

Challenges in Current Drug Delivery from the Potential Application of Pharmacogenomics and Personalized Medicine in Clinical Practice

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Abstract: The recent technological achievements in biotechnology and recombinant DNA technology have provided multiple new methods, molecular targets, and DNA-based diagnostics to pharmaceutical research that can be utilized in assays for screening and developing potential biotechnology-based drugs, as well as in biomedicine, health and pharmaceutical care. Furthermore, such advances opened up new opportunities by applying genetic information data in pharmacotherapy and drug delivery, thus ensuring better drug efficacy and safety in clinical practice. Now the concepts of personalized medicine and pharmacogenomics are likely improving the area of pharmacodynamics and pharmacokinetics, since they favor differentiation of the conventional clinical diagnosis and drug selection into separate molecular subtypes of individuals belonging within a group of patients suffering from the same disease. Genetic polymorphisms have already been detected and analyzed in genes encoding drug-metabolizing enzymes, transporters as well as targets (e.g. receptors). The potential of applying genotyping and haplotyping analysis in future pharmaceutical care could eventually lead to pharmacotyping, i.e. individualized drug delivery profiling based on genetic-bioinformatic data in routine patient care. However, the steps towards this direction of drug delivery in clinical practice still have a long way to go to be fully achieved; until then, the critical evaluation of all available clinical data including pharmacodynamic, pharmacokinetic and genomic must be assessed for ensuring drug efficacy and safety. In this way, there has been great progress in elucidating genetic determinants contributing to the observed interindividual differences in drug disposition and effects, thus implementing current drug delivery with molecular genetics and diagnostics.

Keywords: Pharmacogenomics, Drug delivery, Personalized medicine, Pharmacotyping, Gene polymorphisms, SNPs, Haplotyping, Genotyping, Drug prescribing.

INTRODUCTION

Today a high-quality, comprehensive sequence of the human genome is available, and the efforts for extracting genetic information of practical value in health and pharmaceutical care is a painstaking process for researchers, but still a fascinating expectation for the public [1]. During the last 2-3 decades of the past century, health professionals were confronted with an expanding body of information as well as an impressive number of technological advances related to drug development, therapy and clinical practice. Recombinant DNA (rDNA) technology has provided several new methods, revealed novel molecular targets and created DNA-based diagnostics to pharmaceutical research and biomedicine that can be utilized in assays for screening and developing potential biotechnology-based drugs, or even for improving drug response and patient outcome. Furthermore, new innovative therapeutics are reaching the market, or are under development, including potential new classes of drugs, like antisense oligonucleotides, ribozymes and aptamers (synthetic nucleic ligands) [2-5]. These changes are evolving in parallel with the advancement of new sophisticated drug

delivery systems through the use of micro- and nanoparticles prepared with blends of biodegradable and polycationic polymers to formulate drugs and to enhance drug bioavailability in the body [6-9].

These processes have had a huge impact on our understanding of disease pathophysiology and of drug actions at the molecular level, thus changing pharmacology and pharmacy into a more biology- and biotechnology-oriented direction. Moreover, the complexity in drug response and the importance of being able to predict drug-drug interactions and adverse drug reactions (ADRs) are fundamental aspects in modern pharmacology and therapeutics [10, 11]. The recent elucidation of genetic factors predisposing to specific drug-drug interactions, or ADRs, or even to drug disposition gave new dimensions to drug delivery in certain drug classes [12, 13]. In addition, all this knowledge, derived mainly from genomic data, led researchers to uncover crucial molecular mechanisms involved in vital cellular functions like apoptosis (programmed cell death), differentiation and proliferation permitting the development of new drugs in the areas, among others, of oncology, cardiovascular disorders and degenerative diseases [14-17]. The better knowledge of molecular mechanisms underlying drug response in the body by applying pharmacogenomic principles in clinical practice that is achieved, the bigger the benefits in pharmaceutical

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care in terms of drug efficacy and safety that can be expected. In such a case, however, the application of pharmacogenomics in drug development and delivery raises several ethical and social problems, as well as quality and validation issues of genetic tests that must be clearly addressed before its usage in routine patient care [18].

The purpose of this review is not to provide a thorough overview, but rather to comprehensively present potential implications of pharmacogenomics and personalized medicine in clinical practice, as well as their impact on current drug development and delivery. Furthermore, the clinical use of genomic data for routine drug prescription, the training of future health care professionals and the integration of molecular medicine in clinical trials for drug development will also be highlighted as specific areas and will also be discussed. In any case, it is expected that, in the years to come, functional genomics will provide an expanding body of information on genes and their products implicated in drug response, influencing both future pharmaceutical care and drug prescription.

GENETIC FACTORS INFLUENCING DRUG RESPONSE: ENSURING DRUG EFFICACY AND SAFETY IN CURRENT DRUG DELIVERY

Health care providers and patients have long recognized that people often respond differently to the same drug, both in terms of efficacy and toxicity [19]. The reasons for this interindividual variability in drug pharmacology include several potential risk factors that contribute differently to this phenomenon and are related to the disease pathophysiology and severity, to possible drug or nutrient interactions, to concomitant illnesses, to specific organ function, to age, or even to lifestyle [20]. Genetic factors influencing drug response, both drug kinetics (pharmacokinetics) and dynamics (pharmacodynamics), also contributed to interindividual variability, and their importance has been greatly appreciated by the emergence of pharmacogenomics and personalized medicine [21]. The concepts about the genetic nature of some toxic reactions to drugs or xenobiotics and the notion that at least a part of the variability in drug response may be inherited have long been recognized in 20th-21st century pharmacology [for a review see 10]. In recent years, however, correlation of genetic variations with altered drug efficacy and toxicity in certain individuals indicates that personalized medicine in drug therapy can be applied to some if not all people. Exploitation of genomic information related to genes that encode either drug metabolizing enzymes, drug receptors, or drug transporters is now well accepted in modern therapeutics [22]. It is also well known by now that specific genetic variations, for example, clearly account for monogenic (one gene involved) disorders, like cystic fibrosis, Huntington's disease and Duchenne's muscular dystrophy [23]. Moreover, as it has been shown, and it will be presented in the following sections, individual genetic variations of genes encoding either for cytochrome P450 (CYP) isoenzymes, (e.g. CYP1A2, CYP2D6, CYP3A4) or for drug receptors (G-protein coupled receptors; GPCRs) or even for drug transporters (e.g. P-glycoprotein) play a crucial role in defining drug efficacy and safety in the clinical practice [24-26], (Table 1).

PHARMACOGENOMICS IN CURRENT DRUG DEVELOPMENT AND PATIENT CARE

Among the most exciting recent developments and achievements that have emerged from the whole genome analysis of different organisms and relate to pharmacology and pharmaceutical research are: a) The emergence of pharmacogenomics as a discipline that links drug response with genomic variations of the individuals in genes implicated with the pharmacodynamic and pharmacokinetic effects in the body [27, 28]; b) The DNA microarray (DNA chip) technology which allows rapid analysis of expression of thousands of genes in an organism, thus identifying genes involved in several human disorders as well as in drug response [29]; c) The availability of bioinformatic tools to analyze the load of genomic data and identify novel drug targets and unique structural and functional characteristics in genes and proteins implicated in drug actions at the molecular level [30]; d) The application of new genetic approaches for gene and protein therapy protocols and the development of fascinating site-specific drug delivery systems [7, 8]; e) The advantage of combinatorial chemistry that allows the synthesis of large libraries of low molecular weight compounds for high-throughput screening (HTS) in order to discover pharmacodynamically active agents [31]; and f) Finally, last but not least, the application of proteomics, functional and structural genomics, expression genetics, and genome mapping that emerged for the analysis of all gene products (proteins) serving as drug receptors, or other biological functions [32].

Pharmacogenomics is a major development that is taking place in pharmaceutical sciences today with the progressive transition from genetics to genomics and the attempt to analyze the whole genome of an organism and correlate genotyping with specific drug actions [33]. Pharmacogenomics seems to be the next step in pharmacogenetics that historically has been referred to drug response in relation to individual genetic variation amongst patients. The combined use of DNA microarray technology and automated DNA sequencing permitted the detection of specific single nucleotide polymorphisms (SNPs) in several genes involved in drug response [34]. Moreover, recent data support the notion that groups of SNPs (haplotypes) are inherited together in a stretch of DNA, thus making the efforts to correlate genotypes with specific phenotypic variations in disease diagnosis and drug action more easily attainable by researchers and applicable into clinical practice [21]. These advances are likely improving the area of pharmacodynamics by differentiation of the conventional clinical diagnosis and drug selection into separate molecular subtype groups within patients suffering the same disease.

Several examples of recent pharmaceutical and clinical research pinpoint the molecular mechanisms involved in diverse drug response seen among patients suffering the same disease. Furthermore, genetic polymorphisms in genes that encode either P-gp, or GPCRs, or the enzyme thiopurine methyltransferase (TPMT), or the angiotensin-converting enzyme (ACE), or specific isoforms of CYPs, or arylamine N-acetyltransferases (NATs) and UDP-glucuronosyltransferases (UGTs), are correlate with altered drug response and incidence of ADRs in humans [24-26, 35-40], (Table 1).

Table 1. Examples of Clinically Relevant Genetic Polymorphisms Associated with Altered Drug Response and/or ADRs

Polymorphic gene	Drug	Effect	Reference
CYP2C9	Warfarin	Bleeding risk	[13, 20]
	Phenytoin	Toxicity	
	Tolbutamide, glipizide	Hypoglycemia	
CYP2D6	Fluoxetine	Toxicity	[13, 20]
	Codeine	Toxicity	
Dihydropyrimidine dehydrogenase	5-Fluorouracil	Toxicity	[24, 67]
MDR1 (or ABCB1)	Antiepileptic drugs	Drug resistance	[24, 41]
TPMT	6-Mercaptopurine, 6-thioguanine, azathioprine	Toxicity	[13, 37, 54]
α_2 -adrenergic receptors	-agonists (e.g. albuterol)	Altered drug response	[36, 50]
Angiotensin-converting enzyme (ACE)	-blockers (e.g. propranolol)	Altered drug response	[16, 38, 58]
Apolipoprotein E4 (ApoE-4)	Tacrine	Altered drug response	[19]
-Adducin	Diuretics (thiazides)	Altered drug response	[58]
Angiotensin II type I-receptor (AT-1)	Losartan	Altered drug response	[16]
UDP-glucuronosyltransferase 1A1 (UGT1A1)	Irinotecan	Toxicity	[24, 40]
Human leukocyte antigen (HLA)	Abacavir	Hypersensitivity	[76, 77]
Glutathione-S-transferases (GSTs), XPD & XRCC1 (genes involved in the DNA excision repair system)	Platinum chemotherapeutic agents (cisplatin, carboplatin, oxaliplatin)	Altered drug response	[52, 67]
N-acetyltransferases (NATs)	Sulfonamides Isoniazid, procainamide, hydralazine	Hypersensitivity Toxicity	[11, 39]

The role of P-gp (an ATP-dependent efflux pump belonging to the superfamily of ABC transporters, which include 48 identified members in human) in limiting intestinal, brain and placental transport, as well as in biliary and urinary excretion of its substrates is now well recognized. The variations in its gene (*MDR1* or *ABCB1*) seen amongst several individuals may influence drug disposition and alter drug response [see recent reviews 24, 35]. These mutations are detected in several regions of *MDR1* including domains of the trans-membrane part (5, 6, 11, and 12 domains), or the intra- and extracellular loops, or even the ATP binding sites that might affect the function of P-gp as transporter by altering its binding with drugs and other xenobiotics [24]. The clinical relevance, however, of the characterized genotypes of *MDR1* in certain individuals and ethnic populations has not been accurately established. We still need to pursue this field in order to improve our understanding of the variable P-gp function and response to drugs that are P-gp substrates or inhibitors [35]. Additionally, a recently published report identifies a

polymorphism on *MDR1* designated as *ABCB1* C3435T that is associated with the variable response observed to antiepileptic-drug treatment [41]. On the other hand, the knowledge accumulated thus far shows that most, although not all, drug-substrates of P-gp, are also metabolized by CYP3A4, and these two systems are co-localized in tissues with a major role in drug disposition, such as small intestine and liver [42, 43]. This fact must also be considered together with the recent evidence that some nutrients or phytopharmaceutical preparations (e.g. St John's Wort; *Hypericum Perforatum*) can modify P-gp and CYP3A4 expression and function and thus might interfere and even influence phenotype-genotype correlation studies upon their concomitant delivery with the drugs being studied [24, 44]. This knowledge has already been applied to pharmacotherapy to predict drug-drug or drug-nutrient interactions ensuring drug response and improving patient outcome; whereas, it is integrated into clinical pharmacology teaching courses to implement rational prescription in clinical practice [44-48]. Further elucidation of the molecular

mechanisms implicated in the P-gp role to interindividual drug variability is needed for selective modulation of its function in therapeutic intervention [49].

It is well recognized by now that there is a significant interindividual variability in the therapeutic responses of drugs binding to GPCRs, like α -adrenergic receptors in the general population [36]. For example, thirteen SNPs identified in the promoter and the coding region of α_2 -adrenergic receptor gene were found to be organized into twelve haplotypes. Some of these haplotypes have shown significant divergence in different ethnic populations and this fact is associated with the bronchodilator response to α -agonists in patients with asthma [50]. At the same time, the elucidation of several aspects related to the molecular mechanisms of α_2 -adrenergic receptor signaling has added new information of pharmacological importance about structure and function relationships, as well as coupling of this receptor to multiple effectors [51]. In parallel, understanding of the pharmacological phenomenon related to drug-receptor binding known as "inverse agonism" that has been shown to occur in GPCRs has been reinforced during the last years, allowing better evaluation of drug responses attributed to GPCRs in both issues of efficacy and toxicity [52, 53].

One of the most studied examples in applied pharmacogenomics for the translation of genomic information to guide patient therapeutics is that of TPMT polymorphism and its association with high risk of toxicity in individuals taking thiopurine drugs [37, 54, 55]. At present, eight TPMT alleles have been identified, including three variant alleles designated as TPMT*2 (with G238C mutation), TPMT*3A (with G460A and A719G mutations) and TPMT*3C (with A719G mutation) that account for 80-95% of intermediate or low enzyme activity, and for this reason, they are analyzed during genotyping and haplotyping population studies [see for review 37]. However, even in the case of TPMT polymorphism additional work is needed, through which the translation of genomic data, *via* the wide use of a genetic test with high quality and validity, into specific dosage recommendations of thiopurine drugs in routine pharmaceutical care can be achieved [24, 56].

There have been several attempts in the past few years to establish specific polymorphic gene variants at pharmacodynamic loci related to the cardiovascular system such as ACE, angiotensin II type I receptor (AT-1), apolipoprotein E, α -adducin, and adrenergic receptors that could be used for improving drug response in cardiovascular pharmacotherapy [16, 38, 57, 58]. Although the results that seem to be readily applicable to clinical practice are not those expected thus far from such pharmacogenomic studies, it is expected, however, in the years to come that the association of specific genetic markers with drug response even in complex diseases like these of the cardiovascular system is a realistic expectation.

CLINICAL IMPLICATIONS BY APPLYING GENOTYPING DATA IN PHARMACEUTICAL CARE

Although the prospects for basic research in pharmacogenomics and the generation of considerable amounts of data look very promising, their incorporation into

clinical practice is quite challenging [59]. Furthermore, detailed analysis of the molecular actions of drugs has clearly shown, in some cases, that medicines may exert their effects *via* specific "molecular networks" involving several genes and proteins [10, 60, 61]. This fact highlights even more the existing complexity of modern pharmacology, and makes the possibility of applying personalized medicine into clinical practice a very difficult task. However, efforts towards correlating genotyping or haplotyping information with drug response and, at the same time, identifying new genomic drug targets are considered to be a huge challenge for pharmaceutical research, especially after the completion of several genome-sequencing projects from different organisms [62, 63].

In the meantime, oncology has already been benefited from pharmacogenomics through the availability of a genetic test that identifies specific genotypes in patients accounting for low levels of the enzyme TPMT and predisposes for myelotoxicity of these individuals taking the drugs azathioprine, 6-thioguanine and 6-mercaptopurine (thiopurine-related drugs), as already mentioned above [37, 64, 65]. The pharmacogenomic data for TPMT are so clear and convincing, that recently (October 2002), the Clinical Pharmacology subcommittee of FDA, organized a public hearing to implement the prescription of thiopurine-related drugs based on the pharmacogenomic results of patients, thus minimizing their risk of developing toxic drug effects [66]. Recent advances in cancer pharmacogenomics would also improve chemotherapy outcomes for specific anticancer drugs, like 5-fluorouracil (5-FU), irinotecan and platinum agents [for a review see 67], (Table 1). In particular, specific polymorphisms in the genes encoding the enzymes dihydropyrimidine dehydrogenase and thymidylate synthase have been shown to influence the efficacy and toxicity of 5-FU in certain individuals, although their applicability into clinical practice by selecting patients who are likely to tolerate and respond to 5-FU therapy still remains very complicated [24].

Furthermore, it has been proposed that polymorphisms in the promoter region of the gene encoded for UDP-glucuronosyltransferase 1A1 (*UGT1A1*) may be clinically useful for predicting severe toxicity to irinotecan for certain individuals, thus improving drug delivery and safety [24, 40]. In the case of platinum chemotherapeutic agents (cisplatin, carboplatin, oxaliplatin) several polymorphic genes have been implicated in their efficacy and toxicity. These genes are the *XPD* and the *XRCC1* that encode proteins involved in the cellular DNA excision repair system and that of glutathione-S-transferases (GSTs). However, additional work must be done in order to confirm the applicability of such genetic information into pharmacotherapy of platinum agents by offering, in addition, some predictive value for patient outcome [52].

Although, such clinically significant examples are likely improving cancer pharmacotherapy, it is anticipated, however, that new technological advances permitting faster and less expensive application of whole genome sequencing and genome-wide analysis must happen within the next few years in order for genomic technologies and pharmacogenomic principles to become routine use in pharmaceutical

care. If this happens, a major enforcement to personalized medicine in everyday health and pharmaceutical care will be given. And as the application of genomic technologies to cancer research elucidates crucial and fundamental issues of tumor progression and metastasis, the development and delivery of chemotherapeutic drugs will be improved in clinical practice.

Such an interesting step in understanding human breast cancer progression is considered to be the recently published data on the gene expression profiles of the pre-malignant, pre-invasive, and invasive stages of this type of tumor [68]. Furthermore, great progress has recently been occurred in revealing the structural interactions of the drug Herceptin, (also known as trastuzumab used for the treatment of breast cancer), and its receptor HER2. Herceptin is a humanized monoclonal antibody, whereas its receptor HER2 (also known as Neu, or ErbB2) is a member of the epidermal growth factor receptor (EGFR; also known as ErbB) family of tyrosine kinases and its prescription is based on the expression level of HER2 in the patient's tumor tissue [69]. The recent elucidation of the crystal structure of the entire extracellular regions of HER2 complexed with the Herceptin antigen-binding fragment (Fab) gives new information on drug-receptor structural interactions and this knowledge may lead to better drug design and development of new therapeutics [70]. Moreover, by analyzing gene profiling in cancer treatments we would be able to characterize molecular gene networks, as it happened in the case of acute lymphoblastic leukemia (ALL) where 124 genes were identified to discriminate between different chemotherapeutic agents (methotrexate and mercaptopurine) that are given alone or in combination [71]. Thus, by increasing our knowledge in cancer molecular biology it is expected that better pharmacological interventions will be achieved in the near future.

Another issue concerning drug safety in pharmacotherapy is related to the need of minimizing the incidence of ADRs. In order to gain the full benefits from the application of pharmacogenomics in clinical practice, the predictions of possible drug-drug and drug-nutrient interactions, of insufficient drug action, or even of emergence of ADRs must be attained for routine patient care [72-74]. ADRs remain a major clinical problem, since they contribute either to drug withdrawal from the market, or to patient hospitalizations thus increasing their stay in hospitals and the cost, or even cause a significant number of deaths per year [11]. During the previous years a euphoria in pharmaceutical care existed, since the application of pharmacogenomic concepts in clinical practice is considered to have an important role in reducing ADRs [20, 66, 73]. This impact can be seen with the use of antiretroviral agent abacavir in which about 5% of HIV patients experience a potentially severe hypersensitivity reaction [75]. Recently published pharmacogenomic data have convincingly shown that a specific polymorphism in human leukocyte antigen (HLA) region is highly associated with the incidence of the abacavir-related hypersensitivity reaction [76, 77]. This fact can lead to additional pharmacogenomic studies concerning the possible associations of major histocompatibility complex genotypes with idiosyncratic and allergic reactions to other antiretroviral drugs thus improving their efficacy and safety

[78]. This direction could also finally lead to the establishment of a genetic test for personalized medicine of HIV-1 nucleoside reverse-transcriptase inhibitors, although considerable criticism has been raised over how such research should be incorporated in pharmacotherapy [75].

EVALUATION OF GENOTYPING DATA AND PHARMACOTHERAPY OUTCOME

The fast growing accumulation of genomic data concerning drug action is another challenge to be clarified, since it is of great importance in current drug delivery and biomedicine, whereas the validation and data mining is absolutely based on computerized systems and data integration systems used to support genotyping and haplotyping profiling of individual patients. Moving towards personalized medicine also means existence of tools and diagnostics capable of assessing genome-related clinical information in laboratory medicine and then making the information extracted easily applicable by the physician in routine patient care. This is a very difficult task, since before the transfer of techniques from genomic-related research laboratories to those used for the routine analysis of clinical samples in diagnostic laboratories, these techniques must be firstly assessed for their ethical, social and cost-benefit consequences [79]. Furthermore, the gradual integration of transferring technologies in clinical practice needs the development of carefully selected and evaluated specific genetic markers for the diagnosis of disease and prediction of drug response, as well as the integration and combination of genome-wide linkage analysis with genotyping, gene array and proteomics, (and/or transcriptomics and metabolomics), technologies [80, 81]. These developments of laboratory medicine through the advances made in genomic, proteomic and bioinformatic technologies in recent years also highlight the efforts that must be continued in order to assure the level of quality and validity needed in genetic and molecular diagnostics tests [82]. This means that unified platforms must be developed in order to permit compatibility in handling different data gathered from unrelated sources like that of drug databases, clinical trials, DNA sequencing and functional genomic analysis to ultimately support pharmacogenomics and personalized medicine [83].

PHARMACOTYPING: THE NEXT STEP IN PERSONALIZED MEDICINE?

As already mentioned, genetic variations detected in genes encoding proteins implicated in drug action could affect their function and thus may result in altered drug response (e.g. decreased metabolism, inadequate intracellular transport, impaired function on target site, etc). As a matter of fact, detection of SNPs and establishment of specific haplotypes for several gene products may explain why one patient responds well in drug therapy, while another does not, or even why some people experience serious ADRs. If our understanding to these idiosyncratic pharmacological effects is finally achieved, then drug prescribing could be greatly influenced. In fact, a major transition in pharmacotherapy will happen and the introduction for the first time of the term "pharmacotyping" in pharmaceutical care is suggested here to describe the future drug prescription

process by the physician that might be based on patient's genotyping-haplotyping analysis data. As a consequence, pharmacotyping could be a new dimension of pharmacogenomics and its application in routine clinical practice in the post-genomic era could better depict drug selection and dosage profiling in personalized medicine. Since the future prescription process is expected to be done by the physician in a fully computerized environment with the aid of genomic and bioinformatic information concerning patient status, pharmacotyping better describes this transition in pharmaceutical care (Fig. 1). Such a case means a transition from a drug-selection process mainly based on the physician's own experience, into a more, highly integrated, information-based and computer-aided pharmacotherapy based decision, thus making drug delivery digitized, more efficient and safer. It is very true, that the genetic information derived from such studies must be integrated into clinical practice in such a way to assess simultaneously the risk of ADRs attributed to specific drug specimens. Furthermore, the identification of functional SNPs and establishment of specific haplotypes for genes implicated in drug response, or ADRs, could also be used as a marker for drug prediction effects in a given individual, or even for a specific group of patients. In this way, there has been great progress in elucidating genetic determinants contributing to the observed interindividual differences in drug disposition and effects [60, 84]. However, a standard framework for information-based medicine must firstly be developed, in order to later support an infrastructure for personalized medicine thus achieving pharmacotyping in routine pharmaceutical care. The recent advances in *in silico* modeling for predicting absorption, distribution, metabolism,

excretion (ADME) data for drug development show that this is a realistic expectation in the years to come [85, 86].

TRAINING FUTURE HEALTH CARE PROVIDERS WITH THE PRINCIPLES OF PHARMACOGENOMICS AND PERSONALIZED MEDICINE

The advantage for pharmacologists to apply the principles of personalized medicine seems to go in parallel with the application of pharmacogenomics, but also the serious ethical issues raised from the application of genomic technologies into clinical practice must be taken into account [87]. The role of future pharmacologists in these new concepts of drug therapy will be an increasing demand in pharmaceutical care in order to ensure effective and safe drug delivery to each individual patient. More interestingly, all these achievements and challenges in pharmaceutical research that added new knowledge in pharmacology have already stressed for the need of appropriate adjustments in teaching, curricula and research areas of pharmacology in medical and pharmacy faculties [65, 88, 89]. It is also obvious that better training in pharmacology of future medical and pharmacy students will clearly depend on the development of these new curricula by integrating the new drug-related genomic and bioinformatic technologies into the teaching process and would be beneficial in drug prescribing and pharmaceutical care in routine clinical practice. This is a very difficult task though, since it means the development and introduction of new interactive computer-assisted learning methods related to genes and genomes into the teaching process which would have to be organized into an already tight timetable for completing both theory and practice in pharmacology [90-92]. Finally, another

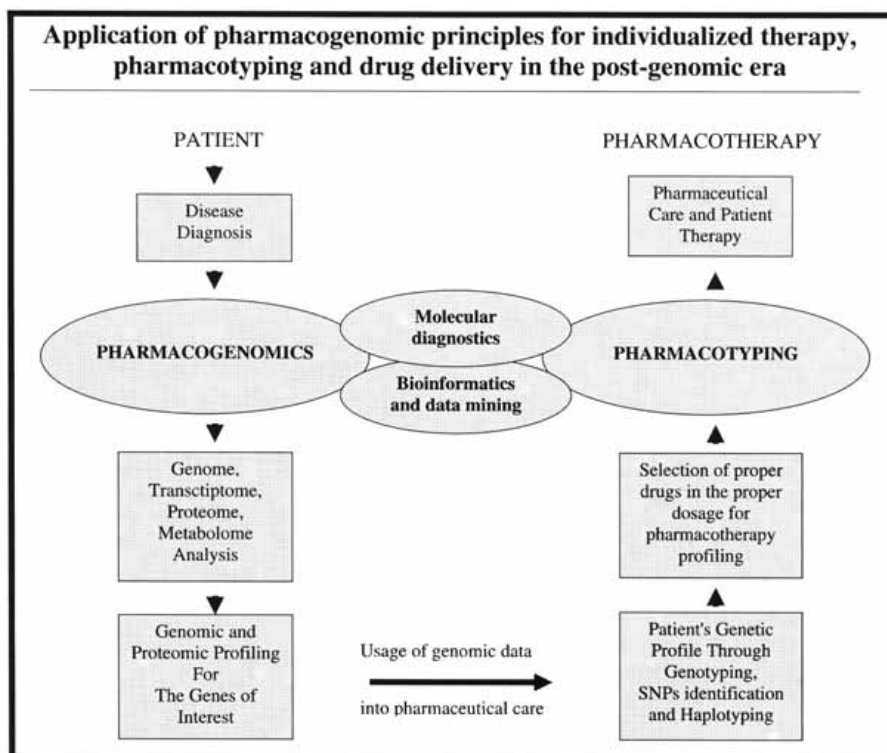


Fig. (1). The interrelation between pharmacogenomics, personalized medicine and drug prescribing for routine patient care.

challenging issue in the design of new pharmacology curricula will be to instruct the students to keep pace with the new scientific knowledge rapidly influencing drug-related aspects even after their graduation. Such profound changes in pharmacotherapy are expected to be eventually enter into clinical practice, thus affecting modern medicine and pharmacy [89-93]. In addition, the positive consequences in clinical practice will be greatly advanced by imperatively incorporating the fundamental principles of pharmacogenomics and personalized medicine into the core curricula of pharmacy and medicine [88, 89]. And for sure, this will be beneficial both for health and pharmaceutical care, as well as for the society and the public in general.

FUTURE PERSPECTIVES

The challenges for scientists after the completion of the initial objectives of the Human Genome Project (HGP), as clearly presented in the vision for the future of genomics research published recently [1], will be to translate the genomic data into transformative new approaches to achieve benefits mainly in health and pharmaceutical care for the public. But consequently, in order for these future achievements in medical genetics, pharmacogenomics and personalized medicine to be fully beneficial for the public in routine patient care, several issues must be addressed, concerning either the education and training of next generation health care professionals, or the development of suitable methods that would permit the smooth integration of genomic knowledge in clinical practice, or even the awareness of the public in ethical and social aspects concerning this type of scientific work [94, 95]. Pharmacogenomic research, especially related to complex diseases e.g. cardiovascular disorders, must take into consideration the influence of multiple environmental and genetic risk factors impacting on several genes with common signal transduction pathways, and in reality is a difficult issue. Therefore, haplotyping of specific genes, whose function in disease pathophysiology and consequently their pharmacological importance has been established, may lead to a further advancement in drug delivery by improving patient outcome in pharmaceutical care. As a matter of fact, the clinical integration of genomic data will be greatly advanced by careful design and experimentation of pharmacogenomic studies, by ensuring genetic test quality, by evaluating and validating the data in routine patient care, and finally, positively affecting the rate by which genotyping data are transformed into personalized medicine, thus generating pharmacotyping concepts as a future dimension of drug delivery.

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