially benefit real-time monitoring for targeted therapy [22,23].

Quantification of errors associated with expert manual contouring of PET-positive lesion in the lung reveals general patterns in what otherwise might be thought of as natural randomness. The current study may allow for the formation of new hypotheses towards improving the accuracy and precision of manual description of PET-positive tumour targets in the lung [24]. A pilot translational study on an NSCLC revealed a new translational approach for tailoring a therapy that can be carried on for every patient who undergoes any kind of surgical resection or core biopsies. A new tool is being proposed that could be tested prospectively in a larger unit of patients to validate the efficacy of ex vivo tumour spheroids as a system to anticipate and study different drug response. The approach would be a new way to select the best treatment out of different choices, making it individualized [25]. Modulating the chromatin state by epigenetic-modifying agents provides scope for precision medicine in patients with lymphoma [26].

Despite the challenges, nucleic acid drugs are expected to have a significant impact on pancreatic cancer treatment. The combination of genetic diagnosis with next-generation sequencing can lead to effective targeted therapy, which may help design precision medicine for pancreatic cancer patients [27]. The observation that liquid biopsy is a promising tool to depict alterations in the mutational landscape of the disease under study, thereby detecting the predominant cancer component in patients with either synchronous or metachronous malignancies to allow stratification of dynamic treatment [28].

The two of the most important path-breaking research in this field, done in 2020, are the involvement of artificial intelligence (AI) and big data in cancer and precision oncology and the finding that ATM-deficient cancers provide new
opportunities for Precision Oncology. NGS provides several clinical applications that can serve as a risk predictor in early detection of disease, accurate prognosis, diagnosis by sequencing and medical imaging, biomarker identification and identification of therapeutic targets in order to discover the novel drug. NGS is known to generate large datasets which demand specialized bioinformatics resources for the purpose of analyzing the data that is relevant and clinically significant. Utilization of these applications of AI, cancer diagnostics, and prognostic prediction enhanced with NGS and medical imaging delivers high-resolution images. Irrespective of the advancements in technology, AI has some challenges and limitations, and the clinical application of NGS remains to be validated. The continuous enhancement and progression of innovation and technology might help AI and precision oncology show great potential [15].

PARP inhibition has always shown great promise in the treatment of BRCA-deficient ovarian, breast, prostate and pancreatic cancer patients. The recent findings revealed that ATM-deficient cancer cell lines, olaparib is not cytotoxic but cytostatic. In addition, it mentioned that a combination of olaparib with an ATR inhibitor is required to induce cell death [29].

8. APPROACH TOWARDS CANCER PREVENTION

Accumulation of genetic changes in a cell with normal DNA leads to the development of a cancerous cell. Among these alterations, some are sporadically acquired, whereas others are genetically inherited in the form of predisposed cancer genes. The identification of cancer predisposition genes has led to the establishment of methods of screening to recognize patients who are “at-risk” of developing cancer and helps them take required measures on individual risk-modification behaviours. An indispensable part of any screening procedure is to have an adequate accepted therapeutic intervention that can change the natural history of the disease [30].

9. BASIC METHODOLOGY FOR DESIGNING PERSONALIZED TREATMENT

- Based on Patients Data Fig. 3
- Based on Drug Response to A Particular Contributing Factor of The Disease Fig. 4

There are many genes whose alterations are responsible for the occurrence of the common types of cancer Table 2. The above table gives an idea regarding the genes that can be

Fig. 3. Methodology for designing personalised treatment based on patient’s data
suspected for mutations related to the disease diagnosed. From the literature study, it is also found that there are several genes that might be responsible for two or more types of cancer, just like it is observed that BRCA1 and BRCA2 are mainly responsible for Breast cancer, but mutations in these genes may also lead to Pancreatic cancer.

Moreover, there are several other deadly diseases Alzheimer's disease, Diabetes type 2, Cardiovascular diseases/ Coronary Artery Diseases, Hypertension, Parkinson's and there are various genes whose mutations can lead to cause each of these diseases. The table is given below Table 3 shows the list of genes that can be suspected for mutations depending on the disease caused. This information can be helpful for both clinical purposes and academic research work.

Personalized Treatment can have multiple approaches, and every approach has its own significance. For example, approaches using bioinformatics help to predict the best possible candidate drug for the trial, whereas nanobiotechnology enhances the efficacy of the targeted drug delivery to the exact location inside the patient's body.

Here is a diagrammatic representation highlighting the other aspects from which one can approach towards Personalized Medicine Fig. 5.

Based on all the papers studied to prepare this review, a pie chart has been made which shows the extent of research done on personalized treatment approaches for different cancer type Fig. 6.
Table 2. List of genes responsible for the different types of Cancer

| SL NO | Disease              | Inheritance pattern                                                                 | Genes associated                                                                 |
|-------|----------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 1.    | Bladder cancer       | Bladder cancer is naturally not inherited. In most cases, tumours result from mutations in the gene that occur in bladder cells during a person's lifetime. | • FGFR3  
• HRAS  
• RB1  
• TP53  
• TSC1  
• Deletion of part or all of chromosome 9. [31] |
| 2.    | Breast cancer        | These cancers are mainly associated with somatic mutations in breast cells that are acquired during a person's lifetime, and they do not cluster in families. In hereditary breast cancer cases, the way that cancer risk is inherited depends on the gene involved. For example, the person's chance of developing cancer can increase if there are mutations in some associated genes that are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell. | • ATM  
• BARD1  
• BRCA1  
• BRCA2  
• BRIP1  
• CASP8  
• CDH1  
• CHEK2  
• CTLA4  
• CYP19A1  
• FGF2  
• H19  
• LSP1  
• MAP3K1  
• MRE11  
• NBN  
• PALB2  
• PTEN  
• RAD51  
• RAD51C  
• STK11  
• TERT  
• TOX3  
• TP53  
• XRC3  
• XRC3 [31] |
| 3.    | Colorectal cancer    | Family history is one of the risk factors for colorectal cancer. It is referred "hereditary" or "inherited" when several generations of a family have colorectal cancer. The presence of several gene mutations that cause colorectal cancer and allow it to be transmitted to family members are discovered. A gene is a block of DNA that holds the genetic code, or instructions, for producing proteins vital to our bodily functions. Hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) are the most commonly inherited colorectal cancers. There is a 50% chance of inheriting the disease-causing gene if the parents carry the genes already. | • APC  
• MLH1  
• MSH2  
• MSH6  
• PMS2  
• TP53  
• TGFB2  
• KRAS  
• SMAD4  
• PTEN  
• BRAF [32] |
| 4.    | Endometrial cancer   | Hereditary endometrial cancer makes up approximately 2% to 5% of all cases. It is common in women in taking drugs like tamoxifen to treat or prevent breast cancer; to some extent, they have a higher risk of endometrial cancer. | • PIK3CA  
• PIK3R1  
• PTEN  
• KRAS  
• FGFR2 |
Usually, women who take estrogen as a part of hormone replacement therapy have a higher risk of developing endometrial cancer.

| 5. Kidney cancer | Inherited kidney cancers are usually not common. Factors like ageing, smoking, obesity, hypertension, exposure to cadmium or specific herbicides can lead to kidney cancer. Sometimes even treatment for kidney failure might lead to kidney cancer. |
|------------------|----------------------------------------------------------------------------------|
|                  | ● ARID1A (BAF250a)                                                              |
|                  | ● CTNNB1 (β-catenin)                                                             |
|                  | ● Epigenetic silencing of MLH1 resulting in microsatellite instability. [33]     |

| 6. Liver cancer  | Mostly, the cases of liver cancer or hepatocellular carcinoma can be attributed to several non-genetic factors such as chronic viral infections and heavy alcohol use. However, a family history of liver cancer does appear to increase the risk of the disease. Certain conditions, such as hereditary hemochromatosis, also increase the risk. [11] |
|------------------|----------------------------------------------------------------------------------|
|                  | ● VHL                                                                          |
|                  | ● MET                                                                          |
|                  | ● FLCN                                                                        |
|                  | ● TSC1                                                                        |
|                  | ● TSC2                                                                        |
|                  | ● FH                                                                          |
|                  | ● SDH [34]                                                                    |

| 7. Lung cancer   | Lung cancer is usually not inherited. The reason behind the majority of lung cancers is smoking — both in active smokers and passive smokers. [36] |
|------------------|----------------------------------------------------------------------------------|
|                  | ● TP53                                                                         |
|                  | ● CTNNB1                                                                      |
|                  | ● IGF2R                                                                       |
|                  | ● BAX                                                                         |
|                  | ● GPC3                                                                        |
|                  | ● STAT3                                                                       |
|                  | ● CDKN1 [35]                                                                  |

| 8. Melanoma      | Most cases of melanoma are sporadic, which means that they occur in people with no apparent history of the disorder in their family. When the disorder is familial, it can be due to shared environmental factors or shared genetic factors or both. The genetic factors are usually inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to increase the risk of developing melanoma. When melanoma occurs as part of a genetic syndrome, the risk of melanoma follows the inheritance pattern of the syndrome. Melanoma, commonly known as familial melanoma, is a genetic or inherited condition. Hence, the risk of melanoma can be passed from generation to generation in a family [15] |
|------------------|----------------------------------------------------------------------------------|
|                  | ● ASAP                                                                        |
|                  | ● ATM                                                                         |
|                  | ● BAP1                                                                        |
|                  | ● BRAF                                                                        |
|                  | ● CASP8                                                                       |
|                  | ● CDK4                                                                        |
|                  | ● CDK10                                                                       |
|                  | ● CDKN2A                                                                      |
|                  | ● EGF                                                                         |
|                  | ● HERC2                                                                       |
|                  | ● IRF4                                                                        |
|                  | ● KITLG                                                                       |
|                  | ● MC1R                                                                        |
|                  | ● MITF                                                                        |
|                  | ● MTAP                                                                        |
|                  | ● MX2                                                                         |
|                  | ● MYH7B                                                                       |
|                  | ● NRAS                                                                        |
|                  | ● OCA2                                                                        |
|                  | ● PIGU                                                                        |
|                  | ● PLA2G6                                                                      |
|                  | ● POT1                                                                        |
|                  | ● SLC2A4                                                                      |
|                  | ● SLC45A2                                                                     |
|                  | ● TERT                                                                        |
|                  | ● TP53                                                                        |
|                  | ● TPCN2                                                                       |
|                  | ● TPCN2                                                                       |
| No. | Cancer Type                      | Risk Factors                                                                 |
|-----|---------------------------------|-----------------------------------------------------------------------------|
| 9.  | Non-Hodgkin lymphoma            | It's mainly due to a weakened immune system. Viruses associated with increasing the risk of Non-Hodgkin's lymphoma are HIV and Epstein-Barr infection. Likewise, bacteria linked to the same include the ulcer-causing Helicobacter pylori. Also, having a family history of lymphoma seem to increase the risk of getting Non-Hodgkin lymphoma [38] |
| 10. | Pancreatic cancer               | There are certain gene mutations, both inherited and acquired, are linked with pancreatic cancer. |
| 11. | Prostate cancer                 | Dozens of genes with inherited variations are studied as possible risk factors for prostate cancer. Moreover, researchers have identified many personal and environmental factors that contribute to an individual’s risk of developing prostate cancer. These factors include a high-fat diet that includes an excess of meat and dairy and not enough vegetables, a largely inactive (sedentary) lifestyle, obesity, excessive alcohol use, or exposure to certain toxic chemical |
| 12. | Thyroid cancer                  | Mostly, papillary thyroid cancers occur in people without a family history of thyroid cancer (sporadic thyroid cancer). Factors that are known to upsurge the chance of developing papillary thyroid cancer are radiation exposure to the head and neck area, iodine deficiency and history of thyroid diseases. |

Conditional inactivation of certain tumour suppressor genes like
- PTEN
- SMAD4
- TRP53
lead to the formation of Prostate adenocarcinoma. Several genomic studies have revealed that familial mutations in HOXB13 and DNA repair genes such as
- BRCA2,
- ATM
- CHEK2
- BRCA1
- RAD51D
- PALB2 results in Prostate cancer [45]
Nearly 5% of thyroid cancers are thought to be familial thyroid cancers [47]. (American Thyroid Association)

Table 3. List of genes responsible for the different types of diseases which can also be treated using Personalized approach

| Diseases                                | Genetic/ Non-genetic Component                                      | Genes responsible                                                                 |
|-----------------------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| 1. Alzheimer’s disease                  | Both Genetic and Non-genetic (environmental) component             | • The most common late-onset gene: APOE e4: increases the risk of Alzheimer's.     |
|                                         |                                                                   | • Other late-onset genes are ABCA7, CLU, CR1, PICALM, PLD3, TREM2, SORL1           |
|                                         |                                                                   | • Another set of identified three genes exist in which mutations cause early-onset Alzheimer's disease. |
|                                         |                                                                   | • Amyloid precursor protein (APP)                                                 |
|                                         |                                                                   | • Presenilin 1 (PSEN1)                                                           |
|                                         |                                                                   | • Presenilin 2 (PSEN2) [48,49]                                                   |
| 2. Diabetes Type                        | Both Genetic and Non-genetic (lifestyle choices) component         | • TCF7L2                                                                         |
|                                         |                                                                   | • ABCC8                                                                          |
|                                         |                                                                   | • CAPN10                                                                         |
|                                         |                                                                   | The majority of type 2 patients possess polygenetic forms of the disease, out of which each gene locus is responsible for only a small amount of risk. Few identified loci to date include transcription factor 7-like 2, calpain 10, peroxisome proliferator-activated receptor γ, and potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11). Individuals with OCT1 polymorphisms have a reduced response to metformin [50]. |
| 3. Cardiovascular diseases/ Coronary Artery Diseases | Both hereditary and also due to lifestyle choices like smoking and unhealthy diet. | • LDLR                                                                           |
|                                         |                                                                   | • APOB                                                                          |
|                                         |                                                                   | • ABCG5, ABCG8                                                                  |
|                                         |                                                                   | • ARH                                                                           |
|                                         |                                                                   | • APOA1                                                                         |
|                                         |                                                                   | • ABCA1                                                                         |
|                                         |                                                                   | • CBS [51]                                                                      |
| 4. Hypertension                         | A genetic trait with heritability estimates of 30–50%. Environmental factors affect the intensity of suffering from this disease. | • AGT gene (angiotensinogen)                                                    |
|                                         |                                                                   | • AGTR1 gene (angiotensin II receptor type 1)                                   |
|                                         |                                                                   | • ATP2B1 gene (ATPase plasma membrane Ca2+ transporting 1)                       |
|                                         |                                                                   | • EDNRA gene (endothelin receptor type A)                                        |
|                                         |                                                                   | • NOS2 gene (nitric oxide synthase 2)                                            |
|                                         |                                                                   | • NOS3 gene (nitric oxide)                                                       |
### Diseases and Genetic/Non-genetic Component

| Diseases                  | Genetic/Non-genetic Component                                                                 | Genes responsible                                                                 |
|---------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Parkinson's disease       | Mostly uninherited. Parkinson disease mostly occurs in people with no apparent family history of the disorder. Specific genetic mutations are identified that can cause Parkinson's disease. But these are uncommon except in occasional cases having many family members affected by Parkinson's disease. Exposure to certain toxins or environmental factors may upsurge the risk of later Parkinson's disease. [53] | - ATP13A2 gene (ATPase cation transporting 13A2)  
- GBA gene (glucosylceramidase beta)  
- LRRK2 gene (leucine-rich repeat kinase 2)  
- PARK7 gene (Parkinsonism associated deglycase)  
- PINK1 gene (PTEN induced kinase 1)  
- PRKN gene (parkin RBR E3 ubiquitin-protein ligase)  
- SNCA gene (synuclein alpha)  
- UCHL1 gene (ubiquitin C-terminal hydrolase L1)  
- VPS35 gene (VPS35 retromer complex component). [54,55] |

#### Diagram

**Fig. 6. Approaches towards personalized medicine**
10. CONCLUSION

In conclusion, we can say that precision medicine holds a great potential in the field of therapeutics. Since it completely focuses on treatment based on the individual’s genetic constitution, keeping in mind the anticipated drug response/ reaction, the chances of side effects are very less. This can be a path breaking achievement for cancer therapeutics as huge numbers of genes are involved in cancer. There are specific aspects of precision medicine which are yet to be explored. Further research and findings can lead to a cure for this so called “uncurable” disease. This treatment approach does not only aim to provide precise medication but also has the ability to take care of the side effects that can arise in a patient from certain conventional medication. As it is already shown in this review, this precise therapeutic approach holds equal scope for other fatal diseases prevailing in the society and active participation of academic institutions, researchers with the medical staffs can only make ‘Personalized Treatment’ successful the in all dimensions Fig. 7.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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