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Integrated Role of Nanotechnology and Pharmacogenetics in Diagnosis and Treatment of Diseases

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Abstract

“One size fits all” is an erroneous paradigm in drug delivery, due to side effects/adverse effects and variability observed in drug response. The variability is a result of genotypic variations (variability in genomic constitution) which is studied in the branch of science called Pharmacogenomics. The variability in drug response is studied by multigene analysis or profiling of whole-genome single nucleotide polymorphism (SNP) and is recorded in terms of the pharmacokinetic (absorption, distribution, metabolism and elimination) and pharmacodynamic (drug-receptor interaction, immune response, etc.) response of the drug. Therefore, a foray into this research area can provide valuable information for designing of drug therapies, identifying disease etiology, therapeutic targets and biomarkers for application in treatment and diagnosis of diseases. Lately, with the integration of pharmacogenomics and nanotechnology, a new facade for the diagnosis and treatment of diseases has opened up, and the prescription pattern of drugs has moved to pharmacotyping (individualized dose and dosage-form adjusted therapy) using nanoplatforms like nanobioconjugates, nanotheranostics, etc.

Keywords: Genome, Personalized, nanotheranostics, Genotyping, Nanomedicines

1. Introduction

By the end of 1950s, pharmacogenetics had become a more established approach for the treatment of diseases. The term ‘pharmacogenetics’ was coined in the year 1959 by Vogel [1] and can be understood as the scientific study of variation in the response of drugs due to heredity of individuals [2]. Though introduced quite early, pharmacogenomics caught attention in the year 1997, with advancement in the science of gene cloning and genome sequencing it was used in conjunction with pharmacogenetics [1]. However, the history of pharmacogenetics can be traced back to 510 B.C. when Pythagoras recognized the dangers of ingesting fava beans that resulted in fatal reaction in some individuals, and later on the reaction was attributed to the deficiency of G6PD in those individuals [3]. Establishment of the rules of heredity by Mendel in 1866 further shaped this field of research alongside

publication of Garrod named “Inborn Errors of Metabolism”. Other studies which further supported the science of pharmacogenetics include occurrence of unusual reactions to drugs on the basis of biochemical individuality studied by JBS Haldane, inborn variation in individuals for phenylthiocarbamide, atropine esterase activity in rabbits and occurrence of hemolytic disease in American soldiers of only African descent upon administration of the drug primaquine [3, 4]. Genetic deficiency of butyryl-cholinesterase (which resulted in death of individuals upon administration of succinylcholine injection for anesthesia) and N-acetyltransferase (responsible for metabolism of the drug isoniazid) further supported the concept of pharmacogenetics [4]. Further investigations also indicated presence of genetic differences at the level of human populations in addition to that of individuals. For example, Africans and Chinese have been found to be slow metabolizers for debrisoquine than Europeans and there is absence of alcohol metabolizing capacity in East Asians [4]. Knowledge of pharmacogenetics has thus given a new dimension to diagnosis, wherein physicians can individualize treatment for each patient, thereby producing better therapeutic response to therapy.

Genes play a vital role in the metabolism of many drugs; cytochromes P450 represent a major family of genes which are involved in regulation of metabolism of the drugs. Cytochromes P450 CYP3A4, CYP2C9, CYP2C19, and CYP2D6 are encoded by different genes and play a significant role in metabolism. A major fraction of the population lacks either of CYP2D6 or CYP2C19 because of the presence of inactivating genetic polymorphisms [1, 5]. Mere appearance of these inactive forms of variant alleles brings about the absence of activity affecting the metabolism of certain drugs metabolized by these enzymes. On the other side, a fraction of population have been found to have higher CYP2C19 or CYP2D6 activity than the normal, and are termed as ultrarapid metabolizers [6, 7]. Phase II metabolism involves conjugation reactions with sulphate, methyl, or glucuronic acid groups which are aided by certain enzymes and presence or absence of these enzymes affect Phase II metabolic reactions. For instance, it has been reported that polymorphism affects methylation of drug mercaptopurine (~0.3% of population lacks thiopurine methyltransferase) [8]. Certain genetic polymorphisms also cause structural alterations in drug targets apart from drug metabolism. Specific receptors on the surface of cells, enzymes, ion channels or transporters can be construed as drug targets. The gene VKORC1, encodes for Vitamin K epoxide reductase to which warfarin and other coumarin anticoagulants bind and has shown to exhibit extensive genetic polymorphism thus affecting drug response. This enzyme regulates regeneration of reduced vitamin K during the blood coagulation process [9]. Besides, indication of variation in drug metabolism and drug targets, pharmacogenetics also helps to discover adverse drug reactions due to exaggerated drug response, interaction with an inappropriate target or an inappropriate immune response to the drug [1].

2. Role of pharmacogenetics in diagnosis

Pharmacogenetics, including molecular genetics, has an essential role in the clinical management of diseases. Genetic testing has unfolded facts related to metabolism of drugs, and designing of personalized therapeutic regimens for safer and more efficient treatment with improved clinical outcomes. Practice of prescribing personalized medicine is gaining importance in healthcare as it helps to make therapeutic decisions based on individual characteristics, including genetic traits, quality of life, and environmental factors. Development in this field of science can provide important inputs which can be beneficial in diagnostics in cardiology (hemodynamics and electrophysiology), neurology, and oncology. Abundantly

prescribed medications like Platelet aggregation inhibitors (PAIs), oral anticoagulants (OAs), antihypertensive and cholesterol-lowering drugs for cardiovascular disease, individual responses and efficacy can vary significantly due to genetic diversity. Genetics pharmacology and pharmacogenomics are genetically personalized guided therapies that optimize treatment and reduce toxicity. Genes have a significant influence on growth, development, health, and drug metabolism.

Human Genome Project (HGP) finished in 2003 helped to identify disease pathophysiology at the molecular level. With progress in bioinformatics and novel sequencing technologies for next-generation sequencing (NGS), sequencing of human genome has become easier, cost-effective and less time consuming. The National Human Genome Research Institute (NHGRI) has launched the DNA Elements Encyclopedia (ENCODE) to discover all functional sequences of the human genome [11]. Likewise, the Cancer Genome Atlas (TCGA) molecularly characterizes over 20,000 primary cancers, identifying and documenting the uniqueness of cancer types. 2.5 petabytes of genome, epigenome, transcriptome and proteomics data have been generated by TCGA to improve the ability to diagnose, treat and prevent cancer [10]. Sequencing disease-related mutant genes in many hereditary diseases and also, sequencing of target of disease-related genes can provide useful data in treatment of diseases. The PharmGKB base (<https://www.pharmgkb.org/>) and PGRN hub database (<http://www.pgrn.org/>) are coordinated with the Pharmacogenomics Research Network (PGRN) to impact treatment [11, 12]. The database from Pharmacogenomics PharmaGKB and Very Important Pharmacogene (VIP) link additional external resources to visualize genotypes, molecules, and clinical information of disease pathway representations to select the optimal regimen [11].

Adjustment of chemotherapeutic dosage according to genetic profile of individuals can also be achieved accordingly, which can help reduction of dose, side effects and toxicity. Genetic markers, HLA-B * 15:02 and HLA-B * 57:01 have been identified via HLA allelic testing of prescription drugs such as abacavir, and carbamazepine, respectively, but most genetic markers rarely reach such a dichotomy. The variability in clopidogrel response due to loss of CYP2C19 allele function is 12%. Heritable fluctuations are estimated to be 72%. This means that other genes are also involved in CYP2C19 variability in response to clopidogrel.

Additionally, the VKORC1 and CYP2C9 alleles account for less than 40% of dose variability upon administration of warfarin, further, rare mutations in genes have recently been reported, which may cause variation of unknown cause. Curtailed understanding of relationship of genetic effects and drug response can affect clinicians' and patients' confidence in genetic testing. It reduces clinical decision making for prediction of probabilities and possibilities. Pharmacological genomics-based clinical trials enhance drugs' development by establishing a correlation between genetic profile and patient outcome during the early stages of clinical trials. Phase III studies can be extended to individuals who have a genetic predisposition to safely and effectively use developmental drugs.

3. Pharmacogenetic tools to identify genetic variants

The three major approaches to detecting genetic mutations associated with drug responses are "candidate mutations", genome-wide association studies (GWAS), and whole-exome sequencing (WES). Genome-wide association studies (GWAS) is related to complete genome screening of hundreds of thousands of single nucleotide polymorphisms (SNPs) rather than candidate genes. Whole-exome sequencing identifies variants in the genome's protein-encoding regions and analyzes the

genomic regions most likely to contain pathogenic variants and are being used frequently in pharmacogenetics of drug metabolism [13].

3.1 Genotyping in polymorphism

SNPs have become an essential marker for genetic research. Genotyping methods are mainly used to identify polymorphisms or SNPs that have great potential for developing new diagnostic markers that allow pharmaceutical and biotechnology research to identify genetic variation. Polymorphism can be detected via microfluidic devices and allows for very rapid fragment separation by high performance liquid chromatography and capillary electrophoresis, enabling detection of biomolecules of interest. Genotyping can be applied in the field of diagnostics, drug discovery, drug delivery, tissue engineering and bio-nanosensors (“lab-on-a-chip”) [16]. High-speed, high-throughput SNP analysis using the innovative biochip nanotechnology based platform is an ideal technique for high-resolution mapping and population genome research and the development of electronic microarray platforms. Moreover, DMET Plus is a chip developed by Affymetrix that covers 1936 genetic variants (including SNPs and copy number variations) across 231 relevant genes. PharmaADME and “Core ADMEGene” comprises of a list of genes and genetic biomarkers that can be used to screen pharmacokinetic variability [14].

3.2 Candidate variants

Candidate gene studies help identify the frequency of genetic marker primarily SNPs present at a higher frequency among patients and healthy individuals. This hypothesis is based on identification of variants of particular genes of interest associated with a genotyped trait which will help in their quantitative assessment. Moreover, these candidate genes are selected for their functional role in pathogenesis or their linkage within chromosomal region. The candidate variants test determined through SNP test generally estimates the frequency of available disease-causing variants in individuals known as the non-functional mutations (indirect associations). These non-functional mutations exhibit strong linkage disequilibrium (LD) with direct association’s functional mutations. Researchers have identified several variants of candidate genes such as VPS35, DNAJC13, HTRA2, NOS3, KCNS2, HAPLN4, USP46, SCN4A, TENM4, and FUS, probably under monogenic essential tremor conditions. However, their confirmation still requires a lot of independent research [15]. The genes NLRP2, FEZ2, CADM2, ANK3, NEK3, NEK7, TUBB, ANKRD1, and BRD2 are genetic mutations responsible for the development of the bipolar disorder (BD) and their detection in genetic tests will facilitate diagnosis. A better understanding of the genes and pathways involved is also needed to target genes that can improve treatment strategies. Further, GWAS and quantitative proteomics studies reveal the most significantly upregulated proteins in neural stem cells and mature neurons with brain damage [16].

3.3 Genome-wide association studies (GWAS)

Genome-wide association study (GWAS) is a technique that accurately and rapidly analyzes samples of the entire genome to determine genetic variation that causes the development of disease. It includes a human genome sequence for reference, a map of human genetic variation, and a computer database with advanced interpretation interfaces. Some of the genetic variations (DNA or genome) identified using GWAS have been shown in **Table 1**. This information will help in better diagnosis, prevention and treatment of common and complex diseases such as

Pharmacogenes	GWAS identified reference no	Structure/key points	Medical condition	Reference
Intronic HMGA2	rs1042725	Intracranial volume	Adult height Polymorphism HMGA2 influences the expression of the insulin-like growth factor 2 gene (IGF2) alongwith pleomorphic adenoma gene 1 (PLAG1)	[17]
Intronic CRHR1	rs17689882	Intracranial volume	Encodes corticotrophin-releasing hormone receptor.	[18]
Intonic GPCPD1	rs2618516	Occipital lobe surface area	Encode protein that hydrolyzes glycerophosphocholine	[19]
FBLN2	rs145212527	Hippocampal volume	Tissue organization and neuron differentiation	[20]
SNVs, LPL, LCAT, APOB, LDLRAP1, HCHOLA4, LDLR, APOB, PCSK	rs693, rs562338, rs506585, rs515135, rs1367117,rs757584	Genes facilitate receptor-mediated endocytosis, recycling, receptor regulation, biliary cholesterol excretion	Severe hypercholesterolemia	[21]
SLC12A3, CLCNKB, PN359k, PL94I, CLCNKA, HNF1B	NM_000339 NM_000085	Genes alter net renal sodium balance and blood pressure variation	Hypocalciuria and hypomagnesemia, Gitelman's syndrome (GS)	[22]
MYH7,TNNT2,TPMTNNI3, MYL2, MYBPC3, ACTC, MYL3	GTR000514111.4	Mutation in these genes may cause increased in TGF- β signaling in myocyte leading to fibrosis.	Familial Hypertrophic cardiomyopathy	[23]
FBN1	rs1036477 and rs2118181	Aortic aneurysm formation	Marfan's syndrome	[24]
NKX2-5, GATA-4, TBX5	rs2277923, rs28936670 rs368418329, rs56166237 rs6489957	The transcription factors for heart development and regulation	Atrial or ventricular septal defects, Congenital heart disease	[25]
NOTCH1	rs13300218-G rs3124592-A	NOTCH1 acts to suppress the default osteoblast mesenchymal flap	The bicuspid aortic valve, califi aortic valve disease	[26, 27]

Table 1.
GWAS identified pharmacogenes and its medical condition.

asthma, cancer, diabetes, heart disease and mental illness. Genome-wide association studies can also help in detection of the risk of drugs for type 2 diabetes, Parkinson's disease, heart disease, Crohn's disease, prostate cancer, and depression. Researchers conducted a genome-wide association study (GWAS) using participants from two groups: sick and similar people without illness. Their DNA samples are collected from participants by taking blood samples or cotton swabs by mouth. Certain genetic mutations occur more frequently in sick people as compared to non-sick people and thus, these variations are "related" to the disease. It has been observed that these genetic mutations identified in the human genome region are related to the cause of the disease. At the same time, the disease may not be directly linked to the cause of the disease, so, the mutation may be "marked" with the variant that actually causes the disease. Therefore, researchers often sequence DNA base pairs in that particular region of the genome to detect the actual genetic alterations that cause the disease to develop. The complete set of DNA, or each participant's genome, is purified and scanned on an automated laboratory machine by placing it on a small chip.

The National Center for Biotechnology Information (NCBI) has developed a genome-wide database of association studies. It collects data repositories related to various diseases known as databases of genotypes and phenotypes (dbGaP) accessible from the NCBI website (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap>). The GWAS initiative was supported by the National Institutes of Health, Pfizer Global Research, and the Genome-wide Association Study (GAIN). GAIN is funding various GWAS studies on bipolar disorder, major depression, type 1 diabetic nephropathy, hyperactivity disorder, schizophrenia, and psoriasis at <http://www.fnih.org>. It can be found at [work/past-programs/genetic-association-Information Network Gain](http://www.fnih.org/work/past-programs/genetic-association-Information%20Network%20Gain). NIH Institute has also launched a genome-level related study at the National Institute of Cardiopulmonary Blood (NLBI) and a flamingham gene study in collaboration with Boston University School of Medicine for cardiovascular and other chronic disorders. Women's health studies have been contributed to the pharmacogenetics research network to investigate the effects of genes on osteoporosis, diabetes, and various responses of individuals to drugs, etc. The National Eye Institute and the National Institute of Neurological Disorders also pushed the Parkinson's disease stroke GWAS study.

3.4 Whole-exome sequencing (WES)

Whole exome sequencing, also known as next-generation sequencing (NGS), sequences the genome's protein regions. With this method, researchers can observe the effect of phenotypes by sequencing only the genome's coding regions. 2–3% of human exomes represent the entire genome, which is the root cause of approximately 85% of known disease-related mutants. Exome sequences can efficiently identify coding variants and find application in population genetics, genetic diseases, cancer research, and cost-effective alternatives to whole-genome sequencing. It also produces a more manageable dataset for faster and easier data analysis than the whole genome approach (a sequence of 4–5 Gb per exome versus about 90 Gb for the entire human genome). Exon sequencing detects exon encoding variants and extends targeted content to provide a more comprehensive view of gene regulation, including untranslated regions (UTRs) and microRNAs. The DNA library can be created in one day and requires only 4–5 Gb sequences per exome. Illumina DNA Prep with Exome Enrichment Kit, AmpliSeq for Illumina Exome Panel, TruSeq DNA Exome, TruSight One Sequencing Panels, Nextera DNA Exome, Library Prep Kit Selector are exome sequencing kits for analyzing coding regions of genomic variants.

In WES procedures, target regions with the fragmentation of genomic DNA are captured by hybridization using a solution of biotinylated oligonucleotide probe. The captured target sequence is isolated using streptavidin beads and subsequently amplified and sequenced after washing and elution. Their quantification helps in preparation of DNA libraries for high-quality whole-exome sequencing. Exome sequencing is useful in identifying Miller syndrome and rare Mendelian disease mutations. The NHLBI “Grand Opportunity” Exome Sequencing Project (GO-ESP) in association with Exome Aggregation Consortium (ExAC) helps to identify diseases associated with rare variants for the development of personalized medicine, and harmonizing patient-specific treatments.

4. Pharmacogenomic database

Pharmacogenetics is a field that provides information related to drug metabolizing enzymes, drug transporters, drug targets, and mutant genes that code for proteins necessary for drug response or toxicity. Next-generation sequencing is carried out by the rapid development of functional genomics that genetically analyzes the most essential mutations, gene copies, changes in the number of genomes and versatile arrays. These pharmacogenomics efforts help physicians prescribe safer and more effective treatments and personalized medications. The joint clinical pharmacology genomics implementation consortium (CPIC, <https://cpicpgx.org/>) project between the online resources PharmaGKB and Pharmacogenomics Research provides guidance on genetic testing to enhance and optimize drug therapy. In addition, the NIH-funded Implementing Genomics in Practice (IGNITE) initiative and the Dutch Pharmacogenomics Working Group (DPWG) in Europe have been developed with a focus on conducting and interpreting genetic testing to guide clinical decision-making. These consortia implement pharmacological genomics services in the clinic to update their knowledge according to pharmacological genomics guidelines. Some pharmacogenomic database and their attributes have shown in (Table 2).

4.1 The pharmacogenomics Knowledge Base (PharmGKB)

The Pharmacogenomics Knowledge Base (PharmGKB), funded by the National Institutes of Health and the Pharmacogenomics Research Network (PGRN), a joint research consortium, was developed at Stanford University to identify genetic mutations that affect drug responses [40]. The PharmGKB website (<http://www.pharmgkb.org>) contains genotypes, molecules and clinical knowledge integrated into the path representation, as well as additional external links to the all-important Pharmacogene (VIP). This is a web-based public repository of genotypic and phenotypic information related to the Pharmacogenetics Knowledge Base (PharmGKB, <http://www.pharmgkb.org>), which supports expression, storage, analysis, etc.) and distribution of pharmacogenetics data [37, 38]. PharmGKB aims to facilitate field research and facilitate the sharing of critical pharmacogenetic datasets. Pharmacological genomics can explain the various reactions (side effects and/or degree of positive response) to a drug due to the presence of specific alleles of the gene that explain the hereditary change. PharmGKB organizes data related to pharmacodynamics and response to medication, changes in pharmacokinetics, changes in molecular and cellular function assays, and changes in gene sequences. All datasets are categorized into these five sets and are also associated with related genes, drugs, and diseases.

Pharmacogenomic database	Attributes	Developed by	References
cBioPortal	Bioinformatics tools for visualization and gene-based analysis of cancer patients' molecular profiles and clinical attributes from large clinical trials.	Memorial Sloan Kettering Cancer Center (MSKCC) Computational Biology Center (cBio) is affiliated with The Cancer Genome Atlas (TCGA) and International Cancer Genomics Consortium (ICGC).	[28, 29]
CellMiner	Enables rapid retrieval of activity ratios of over 20,503 compounds, including 22,379 genes, 92 proteins, 360 microRNA transcripts, and 102 US Food and Drug Administration (FDA) approved drugs.	National Cancer Institute (NCI) Molecular Therapy Center (CMT) and Developmental Therapy Program (DTP)	[30, 31]
Connectivity Map	The CMAP 2.0 software identifies chemicals with similar gene profiling between the corresponding genes, or the gene signature previously identified as a general gene expression modification for one or more known compounds from the CMAP database. The software uses up-regulated and down-regulated query genes representing biological processes to detect both positive and negative connectivity compounds.	Broad Institute of MIT, Whitehead Institute and Harvard Medical School, Massachusetts	[32, 33]
MEDI and NDF-RT (Medication Reference Terminology and The National Drug File - Reference Terminology)	Database as a prescription drug resource to provide a range of unique diseases - drug combinations that suggest significant novelty potential	Developed by the US Department of Veterans Affairs Veterans Health Administration (VHA).	[34, 35]
SPHINX (Sequence Phenotype and Pharmacogenomics Integration Exchange)	This is an external database developed through the eMERGE project which, contrary to assisting doctors in prescribing, determines patient-specific information, mainly patient data and the new PGx from disease drug search engines.	The eMERGEseq initiative aims to identify rare variants. Partner Healthcare (two sequencing centres) with the Baylor Medical College Human Genomic Sequencing Center (HGSC) and Broad Institute has developed SPHINX to develop a series of high-impact genes, single nucleotide polymorphisms (SNVs), And the discovery of genomics by identifying and validating pathogenic variants.	[36]

Table 2.
Pharmacogenomic database.

4.2 The human cytochrome P450 (CYP) allele nomenclature website

The human cytochrome P450 allele nomenclature (CYP allele) (<http://www.cypalleles.ki.se/>) is a web-based analysis of CYP mutant genetic information with molecular and clinical effects. Most of the CYPs on the CYP allele website are polymorphic enzymes involved in the differentiation of foreign bodies but have endogenous functions. The website also contains information related NADPH cytochrome P450 oxidoreductase (POR), an electron donor of the CYP enzyme, which contains 29 CYP genes, so the POR allele is also a stellar allele nomenclature (POR*). This website covers the polymorphic alleles of NADPH cytochrome P450 oxidoreductase (POR) and 29 CYP enzymes' CYP2B6, CYP2C9, CYP2C19, and CYP2D6 genes. Each CYP allele contains information related to various alleles and their nucleotide changes, in vitro and in vivo molecular and functional effects [39].

4.3 The human arylamine N-acetyltransferase (NAT) gene nomenclature committee

Several genetic mutations related to human arylamine N-acetyltransferase (NATgene) in species, humans and other organisms have been identified and the allelic nomenclature for the gene has also been recognized. The committee will assist in the naming arylamine N-acetyltransferase and also its new arylamine N-acetyltransferase allele. The information will be accessible to the international scientific community via the Internet [40].

4.4 Transporter database (TP-search)

Homeostatic exchange between endogenous and extrinsic substances such as ions, small molecules, macromolecules and drugs and transport proteins (transporters) occurs at the systematic, organic, cellular and intracellular levels. Genomics, transcriptomics, and proteomics techniques for transporter genes in normal cellular processes and various pathologies have been integrated to develop the Human Transporter Database (HTD) (<http://htd.cbi.pku.edu.cn>) which indicate the relationship between expression patterns exhibited by transporter genes and polymorphisms and their ligands. Study on a human transporter involved in many fundamental biological processes, including oxidative phosphorylation and myocardial contraction, has shown the link between Mendel's laws and complex diseases. In particular, HTD serves as a well-organized interface to facilitate the research community to retrieve detailed molecular and genetic information for transporters and develop personalized medicine [41].

4.5 UGT alleles nomenclature page

The uridine diphosphate glucuronosyltransferase (UGT) enzyme involved in the glucuronidation of the target substrate makes foreign substances and other endogenous compounds water-soluble for renal excretion. The UGT Allele Nomenclature page describes the UGT1A1 haplotype. Developmental hyperbilirubinemia causes kernicterus or the accumulation of bilirubin in brain tissue. As a result of this, neurological damage occurs which is irreversible, resulting in severe disability or death. Bilirubin levels can be controlled by intensive phototherapy, the efficiency of which decreases with age, and the only alternative left is liver transplantation [42].

5. Role of nanotechnology in pharmacogenomics based diagnosis

Nanobio-labeling is an important tool in biomarker research that uses water-soluble, biocompatible, fluorescent and stable nanomaterials to label cells. Molecular biomarkers can be used in designing of personalized medicine for diagnosis and treatment, identifying cellular changes at the DNA, RNA, biotransformer or protein level. Nanotechnology based devices can potentially screen disease biomarkers at high speed. The tools are developed by identifying biomarkers very specific for the disease that can lead to diagnostic tests. These nanobio-technology-based diagnostic methods, which use direct DNA and protein analysis, can improve speed, accuracy and sensitivity over traditional molecular diagnostic techniques. Nanobiotechnology supports molecular diagnostics, and integration of diagnostics and therapeutics (theranostics) which accelerates personalized medicine [43]. Theranostic applications can help provide optimal treatments and characterize human genomic mutations between populations [44].

According to a report published by Grand View Research, Inc., the global market for pharmacogenomics (theranostics and complementary diagnostics) is expected to reach \$18.3 billion by 2025. These approaches help provide cost-effective treatment and add value to the process, of development. The benefits of using these tests for disease risk prediction, patient stratification, and treatment response monitoring, over traditional methods are expected to provide significant progress in this market [45].

The role of genetics plays a vital role in theranostics, which provides successful and cost-effective therapeutic.

Pharmacological genetics, proteomics, and biomarker profiling based diagnosis using nanotechnology based platforms like liposomes, dendrimers, macromolecular nanoparticles, metal nanoparticles, quantum dots, and carbon nanotubes is providing vital information regarding disease pathology and its treatment. Quantum dots are stable particles which can be used as molecular labels to study the size and span of metastasis besides, predicting early signs of cancer and tracking the effectiveness of drugs targeting the disease. Genzyme Corporation has discovered EGFR mutation detection kits that can be used to diagnose non-small cell lung cancer (NSCLC) [46].

6. Multiple genes interactions on treatment response

Multiple genetic interactions also termed as polygenic inheritance interconnects biological processes and their functional relationships that cause phenotypic deviations and multiple genetic mutations [47]. A retrospective study of 108 Chinese patients with metastatic gastric cancer found nine genes involved in DNA repair (ERCC1, ERCC2, and XRCC1), detoxification of oxaliplatin (GSTP1 and GSTT1), and fluoropyrimidine metabolism (MTHFR) and these can be used to predict clinical response and survival [48]. Similarly, the Mayo Clinic has issued drug-gene pair alerts on 17 drug-gene pairs: Abacavir HLA-B*57:01, Allopurinol HLA-B*58:01, Carbamazepine HLA-B*15:02 and HLA-A*31:01, Citalopram CYP2C19, Clopidogrel CYP2C19, Codeine CYP2D6, Escitalopram CYP2C19, Fluoxetine CYP2D6, Fluvoxamine CYP2D6, Paroxetine CYP2D6, Simvastatin SLCO1B1, Tacrolimus CYP3A5, Tamoxifen CYP2D6, Thiopurines TPMT, Tramadol CYP2D6, Venlafaxine CYP2D6, Warfarin CYP2C9 and VKORC1 which will help physicians treat patients on the basis of the genetic test in response to the alert. These evidence-based guidelines were established by the Consortium for the implementation of clinical pharmacogenomics [49].

7. Pharmacogenomic based diagnosis of cancer

Various cancer portals have been developed for tumor gene profiling and are serving as a powerful tool for discovering and implementing personalized cancer treatments. Large-scale translational bioinformatics and cancer genomics platforms use multi-omics datasets to provide insight into genomic alternations and precision medicine strategies. Development in tools for statistical, mathematical and computational modeling help collect genomic information for molecular profiling, clinical responses to drugs, research on clinical trials, and identification and development of innovative therapies. Transcriptome data from melanoma exons pretreated with ipilimumab was studied to study the effect of pretreatment on activity of tumor-specific new antigens including mutation loading, new antigen loading, and cytolysis in the tumor microenvironment [50]. The Cancer Genome Atlas (TCGA) study performs molecular subtyping of the breast, colorectal and endometrial cancers. Furthermore, TP53 inactivation, MYC proliferation and dysregulated cell cycle checkpoints have been demonstrated through TCGA studies [51]. The role of pharmacogenomics is more pronounced in oncology as compared to other diseases and is indicating that inherited differences in genes affect the body’s response to medications. Pharmacogenetics has revolutionized cancer treatment by genotyping patients in clinical settings that promote the best chemotherapeutic regimens and drug doses with maximum efficacy and minimal risk of toxicity. The Pharmacology Genomics Resources (PREDICT) program for enhanced decisions in care and treatment initiated by Vanderbilt University has simplified consistent dosing. Pharmacogenomic data identified for application in diagnosis and treatment has been shown in (Table 3).

S.no	Pharmacogenomic data	Diagnostic/Treatment Protocol	Reference
1.	Dihydropyrimidine dehydrogenase (DPYD) genotype and fluoropyrimidine dosing	The DPYD gene sequencing and it’s variant has been significantly analyzed by polymorphism (G to A intron 14 (inv14 + 1G > A or DPYD*2A; exon skipping mutation). Dosing of fluoropyrimidine depends on genotyping of DPYD, a rate-limiting enzyme for fluoropyrimidine catabolism.	[52]
2.	Methylenetetrahydrofolate reductase (MTHFR)	Methylenetetrahydrofolate reductase (MTHFR) is an essential regulator of folic acid and homocysteine metabolism. In epilepsy, the concentration of 5-methyl-THF in CSF should be monitored. The CSF concentration of 5-methyl-THF is significantly reduced in most early-onset patients due to restricted transport of folic acid through the blood-CSF barrier and increased demand for choline for meningeal biosynthesis resulting in severity of the neurologic symptoms in MTHFR deficiency.	[53]
3.	Thiopurine S-methyltransferase (TPMT) and thiopurine dosing	The prodrugs azathioprine, 6-mercaptopurine (6-MP) and thioguanine (TG) are inactivated by TPMT and methylated to produce TG active nucleotide (TGN). 6-MP is biotransformed to methylthionosin 5-prime monophosphate, which causes inhibition of de novo purine synthesis and can cause toxic effects. TPMT gene genotyping is used for thiopurine dose assessment in myelosuppression. TPMT test is mandatory before use of mercaptopurine in childhood leukemia.	[54]

S.no	Pharmacogenomic data	Diagnostic/Treatment Protocol	Reference
4.	Uridine diphosphate glucuronosyl transferase (UGT) genotype and irinotecan	Irinotecan is activated to SN-38. UGT1A1 family is involved in glucuronidation of SN-38 and bilirubin. Variation in the number of TA dinucleotide repeats in the TATA element of the UGT1A1 promoter region, is associated with reduced gene expression as well as diminished enzyme activity	[55]
5.	Glutathione S-transferases gene polymorphism and platinum compounds	Glutathione S-transferase (GST) constitutes a family of enzymes involved in detoxification of foreign bodies, including cisplatin-based chemotherapy. Genetic polymorphisms in GST have shown altered efficacy or toxicity in patients with NSCLC (more specifically GSTP1 is associated with improved response to therapy)	[56]
6.	ATP-binding cassettes (ABCB1, ABCC2, ABCG2)	The ABCB1 gene encodes P-glycoprotein. Overexpression of this glycoprotein leads to resistance to specific anti-cancer therapies. There are two synonymous SNPs (C1236T for exon 12 and C3435T for exon 26) and one non-synonymous SNP (G2677T for exon 2), which appear to be regulated by MDR1 * 2 haplotypes, P-glycoprotein upregulation and drugs. ABCG2 (Breast Cancer Resistant Protein) and ABCC2 are involved in irinotecan's metabolism and alter the properties of irinotecans.	[57]
7.	X-ray cross complementing group 1 (XRCC1)	XRCC1 is a DNA repair protein. It is encoded by the XRCC1 gene in humans. SNPs (1301 G > A; Arg399Gln) result in mutations in base excision ability and increased cancer risk. Negative expression of XRCC1 makes tumors more sensitive to platinum-based chemotherapy. Detection of XRCC1 expression in patients with gastric cancer can provide clinical guidance in choosing the optimal adjuvant for therapy.	[58]

Table 3.
Pharmacogenomic data identified for application in diagnosis and treatment.

8. Pharmacogenomic diagnosis for cardiac diseases

Clopidogrel is used in the acute coronary syndrome patients, exhibits variable response in patients due to *2 loss-of-function variant in CYP2C19 as it encodes hepatic cytochrome P-450 2C19 enzyme which is important for clopidogrel bioactivation. Similarly, interindividual variation in response to warfarin is due to polymorphisms in VKORC1 and CYP2C9 and has been led to revision of dosing guidelines for patients by USFDA. Variant of SLCO1B1, which encodes a hepatic uptake transporter, is associated with risk of myopathy with high-dose (80 mg/d) simvastatin [59]. Genetic mutations in thiopurine S-methyltransferase (TPMT), an enzyme that metabolizes azathioprine, result in higher concentration of the azathioprine active metabolite. Combining the immunosuppressant azathioprine and the enzyme thiopurine S-methyltransferase, is used to prevent heart

transplant rejection [60]. Sufficiently robust and predictive genetic information can be used to guide clinical decisions [61]. The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) found a significant association between PGx-guided warfarin dosing [62]. The genes most strongly associated with beta-blocker response are the β -1 adrenergic receptor (ADRB1), the α -2C adrenergic receptor (ADRA2C) and the G protein-coupled receptor kinase-5 gene (GRK5). The ADRB1 gene has two common non-synonymous single nucleotide polymorphisms, p.Ser49Gly and p.Arg389Gly, associated with different responses to beta-blockers in hypertension and coronary heart disease [59]. The genome aggregation database maintains archives the various gene variants. Guidelines for 27 drug-gene pair has been issued by Pharmacogenetics Implementation Consortium, and includes data related to drug metabolizer phenotypes. (extensive metabolizer/slow metabolizer), poor/ultrafast metabolizer, expected rapid metabolizer with a particular diplotype, expected effect size, availability of alternative therapies, and results of drug ineffectiveness or toxicity [63].

9. Pharmacogenomic diagnosis for brain disorders

Only 30–40% patients with central nervous system disorders respond conventional drugs. Around 60–90% of variability in drug response is due to pharmacogenetic and pharmacogenomic factors. Approximately 60–80% of CNS drugs are metabolized via enzymes of the CYP gene superfamily. Neuroleptics are the major substrates of CYP1A2, CYP2D6 and CYP3A4 enzymes. Antidepressants are essential substrates for CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4 and benzodiazepines are vital substrates of CYP2C19, CYP2D6 enzymes. Adoption of genomic medicine have proven to be prognostic tools to accelerate diagnostic accuracy in CNS disorders' etiology and develop novel biomarkers to personalize treatments via pharmacogenetic and pharmacogenomic procedures for drug development and clinical practice [64].

10. Role of nanotechnology and pharmacogenomics in the treatment of diseases

Advances in molecular pharmacology, genomics and nanotechnology are providing enriching clinical results by meticulously highlighting pathogenesis pathways, empowering the capacity for clinical diagnosis, and improving the outcome of drug delivery [65]. Supported by the sophisticated target-guided nanodevices, the intricate genomic information is being incorporated into clinical practice to evaluate complex diseases such as cardiovascular diseases, type 2 diabetes, asthma, cancer and degenerative disorders [66]. Presence of unique genetic variants has been found to be instrumental in predisposing particular individuals to the onset and development of diseases. Nanotechnology based drug delivery systems have developed specialized technical frameworks for the exploitation of genomic knowledge, so as to reduce the risk of disease initiation and progression and drug toxicity [67]. Pharmacogenomics highlights the interplay of the role of genes in disease etiology, disease pathophysiology, disease biomarkers, drug targets, drug effects, and the fate of drugs inside the body. The integrated application of pharmacogenomics and nanotechnology will provides better therapeutic outcomes with minimized side effects and adverse drug reactions during therapy [68].

10.1 Pharmacogenomics

Pharmacogenomics emerged as a science which highlighted the differences in drug response to differences in genetic makeup in particular populations/various ethnic groups. It is the science of genetic polymorphism (genetic variance) that is responsible for variability in drug response and is used as a useful method to assess the association of disease-gene, and gene-drug on drug response based on the human genome. Drugs are formulated and designed to counteract medical conditions and cure ailments, but drugs often fail to demonstrate their beneficial impact in certain patients, resulting in adverse drug events. This drug response variability may be due to genetic differences [69]. The research of hereditary variability in drug receptors or target pathways, heterogeneity in genes that encode drug-metabolizing enzymes or drug transporters, and genetic variation in genes that indirectly affect drug reaction are part of Pharmacogenomics. The main objective of pharmacogenomics is to recognize how genetic differences affect therapeutic efficacy and this knowledge can be used experimentally to personalize the selection of medications and their doses to improve efficacy and safety.

Pharmacogenetic tests have historically focused on specific candidates selected based on our understanding of the pharmacokinetics of the drug, and drug response variability found in patients receiving the medication. Initially, family experiments were used to determine the hereditary existence of inter-individual variations in the disposition of drug or effect of medications, which was then used to understand the genetic cause for monogenic traits. Pharmacogenomics can be seen as a wider approach to elucidate the abundance of genes that are important to pharmacology, including the implications of genetic differences in single genes, the relationship between genes in diverse pharmacological pathways, the phenotype that arises from these differences, and the impact of the phenotype on drug response. Its main characteristics are high-throughput genomic studies in conjunction with their significance to particular drug responses only as target phenotype (i.e., sequence variants in DNA, gene expression analysis, etc.). The structural and functional genomics analysis (**Figure 1**) can be used to understand the use of therapeutic drugs for increased efficacy (with reduction in toxicity) for dosage personalization and new drug development [70]. The structural pharmacogenomics explores the structural difference between individuals' genes while functional genomics evaluate the functional modifications induced by structural variation in the genome. Variations in genes are responsible for the variation in particular functional process inside the body via change in the nature of protein synthesized. Any disorder or deformity may also result due to these functional changes. Both structural and functional pharmacogenomics are effective in predicting, recognizing genetic markers of disease, and planning and optimizing drug therapy in the treatment of that disease [71].

Extremely penetrating monogenic features are several of the genetic polymorphisms characterized to date that affect drug reaction in humans: hereditary variations in a specific gene have such a significant effect on the pharmacokinetics or pharmacodynamics of a drug that cross changes in one gene have a clinically relevant effect on drug response. "These are pharmacogenetics' "low-hanging fruit". However, certain proteins decide the efficacy of certain medications, and hybrid genetic polymorphisms can be identified to determine therapeutic efficacy of several genes along with nongenetic factors. Therefore, new methods are required to classify the appropriate genes, genetic polymorphisms, mechanisms, and processes and; their association with a given drug. The different techniques currently being utilized are genome-wide haplotype analysis, gene regulation tests and proteomic techniques, as well as "candidate gene" approaches focused on

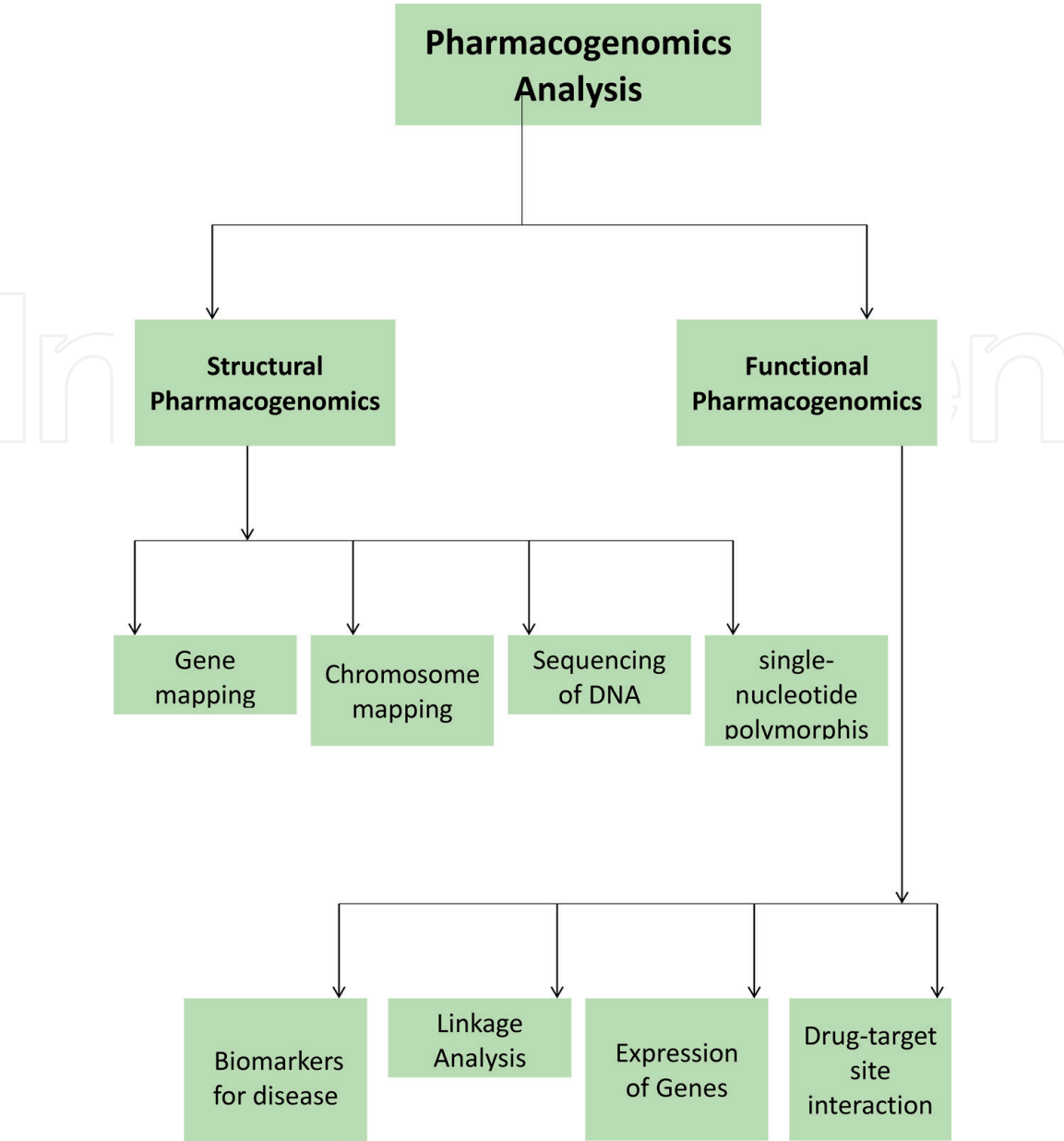


Figure 1.
Structural and functional pharmacogenomics analysis.

established pharmacokinetic and pharmacodynamic considerations. These methods are likely to be important for studies that seek to elucidate polygenic determinants of drug response, with emerging predictive and biological (pathway) models and quantitative genotyping in certain target tissues. Broad clinical trials with uniformly treated and routinely characterized patients, high-throughput genomic approaches, and advanced bioinformatics simulations would entail the clinical validity of these polygenic models. These experiments aim to create a new range of molecular diagnostics (i.e. genotypes) that can be used to enhance drug delivery by reducing toxicity and maximizing efficacy [72].

Nanotheranostics is the field where pharmacogenomics is used in the delivery of drugs for personalized medicines. It is a hybrid of drug therapies and diagnostics. Pharmacogenomics provides an excellent method to quantify several parameters relating to the disorder and its severity, together with treatment, so that medicine can be tailored on the basis of an individual's genotype. Nanotechnology offers a possibility for the development and design of therapeutic strategies, which are capable of concurrently detecting genetic biomarkers for disease along with ongoing drug therapy. Nanotechnological materials such as gold-based nanomaterials,

magnetic nanomaterials, polymeric nanomaterials, carbon-based nanomaterials, silica-based nanomaterials, composite nanomaterials and quantum dots may be used to build such drug delivery systems [73, 74].

10.2 Role of Pharmacogenomics in the identification of drug targets

Structural Pharmacogenomics aims to recognize and verify disease-relevant targets for therapeutic activity (target biomarker) like the EGFR signaling system, PI3K, RAF, MAPK, KRAS AKT markers for various forms of cancers. Pharmacogenomics compares the target biomarkers with disease processes to create a connection between the disease and the biomarker of the experiment, which then helps to define the drug molecule for such a target [75, 76]. Specific genome targets like enzymes, drug carriers, proteins, nucleic acids, chromosomes, cell surface proteins, ion channels, and other bio-molecules contributing to the pathophysiology of the disease have been provided by human genome sequencing. Such possible causes to the pathophysiology of the disease can serve as target sites for drug action (druggable targets). Thus, the pharmacogenomics concept can be used in target recognition, genotyping, structural elucidation, and target confirmation that improve safety and efficacy of medicines. Sequencing of the target genes can be used in the discovery and validation of lead compounds [77, 78].

10.3 Nanotechnology towards making possibility of personalized medicine

Nanotechnology is the development and utilization of materials, devices and processes by manipulating matter at the nanometer range, i.e. at the level of atoms, molecules, and supermolecular structures. The application of nanotechnology in life sciences is in molecular diagnostics, drug discovery, drug delivery and nanomedicine development. The combination of nanotechnology with personalized medicine has created unparalleled and unique opportunities to improve the treatment of many serious diseases. Medicine has been profoundly impacted by this concept over the last decades, shifting its attention to the molecular level under which, applications of nanotechnology as a quickly emerging field appear to fit needs on this size scale. In this reference, nanoparticles offer unique benefits in the design of nanomedicine due to their small size, flexibility, increased surface-to-volume ratio and multi-purpose ligand surface modification in order to obtain targeting of cells/tissues. Nanomedicine is also meant to offer immediate, precise and efficient diagnosis and treatment. In this way, the balance between maximum therapeutic efficacy and lower toxicity is significantly promoted [79, 80].

As the nanomedicine market has expanded exponentially, the most promising technologies and applications for personalized medicine can be identified. Individuality of a person is often expressed in his pathophysiology. In the same extent genes define, the identity of an individual, genetic heterogeneity that can identify the disease phenotype and its drug response. It is reported that each drug has different effects on different types of peoples. Whether in terms of efficacy and safety of these drugs, they show differential behavior due to the complex nature and heterogeneity of individuals (both patients and diseases). With a sound and detailed knowledge of genomics and proteomics and the development of a novel and innovative technology and patient-based molecular profiling, the promise of nanomedicine has opened the path to the future of personalized medicine [80, 81].

Personalized medicine literally means prescribing of particular medications that are ideally suited to the person. Personalized medicine is the perfect way to incorporate modern biotechnology into medicine in order to improve understanding of disease pathomechanism, molecular identification and clinical application.

Nowadays, nanotechnology and genomics fuel expertise and creative practices, allowing both pharmacological strategies and therapeutics measures to be implemented on a personal basis, i.e. designing personalized medications (Innovative Drugs), improving targeted drug delivery and pharmacotyping techniques to the clinical environment for diagnosis and treatment of disease as shown in (Figure 2). “Pharmacotyping” is characterized as the prescription drug mechanism by which clinical and genotyping data are used to instruct physicians to design drug dose regimens for particular patients. These approaches require a comprehensive genetic and molecular history of each patient, which leads to the discovery of specific biomarkers that might influence the progression of the disease and the response to treatment. Personalized medicine is also not only restricted to the study of biomarkers and genetic polymorphisms, but also depends on the development of disease identification techniques and estimation of therapeutic responses [73]. Thus, understanding

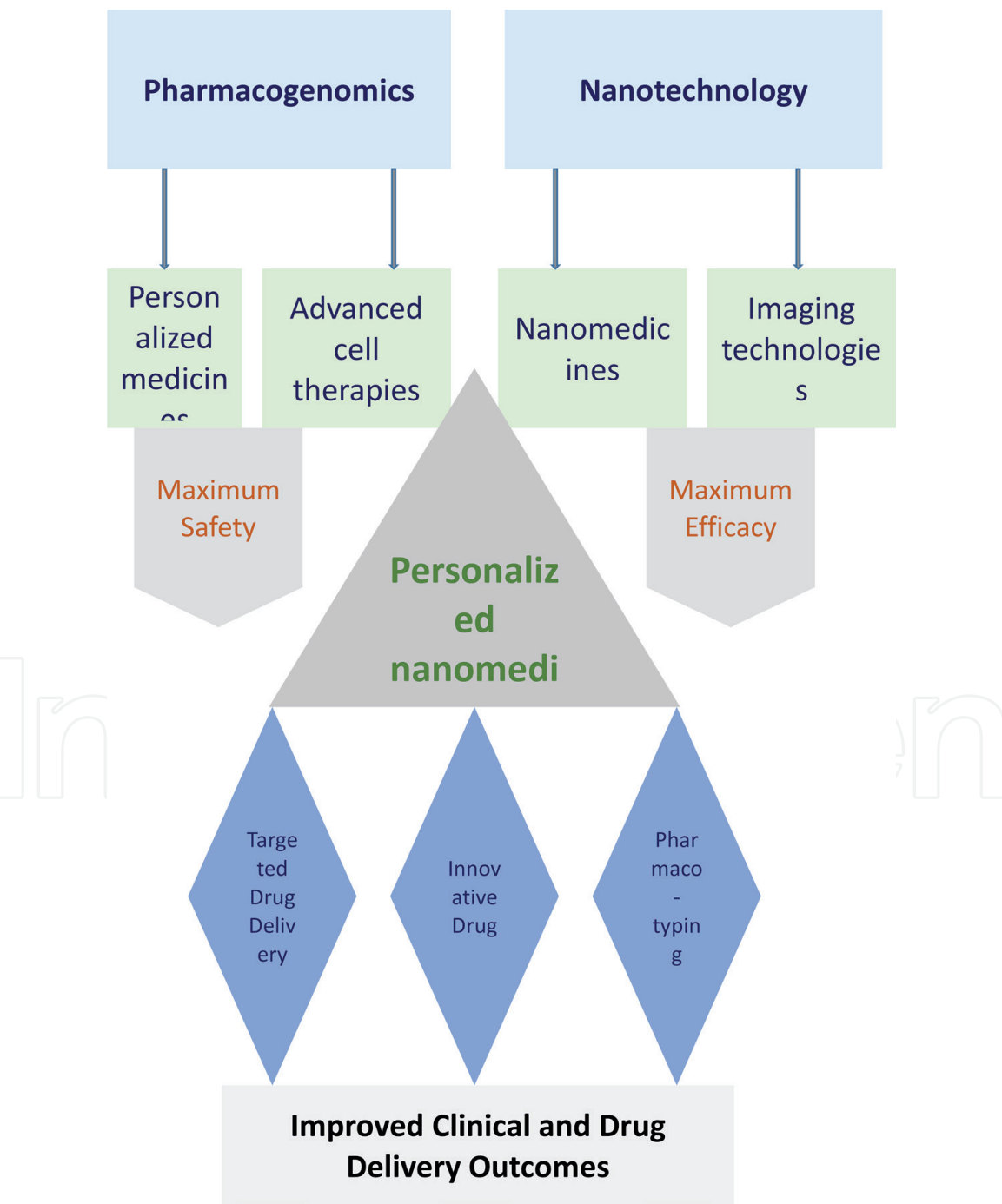


Figure 2.
Integrated approach of nanotechnology and pharmacogenomics to improve safety and efficacy of drugs.

of nanotechnology and genomics could handle the disease and drug response of patients in the form of personalized medicines. In addition, recent developments in nanotechnology have certainly provided the perfect environment for the emergence of personalized medicine as the new approach in the diagnosis of diseases and drug therapy.

10.4 Nanoparticles in personalized medicine

Because of their exploratory features, nanoparticles facilitate the molecular targeting of medicines. Recent studies offered detailed information on the relationship of NPs with biological processes in order to promote their use for nanotheranostics diagnosis, imaging and drug delivery. Today, nanotheranostics have been developed to monitor transcription and translation of genes, recognize cancer cells, control the proliferation of T cells, and manage blood sugar levels. Moreover, blood urea levels can be detected by an implant and normal levels can be restored. Another implant was created for artificial insemination that injects bull spermatoocytes into the bovine ovary by identifying luteinizing hormone levels, especially during ovulation. Any disorder can be treated at the cellular and molecular level by detecting particular biochemical parameters [79]. While several experiments have been performed, relatively few pharmaceutical drug products have been developed as nanotherapeutics in the pharmaceutical market, indicating the uncertainty of formulating active compounds in these formulations. A PEGylated liposome doxorubicin medication called Doxil, approved for therapeutic use by the FDA, is the most popular example of nanoparticle technology for clinical use. The principle of PEGylation was first developed as a means for recombinant protein drugs to improve their circulation and stability. Another FDA approved effective nanoparticle application is Abraxane, in which paclitaxel is formulated with albumin. In an attempt to merge nanoscale therapeutic and diagnostic modalities, separate nanotheranostic agents have been designed to provide flexible platforms for the simultaneous delivery of diagnostics and therapeutics [73].

However, many new materials have arisen as theranostic agents such as gold nanoparticles, carbon nanotubes, metal organic frameworks and iron oxide nanoparticles; problems of safety and bio - compatibility and unspecified tolerance and toxicity need to be evaluated in the clinic. Regardless of these drawbacks, nanotheranostics seem very optimistic to develop personalized medicine [79].

11. Personalized nanomedicines

Personalized nanomedicine may be described as the management of a patient's disease or drug response by the use of nanomedicine in combination with clinical and molecular expertise (e.g. genomics, proteomics, epigenomics and metabolomics) as well as bioinformatics techniques to produce the best possible medical treatment for that person. In addition, by integrating nanotechnology and genomics expertise, personalized nanomedicine may create enhanced profiles for particular demographics and particular patients for prognosis, diagnosis and drug therapy, as well as surveillance through medical science and clinical management (Table 4) [81].

The combination of nanotheranostics with pharmacogenomics will take us to the next level of therapeutics. On one hand, the concept of pharmacogenomics is the latest model research, which has tremendous implications throughout the field of medical science and drug development at genomic and molecular level; moreover, a great deal of work is needed to investigate the maximum capabilities of

Advantages of Personalized Nanomedicines
Personalized nanomedicine is in nano-scale size range
Personalized nanomedicine offers tunability and flexibility
Offers possibility of using labile substances such as siRNA
The active concepts of personalized nanomedicine: encapsulation and safety
Targeted delivery to organs/ tissues/ cell compartments
Probability of responding to a need of specific patient group
Adapting patterns of treatment to each patient (e.g., dosage, frequency, etc.)

Table 4.
Advantages of personalized nanomedicines.

this method in the clinical field. Theranostics, on the other hand, is the technique of early phase diagnosis or disease pathogenesis, combined with concurrent treatment based on a single unit operation diagnosis profile. This not only increases patient health with optimum clinical performance, but also saves significant amounts of money by minimizing excessive care costs. This approach is of significantly more useful in the treatment of life-threatening chronic diseases like cancer, hypertension, Alzheimer disease, and can be implemented to many other ailments [68].

11.1 Personalized nanomedicine in the treatment of cancer

The advancement of personalized nanomedicine is a useful technique in the cancer therapy. Personalized oncology is raising new prospects for the elimination of cancer incidence by specifically targeting anticancer medicines to cancerous cells, target areas on the cell surface and inside the tumor microenvironment. Nanooncology has succeeded in improving the specificity and efficiency of cancer therapies, both by promoting the development and distribution of medications and by reducing clinical toxicity and serious incidents [82]. Personalization of cancer treatment is focused on a deeper knowledge of the pathogenesis at the molecular scale and nanomedicine can play a significant role in this direction. Several nanobiotechnology-relevant components of personalized cancer treatment are given in (Figure 3) [83]. Nanobiotechnology has the ability to enhance early cancer diagnosis and enhance personalized cancer treatment. Molecular diagnostics is the most important aspect of personalized medicine, and nanobiotechnology can play a significant role in its refinement [84].

Dendrimers are a class of nanoscale, core-shell, three-dimensional structures that can be synthesized precisely for a variety of uses. Specialized methods in chemistry allow detailed control over the dendrimer’s physical and chemical properties. They are most effective in the delivery of drugs, but they can also be used to produce new pharmaceuticals with emerging technologies. With several therapeutic target, polyvalent dendrimers interact simultaneously. They can be transformed into new-targeted therapeutics for cancer. Using complementary DNA oligonucleotide primers, dendrimers may be covalently linked to various bio-functional groups, such as folic acid, to create clustered molecules attacking cancer cells that overexpress the high affinity folate receptor [85]. Endothelial $\alpha v \beta 3$ -Integrin-targeted paramagnetic nanoparticles are being used to identify very limited angiogenesis area linked with tumors of nascent melanoma [86]. Nanobodies (Ablynx) are the smallest intact antigen binding fragments that have the full antigen binding capacity of natural heavy-chain antibodies. Nanobodies are prospective era of antibody-based treatments as well as diagnostic tools for diseases like cancer.

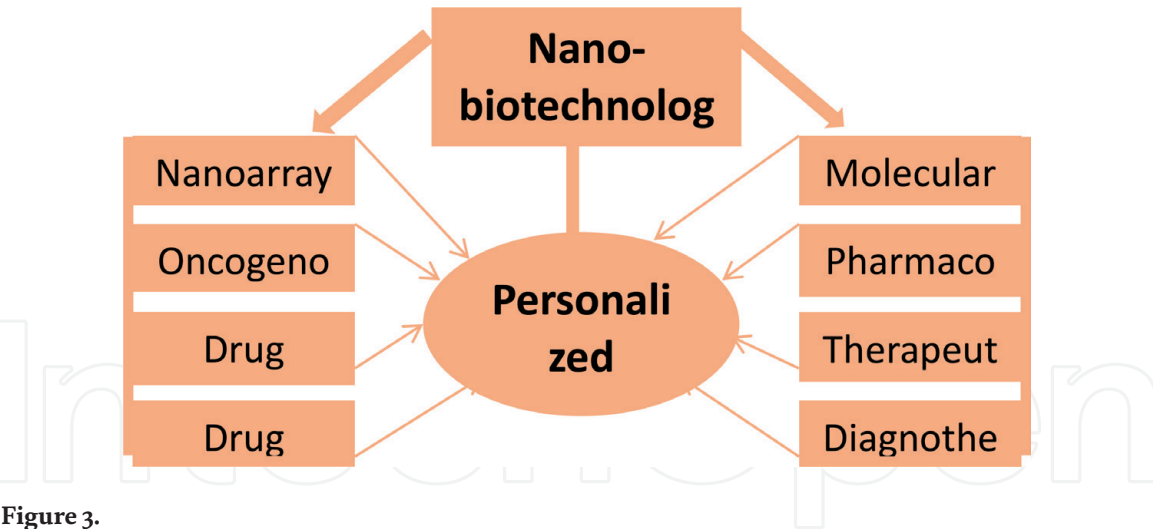


Figure 3.
Function of nanobiotechnology for personalized cancer treatment.

Nanobodies have a relatively high specificity and low endogenous toxicity. They can tackle therapeutic targets that are not readily detected by traditional antibodies such as enzyme active sites. Nanobodies have the ability to be produced as personalized cancer therapies [87]. Nanotechnology is revolutionizing the treatment of cancer as it can alter its diagnosis, clinical path, and prognosis. Before treatment, cancer molecular profiling may be extremely prognostic and predictive of clinical responses or recurrence, encouraging the most effective treatment to be prescribed with each specific cancer.

11.2 Personalized nanomedicine for targeting CNS diseases

Central nervous system (CNS) disorders are increasingly worldwide due to changing demographics. Three factors make this field especially challenging as, pathogens are slowly evolving and impossible to diagnose early or anticipate, response to medication is highly dependent on the individual patient and always needs to be personalized, and drugs must pass the blood brain barrier [88]. Therapeutic agents commonly used to treat CNS diseases have shown considerable efficacy. However, the failure of these medicines to pass the blood–brain barrier (BBB) and the inefficacy of technology to ensure localized delivery of drugs in disease-specific areas of the brain have impeded full CNS disease management. Nanoparticle- based targeted drug delivery to the brain will play a significant component in designing personalized treatment of neurological disorders by enhancing molecular diagnosis and pathomechanisms. For CNS drug delivery system, different types of nanoparticles (gold, silica, hydrogels, liposomes, magnetic nanoparticles, etc.) have been investigated. Such examples of the use of personalized treatment-based nanotechnology to treat CNS diseases are as follows: [89].

Gene silencing technologies focusing on small interfering RNA (siRNA) have shown great potential for the treatment of brain-associated diseases. However, successful and systemic delivery of siRNA to the brain appears difficult due to biological challenges such as enzymatic depletion, short-lived circulation, blood–brain barrier (BBB), relatively low tissue penetration, cell endocytosis, and cytosolic transport. Nanotechnology provides an interesting opportunity to overcome these problems in the delivery of siRNA to brain in combination with chemical and biological alteration strategies [90].

Alzheimer’s disease (AD) is a major public health concern worldwide. The challenge in treating the disease is partly attributed to the uncertainty of the signs and symptoms, the still limited understanding of its pathways and the presence of

latent, asymptomatic, condition. While several drugs are constantly screened in clinical trials for the treatment of Alzheimer's disease, the unpredictable patient response and often-serious adverse effects provide space for development for personalized nanomedicine [91]. In a study involving AD, the brain region was irradiated with low gigahertz electromagnetic fields after binding of gold nanoparticles to β -amyloid plaques. The energy level was quite low for healthy cells to be affected. This study can be used effectively in the treatment of CNS disorder involving protein aggregation [92].

A "nanozyme" consists of a composition of the nanoparticle, an enzyme and a moiety for recognition. In Parkinson's disease (PD), oxidative stress degrades the main dopaminergic receptors in the brain resulting in inflammation. It is also assumed that catalyzing the enzyme might be beneficial in therapy. Nanozyme, encapsulating catalase, and macrophages extracted from bone marrow linked to a recognition moiety, when administered, showed that navigation of the nanozyme into the region of brain's inflammation. As a result, better distribution and improved bioavailability are achieved through the BBB [93].

11.3 Personalized nanomedicine for cardiovascular diseases

The development of cardiovascular diagnosis is now being influenced by nanosystems that can both detect and treat disease with a targeted delivery system. Nanotechnology has the ability to significantly accelerate the acceptance of personalized medicines in area of cardiovascular research by allowing production of fast, multimode point-of-care identification of single nucleotide polymorphisms (SNPs). This will, in essence, include information on the dangers associated with the progression of particular coronary disorders and pharmacogenetic advice on appropriate treatment for individual patients. In order to be clinically effective, the ideal method would need to be convenient, reliable, capable of simultaneous calculation of multiple genotypes and capable of conducting the full study without user intervention [94]. The different approaches to nanomedicine used in the form of nanocardiology have been mentioned in (Figure 4).

The possibility of cardiovascular procedures for the treatment of cardiovascular disorders appears to be interconnected with nanosystems capable of providing pathological diagnosis and treatment by means of changeable and regulated targeted systems. The dual potential of nanoparticles for visualization and selective distribution of therapeutic drugs to patients with cardiovascular disease would be a great opportunity for personalized medicine. By combining target drug delivery and molecular imaging with magnetic resonance imaging, the functions of serials by expressing epitope can be identified. At the desired target, monitoring and treatment validation will clear the way for individual treatments [95].

11.4 Personalized nanomedicine for bone disorders

Osteoporosis is the most common metabolic bone disorder, and osteoporosis susceptibility genes (ESR1, LRP5, SOST, OPG, RANK and RANKL) are involved in three biological pathways: the estrogen endocrine pathway, the Wnt/ β -catenin signaling pathway and the RANK/RANKL/osteoprotegerin (OPG) pathway [96]. Estrogen plays an essential role in bone biology through binding to two different estrogen receptors (ESRs), ESR1 and ESR2. Women's Health Initiative performed a randomized controlled trial of hormone therapy, in which oral conjugated 0.625 mg equine estrogen with or without 2.5 mg medroxyprogesterone acetate was administered and showed significant reduction in postmenopausal risk of osteoporosis [97]. Vascular endothelial growth factor A (VEGFA), is highly expressed

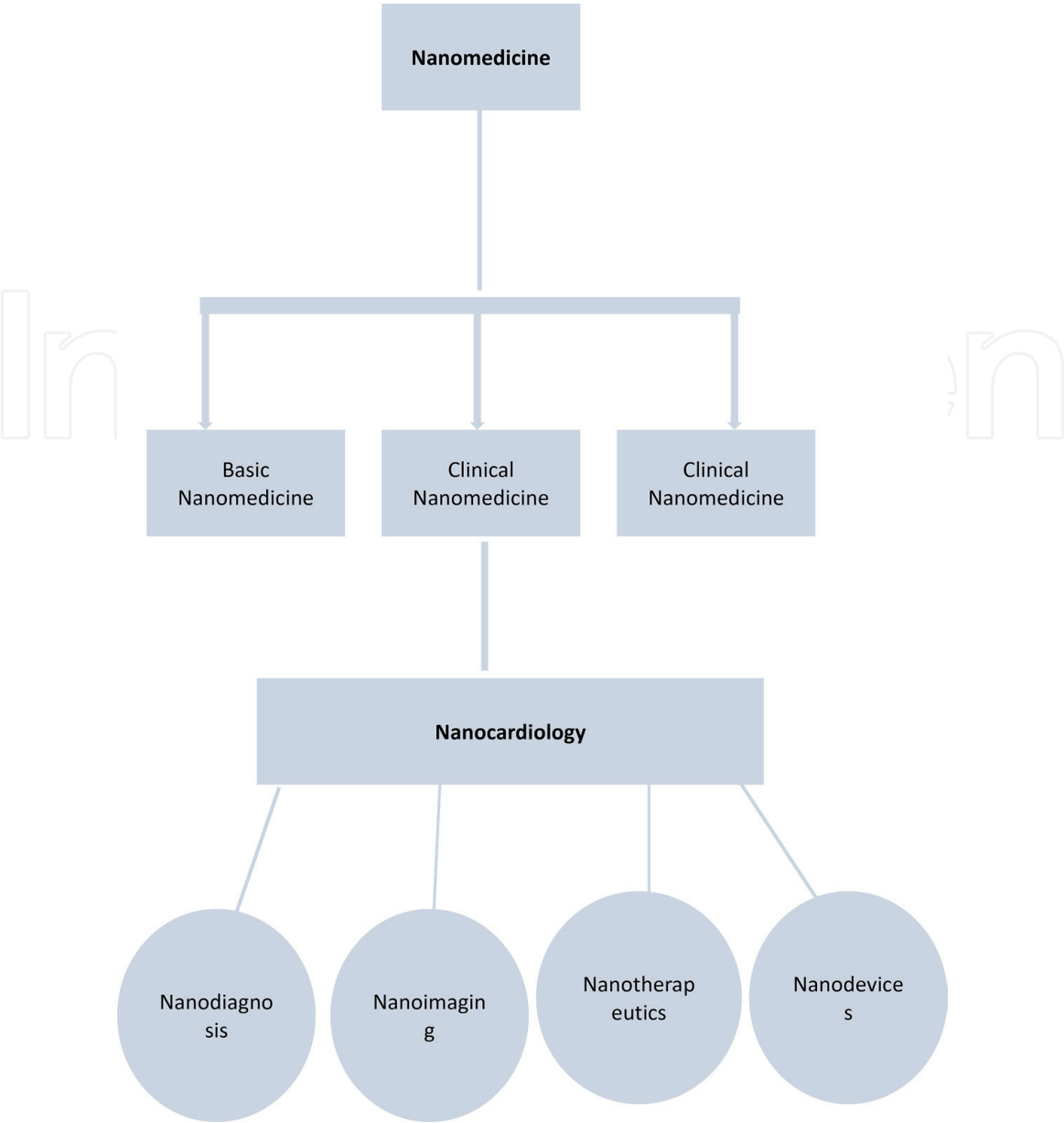


Figure 4.
Nanomedicine in the context of nanocardiology for cardiovascular disease management.

in osteocarcinoma (OS) and acts as an autocrine survival factor for tumor cell themselves. OS cell-specific aptamer (LC09) -functionalized PEG-PEI-Cholesterol (PPC) lipopolymer encapsulating CRISPR/Cas9 plasmids encoding VEGFA gRNA and Cas9 in both orthotopic OS and lung metastasis, showed effective VEGFA genome editing in tumor, decreased VEGFA expression and secretion, inhibited orthotopic OS malignancy and lung metastasis [98]. Zhang et al. evaluated G-protein-coupled Receptor Kinase Interactor-1(GIT1), as a target for the treatment of osteosarcoma and suggested that knowdown of GIT1 inhibited cell invasion and VEGF release in vitro and suppressed tumor growth, invasion, and angiogenesis in vivo, and also resulted in downregulation of hypoxia-inducible factor1 α (HIF1 α) and extracellular signal-regulated kinase (ERK1/2) pathways [99]. Moreover studies have shown that ALDH1B1, a subfamily of Aldehyde dehydrogenases (ALDHs), is upregulated in OS. Silencing of ALDH1B1 could inhibit the growth of xenograft tumor and knockdown of the same has shown to cause cycle arrest in G1 stage of OS cell in vitro cycle. Moreover, inhibition of ALDH1B1 expression could increase the sensitivity of chemotherapy [100]. The siRNA nanocarriers of chitosan-folic acid efficiently transferred the astrocyte elevated gene-1 (AEG-1)

into the osteosarcoma cells, and knockdown of AEG-1 resulted in the inhibition of tumor cell proliferation and invasion [101].

11.5 Personalized nanomedicine for kidney disorders

The development of highly accurate biomarkers is essential for optimizing the management of kidney diseases. Various biomarkers of kidney diseases have been identified using proteomic techniques. Sequencing and genotyping can also help diagnose and treat kidney stones, cystic kidney disease, glomerulonephritis, and chronic kidney disorder. Besides, the pharmacogenomics predictors can help predict early-onset chronic kidney disease (CKD). Allelism in basement membrane-associated Fraser complex (FRAS1, FREM1, FREM2, GRIP1) is observed in CKD [102]. However, only a few of these biomarkers could be potentially used in clinical practice for development of personalized medicine. CKD273, has been validated and used in an interventional trial as a biomarker for early CKD detection, and has received a 'Letter-of-support' from the FDA [103].

The angiotensin-converting enzyme (ACE) gene encodes ACE, involved in the renin-angiotensin-aldosterone system and kinin-kallikrein pathway. ACE inhibitors are currently used in CKDs as renoprotective which reduce proteinuria and blood pressure. The genotyping approach is being used in patients with CKDs or transplantation, to treat patients who are nonresponsive to drugs. The polymorphism of Immunoglobulin Fc receptor (FcγRIIIa) increases rituximab affinity by 10 folds and such polymorphisms may influence the efficacy of drugs. From transcriptome study on peripheral blood mononuclear cells (PBMCs) of uremic patients, the genes macrophage migration inhibitory factor, IL-8 receptor β and chemokine ligand 12 have been identified as potential therapeutic targets for reduction of inflammation in dialysis patients [104]. Gold (Au) and poly-lactic-co-glycolic acid (PLGA) nanoparticles (NPs) loaded with fenoldopam (FD) targeted to dopamine-receptor type-5 (DR5) on primary cilia have been evaluated for the treatment of vascular hypertension in polycystic kidney disease (PKD) model through cilia targeting [105]. Podocytes play a pivotal role in the progression of various kidney-related diseases. Vascular Cell Adhesion Molecule-1 (VCAM-1) expression is increased by podocytes upon TNF α -activation for up to 24 h and anti-VCAM-1 antibody can be employed as a ligand to facilitate the uptake of nanocarriers under inflammatory condition. Anti-VCAM-1-rapamycin-SAINT-O-Somes (lipid-based nanocarrier system) has been found to deliver the potent immunosuppressant rapamycin to TNF α -activated podocytes [106].

11.6 Personalized nanomedicine for gastrointestinal disorders

Functional gastrointestinal disorders (FGIDs) associated with impaired upper gastrointestinal (GI) due to delayed gastric emptying (GE), reduced gastric accommodation (GA), and functional lower GI symptoms including constipation-predominant irritable bowel syndrome, pelvic floor dyssynergia, colonic inertia, diarrhea-predominant irritable bowel syndrome, bile acid diarrhea, or act as a specific target for personalized medication. Hence, gastric relaxants or central neuromodulators, prokinetics are being used for personalized medicines in Functional Gastrointestinal Disorders (FGIDs). Personalized nanomedicine integrated with pharmacogenomics relates drug pharmacokinetics and drug enzymatic activity, specifically of CYP2D6, 2C19 and 3A4, to treat patients with FGIDs [107].

Orally delivered micellar nanoparticles, loaded with indomethacin developed by Yoshitomi et al., has potent nitroxide radical and ROS scavenging activity to treat small intestinal disorders [108]. Similarly, colon targeted hyaluronan-cisplatin

Drug Name	Nanoformulation	Indication	Phase	References
DaunoXome/ Daunorubicin	Liposome	Acute myeloid leukemia, solid tumors, first-line treatment for patients with advanced HIV-associated Kaposi's sarcoma	Marketed	[114]
Genexol-PM/ Paclitaxel	PEG-PLA polymeric micelle	Breast, lung and ovarian cancer	Marketed	[115]
Abraxane/ Paclitaxel	Albumin nanoparticles	Metastatic Breast Cancer; Non-Small Cell Lung Cancer	Marketed	[116]
Doxil/Doxorubicin	PEGylated liposomes	Ovarian Cancer; Sarcoma; Myeloma	Marketed	[116]
Aroplatin/Cisplatin analog (L-NDDP)	Liposome	Malignant Mesothelioma	Phase II	[117]
DepoDur/ Morphine sulfate	Liposome	Pain management	Marketed	[118]
Invegasustenna/ Paliperidone palmitate	Nanocrystal	Schizophrenia	Marketed	[119]
Diprivan/Propofol	Nano-emulsion	Anesthetic	Marketed	[120]
siRNA transthyretin inhibitor	Lipid nanoparticles	Amyloidosis	Phase III	[121]
Tricor/Fenofibrate	Nanocrystal	Hypercholesterolemia	Marketed	[122]

Note: PEG: poly (ethylene glycol); PLA: poly (lactic acid), PM: Polymeric miscelles, NSCLC: Non-small cell lung cancer, siRNA: Small interference RNA. www.clinicaltrials.gov

Table 5.
List of nanomedicines under clinical evaluation to target various diseases.

conjugated nanoparticles (HCNPs) has been developed by Tsai et al. for colon-specific drug delivery [109]. Also, CD98 siRNA/polyethyleneimine (PEI)-loaded NPs developed by Laroui et al. has shown down-regulation of intestinal CD98 for the treatment of colitis [110]. In addition, CS-TPP/IL-21 nanoparticles, Methotrexate loaded and folic acid conjugated guar gum nanoparticles (MTX-FA-GGNP), and deoxycholic acid conjugated nanoparticles (DexDA) loaded with retinoic acid have shown beneficial results in colorectal cancer [111–113].

Nonalcoholic fatty liver disease (NAFLD), including steatosis, fibrosis, and cirrhosis, leads to hepatocellular carcinoma. The CYP enzymatic activity that metabolizes different drugs can be affected by NAFLD. Hence, personalized treatment in all NAFLD patients is done through genetic profiling of the patient besides taking into account gender, environmental factors, diet habits, and CYP pattern to determine effective drug treatment. The polymeric nanoparticles such as the Smart Insulin L-490, a kind of personalized nanotheranostics, estimates patient glucose level and responds to the stimulus by releasing appropriate amount of insulin (Table 5) [123].

12. Future prospects

Regardless of contributions made by scientists, the adoption of pharmacogenetic testing in the clinical application has not been up to great extent [124]. The clinical

trial of Tailor PCI study on the drug clopidogrel may increase the testing rates but presence of cheaper alternatives that does not require any pharmacogenetic testing may reverse the scenario [1]. Genome wide association studies which purport to give the well replicated data on genetic risk factors for complex diseases support the future of advanced application of pharmacogenetics. These novel risk factors may serve as potential therapeutic targets for the newly developed drugs and proper information about the patient genotype for these vital targets may affect the art of prescribing these drugs [125, 126]. Owing to these technology advanced settings, it is more likely that the pharmacogenetic knowledge will be available routinely in the near future, which will affect the science of prescribing drugs.

13. Conclusion

Pharmacogenomics is progressing in the form of personalized medicines in the world today. The main purpose of personalized therapies is to improve healthcare through the application of emerging technology. In these innovations, nanotechnology plays a key role with integration of pharmacogenomics to improve diagnosis and therapeutics at the individual level treatment. With this approach the introduction of personalized nanomedicine, has provided a major stimulus to the medicine and pharmacy disciplines to include advanced clinical therapies, disease management, diagnosis, and delivery of drugs.

Conflict of interest


The authors declare no conflict of interest.

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