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Pharmacogenomics: Overview, Applications, and Recent Developments

Rahul Shukla

Abstract

Pharmacogenomics is defined as the study of genes and how an individual response is affected due to drugs. Pharmacogenomics is an emerging new branch with combination of both pharmacology (the branch of science that deals with study of drugs) as well as genomics (the branch of science that deals with study of genes) for development of effective doses and safe medications tailored according an individual patient genetic makeup. Human Genome Project is one of the crucial projects in which researchers are developing and learning relation in genes and its effect on the body's response to medications. Difference in genetic makeup provides difference in effectiveness of medication and in future to predict effectiveness of medication for an individual and to study existence of adverse drug reactions. Besides advancement in the field of science and technology till date pharmacogenomics hangs in infancy. There is limited use of pharmacogenomics, but still, novel approaches are under clinical trials. In near future, pharmacogenomics will enable development of tailor-made therapeutics for treating widespread health problems like neurodegenerative, cardiovascular disorders, HIV, cancer, asthma, etc.

Keywords: pharmacogenomics, genomics, proteomics, personalized medicines, tailored drugs

1. Pharmacogenomics: overview

Due to variability existence among individuals against drug therapy response, it is a challenging task to predict the degree of effectiveness of a medication to a particular patient. As we know various clinical factors which are known to affect drug response, for example body size, age, sex, hepatic and renal function, and associated drug use (**Table 1**). Along with these clinical factors, some pharmacological factors also play a major role which includes differences in metabolism, drug distribution and drug directed proteins [2, 3]. Recently, major causes of interindividual differences are shown by variations in genes encoding cytochrome P450 (CYP) and other metabolizing enzymes in plasma concentrations of some drugs [4, 5].

Pharmacogenetics and pharmacogenomics can be used interchangeably. Though, Pharmacogenomics refers to the whole range of genes that are related to the determination of drug efficacy and safety whereas pharmacogenetics means monogenetic variants which alter the drug response [6, 7]. Pharmacogenomics is defined as study of genes and how they affect an individual response to the

Factors	Effects
a. **Genetic factors**	
Drug-metabolizing enzymes	Drug metabolism (pharmacokinetics)
Therapeutic targets	Drug efficacy (pharmacodynamics)
Targets of ADRs	Drug toxicity
Drug transporters	Drug disposition
b. **Environmental factors**	
Environmental chemicals, alcohol drinking, combined drugs effect, and dietary substances	Drug efficacy, toxicity, and pharmacokinetics
c. **Physiological factors**	
Age, sex, pregnancy, exercise, disease state, starvation	Drug efficacy, toxicity, and pharmacokinetics

Table 1.
Genome-wide association studies in pharmacogenomics [1].

administered drugs. Pharmacogenomics is emerging new branch with combination of both pharmacology (branch of science which deals with study of drugs) as well as genomics (the branch of science which deals with study of genes) for development of effective doses and safe medications tailored according an individual patient genetic makeup (**Figure 1**) [8, 9].

Basically, the concept for pharmacogenetics was left unknown for more than 50 years. This study underlined to the molecular mechanisms in account for their variation in responses to drug due to inherited characters and in drug development process. Pharmacogenomics applications can be employed in the improvement of discovery of new entities and its development with two possible ways: target the new drug targets or development of new entity to overcome drug resistance, and another way is to optimize the pharmacokinetics and metabolism of drug for reduction of the drug level variations [10]. In fact, personalized drug therapy or individualized drug therapy is not an easy task. It needs many folds as there may be a lack of information regarding drug action, genomic elements of important disease pathogenesis, especially for complex diseases. Also, large scale clinical studies are sometimes becoming a big challenge for the researchers [11]. The correlation of pharmacogenomics and cancer would expand the specific anticancer drugs with better chemotherapeutic outcomes [12–15]. There are prominent examples with recent clinical and pharmaceutical restrains where the molecular based mechanisms are involved in various drug responses were observed among the patients and diagnosed with the similar diseases [16, 17]. Moreover, various polymorphisms existence at genetic levels in genes found to have association with alteration in responses of drug and rate of ADRs in humans (**Table 2**) [18].

Finally, pharmacogenomics-based development of drug and its regulation will open the doors for new as well as targeted drug development for promoting safe, effective, and cost-effective drug therapy for individual. The theoretical origin for pharmacogenomics is outlined by Sir Archibald Garrod's in book entitled as "1939 Inborn Factors of Disease" [19].

Pharmacogenetics is the study of how an individual person's genes respond to a drug. This branch is associated with genomics is genetic level studies with functional studies and pharmacology (includes pharmacokinetics and pharmacodynamics). All these branches together aid in the development of safe, and effective medications along with doses which are probably tailored to an individual persona genetic makeup [20–24]. Pharmacogenetics is indicated as major clinically proven
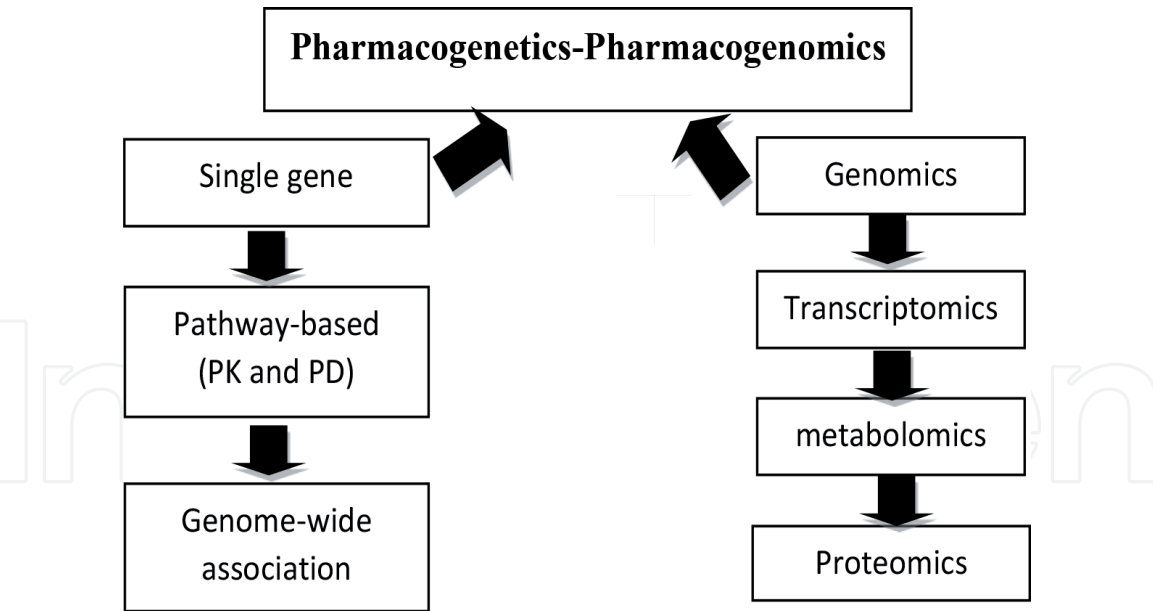
Figure 1.
Development of pharmacogenomics and pharmacogenetics.

Polymorphic gene	Drug	Effect
CYP2C9	Phenytoin	Toxicity
	Warfarin	Bleeding risk
	Glipizide	Hypoglycaemia
TPMT	Anticancer drugs like 6-thiopurine, 6-Mercaptopurine, azathioprine	Toxicity
Human leukocyte antigens (HLA)	Abacavir	Related to hypersensitivity
N-acetyltransferase (NATs)	Sulphonamides, hydralazine, Isoniazid	Toxicity, hypersensitivity
UDP-glucuronosyltransferase 1A1 (UGT1A1)	Irinotecan	Toxicity
CYP2D6	Codeine	Toxicity
	Fluoxetine	Toxicity
MDRI	Antiepileptic drugs	Drug response

Table 2.
Genes with altered drug response.

application in terms of advancement in human genomic science. This potentiates a revolution in drug therapy. As a result, diseases which range from depression to viral infection and from childhood leukemia to hypertension are treated or controlled for enhancing the quality of life of patient. Most medicines at present are available as "one medication fits all" but they sometimes were not capable to work same to everyone. So, it is difficult to envisage who will have benefit result and who will have negative side effects. Also, the knowledge which scientist have acquired due to extensive work on Human Genome Project and are learning about inherited variations of genes and there effect on body's response to medications. Conditions in which responses of an individual to certain drugs include Stevens-Johnson syndrome or epidermal toxic necrolysis, clopidogrel resistance, malignant hyperthermia, warfarin sensitivity and its resistance and thiopurine S-methyltransferase deficiency [25].

2. Application

Many common diseases having high morbidity as well as mortality rates have now known with well-established genetic components. The degree of role of genetics has been predicted for diseases like obesity and diabetes according to their sibling analysis [26, 27]. In the same way, some rare gene mutations can provide a vision into the more complex biological processes [28]. For instance, when the subject possesses extreme levels of HDL in their blood, one can easily demonstrated the influence of CETP (cholesteryl ester transfer protein) on patients HDL levels [29–31]. In another case, a person having deactivating mutations due to the Janus kinase 3 (JAK 3) gene shows severe combination of immune-deficient syndrome, as sometimes inhibition of JAK3 was expected to affect the human immune suppression [32, 33]. Hence, this led to a new investigation on drugs having CETP inhibition and JAK3 inhibition with the help of pharmacogenetics [34]. Also, with the advent of pharmacogenomics, the path of relationships between disease state and human genes has now established which led to the suitable selection of therapeutic targets.

Nowadays, many academic institutions and Pharmaceutical companies are moving toward the investigation on the relationship between disease phenotypes and genetic variations to better categorize diseases [35, 36]. Although the collection of medical phenotypes having linkages with samples of DNA provides a prominent opportunity for examine the genetic variation which are present in patients. Investigation of genetic variation can be done by collection of DNA of particular patient. This is characterized in a study where DNA from a person involves in trails of lipid lowering demonstrated a swift connection between phenotypic novel lipase gene family and for HDL levels. As per literature reports, above mentioned studies are based on a sound hypothesis which is linked to candidate's biological gene selection. Now it is easy to cross-examine the genome selection which is solely depends on phenotypic criteria [10, 37]. These stages have now substituted around 300,000 SNPs across the genome, by exploiting only few haplotype-defining SNPs. Perlegen sciences have developed newly genotyping technologies which has with a capability of genotyping mass hundreds or thousands of markers with the help of high-density based oligonucleotide arrays linked with restriction enzyme-based genomic reduction. However, as these technologies advances, still exact number of haplotype-defining SNPs is uncertain. Some findings are recently reported relation to assess polymorphisms across selected gene regions recommends that, it is necessary to reach an r^2 of >0.8% in order to detect more than 80% of all haplotypes. Due to HapMap project progression with defined LD patterns linkage, scientist working on genes will thorough assess to the degree of LD in a represented regions or selected regions. This will enable to explore more around selection of SNP regardless design of study [38, 39]. As genome approach does not depend upon selection of candidate genes, so understanding on complex diseases such as psychiatric or cardiovascular diseases will become more efficient. Some researchers believed that the new horizons on LD coverage about insights of human genome and SNP density will show the perception of a substantial genomic portion areas and its relation with interest of phenotype [40, 41]. To assess the Perlegen Sciences chip-based array-based platform and to justify the haplotype tagging approach for the identification of genetic associations, 7283 SNPs connecting 17.1 mega bases (Mb) of DNA were genotyped for detecting linkages with HDL levels. Further, SNPs were connected with 50 CETP haploblock gene were found out as the most valuable association in dataset. The companies like Perlegen and project like Hap Map project recently declared their purpose to provide it SNPs markers into public provinces to further advent to basis for such kind of experiments which help in the scientific community [42, 43].

Pharmacogenetics significantly expands the therapy outcomes and drug uses. Medications may prescribe in low dose under strict monitoring to patients which shows genetically predisposed to their adverse events. This would probably helpful for drugs having narrow therapeutic index such as warfarin may be started gradually in patients having VKORC1 genotype linked with improved warfarin sensitivity. With the help of pharmacogenetics, it is now possible to reduce the number of subjects to conduct any experiment and chances of error may be eliminated for many diseases [44, 45].

On the contrary, clinicians may be able to minimize possible adverse effects with the aid of genetic information for matching suitable drug to suitable patient at an appropriate dose. For instances, traditional approach to the management of hypertension involves the trial of numerous anti-hypertensive drugs till the desired blood pressure achieved with adequate drug tolerability. In this case, few initial drugs/agents fail to produce lower blood pressure or shown intolerable adverse effects. This way of selection of drugs took long time which ultimately suffered by patients. On the contrary, Pharmacogenetics, based on the patients' DNA, offers the greatest response with the best tolerability of the drug. Based on genetic regulator of cellular functions, pharmacogenetics may be able to produce new drugs with less adverse effects. For example, chromosome translocation and its derived enzymes are responsible for causing life-threatening chronic myeloid leukemia (CML) which led to accelerate FDA approval of inhibitor of translocation-created enzyme Imatinib [46]. In the end, this core subject improves the quality and cut-down the total costs of healthcare by minimizing the number of adverse reaction and reduce treatment failures gives rise to the discovery of new genetic targets for disease management [47–49].

3. Case studies

3.1 Thiopurine therapy and TPMT (thiopurine methyltransferase) testing

Thiopurine are the categories of drugs that are used to conquer the normal activity of the body's immune system. In short, these are called antimetabolites chiefly used as an antiproliferative as well as immunosuppressants such as mercaptopurine and azathioprine. 6-mercaptopurine daily administered for 3–4 years for treating childhood leukemia, while azathioprine which is a prodrug of 6-mercaptopurine prescribed for treating inflammatory bowel disease (also known as Crohn's disease) [50]. TPMT methylates thiopurine compounds. S-adenosyl-L-methionine acts as methyl donor and converts it into S-adenosyl-L-homocysteine [51, 52]. So, TPMT metabolizes various thiopurine based drugs with mechanism of S-adenosyl-L-methionine while S-methyl acting as donor, while S-adenosyl-L-homocysteine acting as a derivative. Genetic polymorphism which affects basically enzymatic activity has association with variations in toxicity and sensitivity within individuals due to such drugs. Nearby 1/300 individual is lacking for this enzyme. TPMT has not recognized to have any phenotype in the absence of encounter drug. TPMT is now enlists by FDA as a pharmacogenomic biomarker for various adverse drug reactions related to cisplatin such as cisplatin-induced ototoxicity in teenagers [47, 53–55].

Patients having identical alleles at equivalent chromosomal loci accumulate unnecessary thioguanine nucleotides levels (up to 10-fold higher related with wild types) and treatment with standard dosages of drug and leading to a hematopoietic toxicity (pancytopenia and myelosuppression) which is life-threatening condition [56, 57].

In more concise way, patients having heterozygous gene variations are also at high risk in terms of toxicity and dosage reductions is prior in these cases up to their tolerate therapy. According to pharmacoeconomic studies, the determination of the TPMT genotype is cost-effective and it must be checked prior to the start of therapy. According to a review of the literature, it was found that TPMT testing with clinical performances for myelosuppression was estimated with specificity of 89%, sensitivity of 32%, 9% PPV and NPV of 97% (**Table 3**). The low estimated value represents low incidence of severity in myelosuppression especially in those patients who are carrier of not less than one defective allele. Researchers have estimated the net cost for avoidance of serious events of myelosuppression. Out of 1000 patients receiving azathioprine, only 3.2% (equivalent to 32 cases) have founded with severe leukopenia and TPMT screening avoided as third of those trials [50, 58].

Iorio and co-workers have analyzed drug responses on various human cancer cell lines. The mapping was done for around 11K tumors obtained from different 29 different human tissues as per Cancer of Genome Atlas (TCGA) enlisted from 1000 cancer cell lines as per Genomics of Drug Sensitivity in Cancer resource. In another event, TCGA patient gene expression was studied for drug response. In this, more than 140 gene drug interactions were studied with specific somatic biomarkers [59–61].

3.2 Abacavir therapy and HLA testing

Abacavir which is HIV-1 nucleoside with reverse transcriptase inhibition is employed for management of HIV/AIDS. It is well tolerated but sometimes shows common to more severe side-effects which include lactic acidosis, hypersensitivity [62]. In some studies, it was observed that a genetic testing/marker can help in predicting whether a HIV-infected patient is at high risk of abacavir induced severe hypersensitivity reactions (approx. 5% of patients) [63, 64]. This hypersensitivity reaction accompanies with lethal gastrointestinal symptoms, rashes, and fever. This reaction is life threatening, particularly if drug is restarted and discontinued. One study has shown about an occurrence of human leukocyte antigen (HLA) B05701 is main cause of hypersensitivity [45, 65]. Based on the Australian cohort, patients were 114 times more hypersensitivity due to HLA-B5701 allele reaction, whereas in an industry-sponsored study revealed that patients with the HLA-B5701 allele was associated with 24 times more likely to experience of hypersensitivity reaction [45]. Thus, one way to solve this issue is genetic testing which integrates pharmacogenetics into the clinical practice. The distribution of HLA-B5701 allele can be detected in many worldwide populations (**Table 4**).

3.3 Statin therapy and polymorphic angiotensin-converting enzyme

Statins (HMGCoA) reductase inhibitors most often used in management of hypercholesterolemia condition accompanying with elevation in risk to coronary heart disease [66, 67]. Due to increased number of cases of hypercholesterolemia along with volume of statins related prescriptions in US, it creates a significant interest in optimization of costs related to these therapies [31]. Recent investigations have told that polymorphism in I/D angiotensin converting enzyme (ACE) has correlation with risk of heart related syndromes in men when treated with statins [68–70]. Next 2 years of statin medication, in which males who are having DD genotype (equivalent to 27% of patients) shown to have no effect on the risk of coronary heart disease (with relative risk factor of 1.34), in comparison to males with ID (equivalent to 21% of patients) present a marked decreased in risk of coronary cardiovascular disease (with relative risk rate of 0.87), II genotype

Clinical performances	(%)
Percent responders	40.0
Sensitivity	75.0
Specificity	66.7
Frequency mutation	50.0
Positive predictive value (PPV)	60.0
Negative predictive value (PPV)	80.0

Table 3.
Clinical performances of the test.

Population group	HLA-B5701 carrier frequency range (%)
Asian	00–6.5
Southwest Asian	4–19.5
Middle Eastern	0.5–6.2
African	0.0–3.5
European	1.5–10.5
Mexican	0.0–4.2
South American	1.2–3.2

Table 4.
Allele frequency of HLA-B5701 allele in various population groups.

(equivalent to 22% of patients) having relative risk of 0.23, thus concluding that patients bearing DD genotype did not take advantages from statin treatment. Also, testing of I/D genotype might results in cost effective as few patients presents the I/I or I/D genotype [70].

3.4 Muscle relaxant succinylcholine and antitubercular drug, INH

These two conventional illustrations of pharmacogenetics involve the genetic variation along with enzymatic metabolism (enzymatic hydrolysis and acetylation). Both act as a monogenic trait and involved PK variations because of inheritance differences [71, 72]. It was observed that some patients with succinylcholine treatment experienced a serious and lethal adverse event i.e. prolonged muscle paralysis which is due to inherited "atypical" butyryl cholinesterase enzyme (BCHE). Later, it was established that BCHE allele which encodes the most usual atypical form of enzyme comprised with a nonsynonymous coding i.e. single nucleotide polymorphism (nSNP), G209 > A, results in Asp70 > Gly change in encoded amino acid which altered active sites of enzyme [73, 74]. But atypical BCHE has less ability to catalyze the succinylcholine hydrolysis and could resist to inhibition due to dibucaine compound [37, 75].

Tuberculosis is the most problematic disease of both developing as well as under-developed nations. The conformity to patients with tuberculosis is due to common lethal adverse reactions and supposed to have important aspect providing high prevalence [76, 77]. Many investigations showed that the polymorphisms of N-acetyl transferase 2 (NAT-2), CYP2E1 as well as glutathione S transferase (GST-1) would be able to influence concentration of liver toxic isoniazid metabolites in plasma. Some polymorphic genes contribute in the INH induced hepatotoxicity by

altering the anti-oxidant enzyme expression, these gene polymorphisms include glucuronosyltransferase (UGT), basic region of leucine zipper factor family (CNC) homolo (BACH), human leukocyte antigen (HLA), nitric oxide synthase (NOS) and Maf basic leucine zipper protein (MAFK). Till date the above mentioned studies encounter with many limitations [77–79].

3.5 Warfarin

Warfarin is a medication that is commonly used as an anticoagulant which means blood thinner. It aids in treating blood clots such as pulmonary embolism and deep vein thrombosis, and to prevent heart diseases associated with clotting. It has very narrow therapeutic index [80, 81]. However, warfarin therapy may result in complicated adverse reactions including both coagulation and hemorrhage. The racemic mixture of warfarin, S-form is 3–5 times more potent in comparison to R-form of an anticoagulant, and easily gets metabolized due to genetically polymorphic CYP450 isoform i.e. CYP2C9 [82]. CYP2C9 exists in two common polymorphic form, Arg144 > Cys (CYP2C9*2) as well as Ile358 > Leu (CYP2C9*3) modifications in coded sequence of amino acid, with nearly 12 and 5%, respectively. These forms vary between 8 and 10% in Caucasians, with minor occurrence in subject from Southeast Asia. A report in 1999, which confirms patients with one or two common CYP2C9 variant alleles, requires a "low" warfarin dose. These subjects had a risen risk of hemorrhage during warfarin therapy. In 2004, the gene encoded targeting VKORC1 (vitamin K epoxide reductase complex 1) was cloned. In a study, it was found that patients with VKORC1 type of haplotypes requires low dose, the average warfarin maintenance dose was nearly half for subjects with haplotypes having high dose maintenance. In this study, the grouping of both VKORC1 haplotyping as well as genotyping for CYP2C9 described around 25% of dose variance in warfarin. Other studies reported similar results in 2005. The Pharmacogenetics Knowledge Base (PharmGKB), in which data base is reinforced by the National Institutes of Health (NIH) along with part of the NIH Pharmacogenetics Research Network (PGRN), originated an association for consolidation of warfarin pharmacogenetic data throughout the world [83, 84]. In this evaluation of variation in genetic drug target as well as drug metabolism if and only if when VKORC1 and CYP2C9 haplotypes were determined. The figure demonstrates a schematic illustration of both pharmacokinetic (CYP2C9-dependent) as well as pharmacodynamic (VKORC1-dependent) pharmacogenomic aspects that effects final dose of warfarin (**Figure 2**).

It is important to know that by identifying the individual genetic properties, we can improve the dosing of warfarin. In general, VKORC1 haplotypes have three-fold greater effect on an individual's warfarin dose than CYP2C9. Both can play a vital role in the potential for estimating the therapeutic warfarin dose. In August 2007, FDA approved a change in labeling of warfarin package stating, "lower starting doses should be considered for patients with some genetic alterations in VKORC1 and CYP2C9 enzymes" [80].

4. Outlook

These cases prove that patient care could be improved effectively by pharmacogenetic based approaches. Although, the allelic occurrences of the gene alterations must be visibly defined in the subjects studied must be well established. Out of above-mentioned cases, no one is absolute, so it is better to perform the sensitivity analyses as well as to regulate the robustness of conclusion with variation in probabilities [85, 86]. Move onward, it is utmost important for maintaining the possible
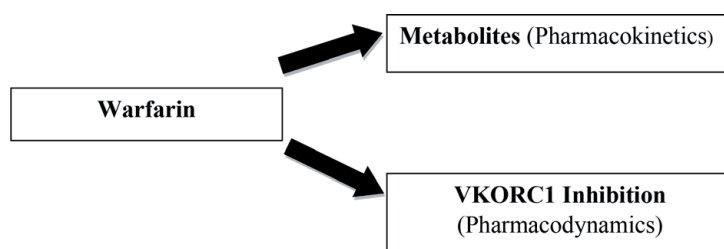
Figure 2.
Warfarin pharmacogenomics.

cost-effectiveness of few recently published pharmacogenetic associated reports, for instance, vitamin K epoxide reductase gene variants envisage the warfarin response [87–89]. Lastly, it will be significant to collect pharmacoeconomic and pharmacogenetic statistics together during industry-funded clinical trials for bringing cost effective theragnostic in a sensible manner [90, 91].

5. Conclusion

Individualized therapeutics or tailor-made therapy is one of the major goals of pharmacogenomics. In relation to inheritance other factors also contribute to individual therapeutics due to variation in response to administration of drug. Recently many developments in the field of pharmacology and genomics have made possible for physicians to achieve individualization of therapeutics. These recent developments create possibility of thorough basis of particular drug for particular patient with motive of tailor-made therapy. Futuristic development in field of pharmacogenomics has paved the way to new emerging fields of pharma-coproteomic, pharmacotranscriptomics, and pharmacometabolomic. These new branches of science make it possible to achieve the concept of treat each patient as unique, complex, fascinating individual. At the end doubts about achieving individualized therapeutics with the help of this integrated system is still a dream in 21st century era.

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Conflict of interest

The authors declare no conflict of interest among themselves.

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