

Pharmacogenomics and Clinical Pathogenesis

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Abstract- Pharmacogenomics are very important and refers to drug discovery based on knowledge of genes, but it is a discipline that offers insight into aetiologic mechanisms, and possible prevention and treatment.

Keywords- Pharmacogenomics, Pathogenesis, Gene therapy, Metastasis.

Introduction

Current research advances in genomic and proteomics medicine have contributed to the acceleration of our understanding regarding the pathogenesis of dementia, improving diagnostic accuracy with the introduction of novel biomarkers and personalizing therapeutics with the incorporation of pharmacogenetic and pharmacogenomic procedures to drug development and clinical practice. Bioinformatics branch data standards began with a historical perspective on biochemical nomenclature standards. Many file format standards were soon developed to convey increasingly complex and voluminous data, which nomenclature alone could not effectively organize without additional structure and annotation. As areas of biochemistry and molecular biology have become more integral to the practice of modern medicine, broader data representation models have been created, from co-representation of genomic and clinical data as a framework for drug research and discovery to the modelling of genotyping and pharmacogenomics therapy within the broader process of the delivery of health care [1]. The main role of a cost-effective treatment is to halt disease progression via modification of the functional cascade involving AD genomics, transcriptomics, proteomics and metabolomics. Pharmacogenetic and pharmacogenomic research strategy may account for 60-90% of drug variability in drug disposition and pharmacodynamics [2]. The sequencing of the human genome project inaugurated a new era in both fundamental and applied genetics and the emergence of new technologies for probing the genome has transformed the field of pharmacogenetics and made personalized genomic profiling and high-throughput screening of new therapeutic agents all but a matter of routine. One of these technologies, molecular combing, has served to bridge the technical gap between the examination of gross chromosomal

abnormalities and sequence-specific alterations [3]. Phenylketonuria is the most common inborn error of metabolism and of tetrahydrobiopterin is a new, alternative treatment method, effective in some phenylketonuria-patients. The dietary treatment becomes less restrictive in such patients, quality of life rises in them substantially. Phenylketonuria-causing mutations strictly determine susceptibility to tetrahydrobiopterin in a given patient [4]. The field of oncology has seen the introduction of several efficacious chemotherapeutic agents. Research has now focused on individualizing treatment strategies by incorporating a combination of physiological variables, genetic characteristics and environmental factors together with the traditional tumor characteristics that currently drives clinical decision making [5]. Pharmacogenomics is a field of study at the interface of the disciplines of genomics and pharmacology, strives to understand the interaction between genes and the response to therapeutics. Its introduction into clinical research trials and medical practice promises to optimize the effectiveness of medications, reduce the adverse effects experienced by patients, and improve the research and development of new therapeutics. However, while pharmacogenomics promises tremendous health benefits it is still crucial to critically analyze the ethical, social and legal issues surrounding these developments [6]. The development of novel active regimens, individual optimization of cancer chemotherapy has been attempted in order to reduce toxicity and enhance tumor response. The rare and limited contributions of pharmacokinetic studies, pharmacogenomic studies are increasing the potential to realize the therapeutics against gastric cancer. Despite the limited data, pharmacogenomics in gastric cancer have provided a number of putative biomarkers for the prediction of tumor response to chemotherapies

and of toxicity [7]. Pharmacogenomics is expected to become one of the ways by which various drug development problems can be broken down and solved. In fact, the field of pharmaceutical development seems to be using pharmacogenomics increasingly as a means of both drug selection and proper dosage determination. Pharmacogenomics can be put to practical use, however, scientific and technical issues must first be resolved, after which social and ethical issues must be addressed [8]. The development and therapy of colorectal cancer (CRC) with the introduction of new cytotoxic and targeting agents is making a significant improvement in progression-free and overall survival has been achieved [9]. The basic fundamental principles of pharmacokinetics (PK) and pharmacodynamics (PD) is applied to understanding the application of pharmacogenetics (PGx) in a clinical setting. PGx establishes connections between the disciplines of pharmacology and genetics. One component of PGx involves establishing relationships between phenotypes and genotypes with respect to predicting the response of medications in individual patients [10]. Polymorphic alleles in the human genome have been identified as affecting numerous drug responses [11]. A Pharmacogenomic study indicates changes in the expression of genes of potential mechanistic relevance [12]. Pharmacogenetics is the term used about genetically determined variability in the metabolism of drugs. Pharmacogenomics refers to drug discovery based on knowledge of genes, but it is a discipline, which offers insight into aetiologic mechanisms, and possible prevention and treatment. The rapidly growing field of pharmacogenomics is going to influence our everyday practice of medicine in the immediate future [13].

Pharmacogenomics and its application to clinical pathogenesis

The research application of pharmacogenetic results requires demonstrable correlations between a test result and an indicated specific course of action. Computational decision-support tool combines patient-specific genotype and phenotype information to provide strategic dosage guidance. Estimating quantitative and temporal parameters associated with the metabolism- and concentration-dependent response to warfarin, provides the necessary patient-specific context for interpreting international normalized ratio (INR) measurements [14]. The application of pharmacogenetics in testing individual polymorphisms of two genes CYP 2C9 i.e., pharmacokinetics of warfarin and VKORC1 (sensitivity on warfarin) is promising tactics leading to a safe anticoagulation. The first of two applications of pharmacogenetics is assessment

of the daily dose of warfarin for individual patients even before starting the therapy. The second is the risk stratification of already warfarinized patients: The carriers of variant genotype are in a greater risk of bleeding complications [15]. The predictive genetic association that in many respects represents a test case for the clinical application of pharmacogenetics highlights the fine specificity of HLA-restricted immunity, here directed against a drug-specific antigen rather than an allogeneic molecule (as occurs in transplantation) or a pathogenic organism as in viral infection. Also, these examples also demonstrate that successful implementation of pharmacogenetic screening requires that a range of criteria be adequately addressed. These include pharmaceutical factors e.g., lack of alternative treatments with similar or improved cost effectiveness, safety, and efficacy, clinical factors e.g., accurate diagnosis of the adverse event, in this case provided by clinical diagnostic criteria and adjunctive epicutaneous patch testing, sufficient objective evidence of the test's predictive value and generalizability, as well as availability of quality-assured laboratory services that are responsive to the needs of targeted genetic screening [16]. Human glucocorticoid receptor alpha (GRalpha) is a nuclear hormone receptor that regulates multiple physiological and pathophysiological processes. There are more variations in both physiological and therapeutic response to glucocorticoids. Multiple previous studies suggested that genetic polymorphisms in GRalpha (NR3C1) might play an important role. The aim of the study was to identify and determine the functional implications of common genetic variation in NR3C1 [17]. The clinical application of pharmacogenetics may be used in that of antipsychotic and antidepressant drug treatment because there is a special need for individualized therapy in psychiatry. The pharmacokinetics of many TCAs, some SSRIs and other antidepressant drugs is significantly altered by polymorphisms; however, some controversy still exists as to whether therapeutic efficacy may be improved and/or adverse events can be prevented by genetically driven adjustment of drug dosage. Pharmacogenetic diagnostics may be an important factor in individualizing drug treatment according to the genetic make-up of the patients [18]. The progress made in the field of pharmacogenetics and pharmacogenomics using a five-stage architecture, which includes 1) determining the role of genetics in drug response; 2) screening and identifying genetic markers; 3) validating genetic markers; 4) clinical utility assessment; and 5) pharmacoeconomic impact. Examples are provided to illustrate the identification, validation, utility, and challenges of these pharmacogenetic and pharmacogenomic markers, with the focus on the current application of this knowledge in

cancer therapy [19]. The mechanism of action and metabolism of anticoagulants has become available only recently. The pharmacogenetics of warfarin and its clinical application has grown exponentially and Dosing algorithms have been developed and continue to be refined that incorporate the polymorphisms of P450 2C9 and vitamin K epoxide reductase [20]. The complexities of human drug response are sufficiently well understood to transform the field of pharmacogenomics from a descriptive science to a predictive science. Clinical application of these markers is currently limited by lack of knowledge about the effects of modifying genes, about their prevalence and risk contribution in different ethnogeographic populations, and by fragmentary information about how genetic factors interact with physiologic or pathologic and other environmental factors [21]. Now days, 'fixed-dosage strategy' approach to medicine, means there is much inter-individual variation in drug response. Polymorphism in the cytochrome P450 (CYP) family is having impact on the fate of pharmaceutical drugs [22, 23]. Pharmacogenetics is the study of the role of inheritance in variation in drug response phenotypes functional validation of candidate genes and the use of genome-wide techniques to gain mechanistic insights is emphasized for the establishment of biological plausibility and as essential follow-up steps after the identification of candidate genes [24]. Gene polymorphisms, which can impact on the pharmacodynamics of anticancer agents used in the treatment of colorectal cancer and is the case for thymidylate synthase, for methylenetetrahydrofolate reductase and for UGT 1A1. Polymorphisms of UGT 1A1 are considered as potential indicators of a risk of toxicity treatment by irinotecan. Clinical trials are in progress so as to validate the clinical usefulness of these germinal genetic analyses so as to select treatments/doses adapted to individual profiles [25].

Pharmacology of pharmacogenomical gene therapy

Single nucleotide polymorphisms (SNPs) can be used in clinical association studies to determine the contribution of genes to drug efficacy and this work was to evaluate the feasibility of using SNP information of the Han Chinese in Beijing (CHB) population from the HapMap database for clinical association studies in the Taiwanese (TWN) population [26]. Pharmacogenetics and Pharmacogenomics Knowledge Base, PharmGKB, curates pharmacogenetic and pharmacogenomic information to generate knowledge concerning the relationships among genes, drugs, and diseases, and the effects of gene variation on these relationships. PharmGKB curators collect information on genotype-phenotype relationships both from the literature

and from the deposition of primary research data into our database. Their goal is to catalyze pharmacogenetic and pharmacogenomic research [27]. C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene has been proposed as a pharmacogenomic marker for toxicity of methotrexate (MTX). The relationship between the C677T gene polymorphism and toxicity and efficacy of MTX in patients with rheumatoid arthritis (RA) on folate supplementation is studied [28]. Standard anticancer therapy based on one size fits all modality has been determined to be ineffective or to be the cause of adverse drug reactions in many oncologic patients. Many pharmacogenetic and pharmacogenomic studies so far have been focused on toxicity of anticancer drugs such as 6-mercaptopurine, thioguanine, irinotecan, methotrexate, 5-fluorouracil (5-FU). Variation in genes is known to influence not only toxicity, but also efficacy of chemotherapeutics such as platinum analogues, 5-FU and irinotecan. The majority of current pharmacogenetic studies focus on single enzyme deficiencies as predictors of drug effects; however effects of most anticancer drugs are determined by the interplay of several gene products and effects are polygenic in nature [29]. Genomic studies of ADHD are reviewed for candidate dopamine genes and studies selected to distinguish catechol-o-methyltransferase (COMT) and dopamine transporter (DAT-1) effects. Pharmacogenomic findings for the COMT gene are in agreement with the 1977 observations of Sprague and Sleator, who reported that at low psychostimulant doses, children with ADHD showed a remarkable improvement on a short-term memory test at all levels of task load, whereas at higher doses, there was a significant decrement in performance on the more difficult versions of the task, corresponding to an 'inverted 'U' shaped curve' [30]. Renin Angiotensin System (RAS) inhibitors comprise some of the most commonly used medications in coronary artery disease (CAD) and its related syndromes. RAS inhibitor pharmacogenomic studies, which have evaluated RAS polymorphisms that either elucidate mechanism via surrogate endpoint measurements, or predict efficacy via clinical outcomes in CAD related syndromes. Regardless of the endpoint, none of the RAS genotypes conclusively predicts efficacy of RAS inhibitors and results of the pharmacogenomic studies were often in direct conflict with one another [31]. For prevention of joint destruction in rheumatoid arthritis, optimal management of therapy with disease-modifying antirheumatic drugs is essential. Pharmacogenomic evidence, if reliable, may be incorporated in the treatment of rheumatoid arthritis to achieve a more efficient activity control with minimized adverse events [32]. Interferon-

beta (IFN-beta) is routinely prescribed as an immunomodulatory treatment for multiple sclerosis (MS), but is associated with variable clinical efficacy. Early predictor of response status would allow more rational provision of this therapy. Both pharmacogenomic and expression analysis have highlighted IFN-beta regulated genes which may influence treatment efficacy [33]. Integrative functions of PPARs are also reflected in their ecogenetic profile, when the variants underlying pharmacogenetic interactions were also shown to modulate the effect of lifestyle factors. Pharmacogenomic assessment is warranted for the new potent ligands of multiple PPAR isoforms as many have displayed serious side-effects in a limited number of treated subjects. The advent of genomic, transcriptomic and system biology-level approaches, integrating knowledge from model systems and human biology, should greatly facilitate the transition to individualized PPAR-based therapies [34]. Sex-selective toxicity could be attributed to sex-related differences in pharmacokinetic and pharmacodynamic properties of these drugs. Systematic pharmacogenomic investigation into sex difference in chemotherapeutic toxicity potentially presents an opportunity to assess the effects of multiple genetic factors or gene networks on sex-related differences in the toxicity of anti-cancer drugs [35]. Pharmacogenetics and pharmacogenomics knowledge base (PharmGKB, <http://www.pharmgkb.org>) is a publicly available internet resource dedicated to the integration, annotation, and aggregation of pharmacogenomic knowledge. PharmGKB is a repository for pharmacogenetic and pharmacogenomic data, and curators provide integrated knowledge in terms of gene summaries, pathways, and annotated literature [36].

Immunology of pharmacogenomic gene therapy

Psoriasis is a chronic inflammatory skin disease in that epidermal hyperplasia results from skin infiltration by type I T lymphocytes and release of associated cytokines. A multifunctional cytokine, rhIL-11, modulates macrophage and type I T-lymphocyte function in cell culture and shows anti-inflammatory activity in animal models. Amelioration of disease by rhIL-11, as shown by reduced keratinocyte proliferation. Cutaneous inflammation, was associated with decreased expression of products of disease-related genes, including K16, iNOS, IFN-gamma, IL-8, IL-12, TNF-alpha, IL-1beta, and CD8, and with increased expression of endogenous IL-11 [37]. Asthma is a complex genetic disorder involving the interplay between various environmental and genetic factors. Atopic asthma is found to be strongly familial; however the mode of inheritance is controversial. A large number of studies have

been carried out and a number of candidate genes have been identified. Genes who are associated with asthma in one population may not be associated with asthma in another population. In addition to the involvement of multiple genes, gene-gene interactions play a significant role in asthma. A number of novel therapeutic targets have been identified and drugs are being developed for better efficacy with less side-effect. With the rapid progress in the identification of genes involved in various ethnic populations combined with the availability in future of well-targeted drugs, it will be possible to have appropriate medicine as per the genetic make-up of an individual [38]. Real-time RT-PCR is used to study the cutaneous expression of several cytokines during experimental immunomodulatory therapy of psoriasis by Interleukin-10, and demonstrate that the technique is suitable for pharmacogenomic monitoring of cytokine profiles [39]. Ascomycin macrolactam pimecrolimus is a novel inflammatory cytokine release inhibitor that so far has not been administered systemically to humans. Gene profiling identified a common genomic profile with a downregulation of genes associated with inflammation but no changes in gene expression linked to drug-related side-effects. Pimecrolimus taken orally is highly effective in a concentration-dependent manner in patients with psoriasis and on a short-term basis it is well tolerated and this is confirmed by its pharmacogenomic profile [40]. C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene has been proposed as a pharmacogenomic marker for toxicity of methotrexate (MTX) and relationship between the C677T gene polymorphism and toxicity and efficacy of MTX in patients with rheumatoid arthritis (RA) on folate supplementation [41]. Therapeutic modulation of psoriasis with targeted immunosuppressive agents defines inflammatory genes associated with disease activity and may be extrapolated to a wide range of autoimmune diseases. Cyclosporine A (CSA) is considered a gold standard therapy for moderate-to-severe psoriasis. Clinical trial is conducted with CSA and analyzed the treatment outcome in blood and skin of 11 responding patients. In the skin, as expected, CSA modulated genes from activated T cells and the type 1 pathway, i.e., p40, IFN-gamma and STAT-1-regulated genes. Genomic signature of successful treatment of psoriasis may serve as a reference to guide development of other new therapies [42]. The prediction of response (or non-response) to anti-TNF treatment for rheumatoid arthritis (RA) is a pressing clinical problem. A genome-wide association study is conducted using the Illumina HapMap300 SNP chip on 89 RA patients prospectively followed after beginning anti-TNF therapy as part of Autoimmune Biomarkers

Collaborative Network (ABCOn [Autoimmune Biomarkers Collaborative Network]) patient cohort. Response to therapy was determined by the change in Disease Activity Score (DAS28) observed after 14 wks [43]. The allelic variation of three enzymes involved in 6-mercaptopurine/azathioprine (6-MP/AZA) metabolism and evaluates the influence of these polymorphisms on toxicity, haematological parameters and metabolite levels in patients with acute lymphoblastic leukaemia (ALL) or inflammatory bowel disease (IBD) [44]. HIV infection is a serious but treatable disease and current treatment is limited by development of resistance and high rates of adverse drug reactions. Antiretroviral therapy is especially suitable for pharmacogenomic investigation as both drug exposure and treatment response can be reliably measured. Increasing knowledge about genes implicated in pharmacokinetics, mode of action, efficacy and toxicity of drugs has already provided relevant results for clinical practice, for example: The strong association of the abacavir hypersensitivity reaction with HLA-B*5701 permits testing patients for the allele, and if present avoiding the drug and therefore preventing the reaction [45].

Pharmacogenomics strategies

Breast carcinogenesis involves genetic and epigenetic alterations that cause aberrant gene function. Recent progress in the knowledge of epigenomics has had a profound impact on the understanding of mechanisms leading to breast cancer, and consequently the development of new strategies for diagnosis and treatment of breast cancer. Epigenetic regulation has been known to involve three mutually interacting events--DNA methylation, histone modifications and nucleosomal remodeling. These processes modulate chromatin structure to form euchromatin or heterochromatin, and in turn activate or silence gene expression [46]. Development and therapy of colorectal cancer (CRC), it still remains one of the major cancer related deaths throughout the world. It will be critical to identify molecular markers that may help to assess therapeutic response and outcome in CRC. Validation of predictive and prognostic molecular markers will enable oncologists to tailor patient specific treatment strategies for the individual patient according to the molecular profile of both the patient and their tumor. Individualized therapy will help to improve therapeutic efficacy and to minimize toxicities and therapeutic expenses [47]. Pharmacogenetics is to develop strategies to personalize treatment and tailor therapy to individual patients, with the goal of optimizing efficacy and safety through better understanding of human genome variability and its influence on drug response. Pharmacogenomics research related to the

treatment of pediatric ALL. These studies illustrate the promise of pharmacogenomics to further advance the treatment of human cancers, with childhood leukemia serving as a paradigm [48, 49]. The substantial inter- and/or intra-individual variation in clinical outcome, future improvements will likely require the incorporation of a novel anticancer drug, pharmacokinetically guided administration of CDDP or 5-FU, and identification of potential responders by patient genetic profiling prior to treatment. Latest information on incidence, risk factors, biomarkers, therapeutic strategies, and the pharmacokinetically guided or genotype-guided administration of CDDP and 5-FU can be used for future individualization of esophageal cancer treatment [50]. Many physicians are reluctant to prescribe oral anticoagulation therapy (OAT) because of the fear of haemorrhagic complications. Changes in patient health, lifestyle or diet and other drugs can alter the effectiveness of oral anticoagulants. These potential interferences, added to the fact that each individual has a different reaction to these drugs, requires that therapy is monitored regularly. Relevant articles were identified through a search of MEDLINE and included publications reporting on intensity of anticoagulation, the initiation of therapy and the role of pharmacogenetics, the transition from primary to secondary care, management by specialized clinics using decision support software and home-testing. Implementation of these strategies would increase the use of oral anticoagulants by physicians and offers the potential to improve patient safety and reduce adverse events [51]. Traditional mechanism elucidation strategies are narrow and often focusing on the identification of solely the molecular target. Methods which can offer additional insight into wide-ranging molecular interactions required for drug effect and the biochemical consequences of these interactions are in demand. Genomic strategies have made impressive advances in defining a more global view of drug action and are expected to increasingly be used as a complimentary tool in drug discovery and development [52]. Angiogenesis is controlled by a balance between pro- and anti-angiogenic factors. Studies in mice and human beings have shown that this balance, as well as the general sensitivity of the endothelium to these factors, is genetically pre-determined. In an effort to dissect this genetic basis, different types of genetic variability have emerged: mutations and translocations in angiogenic factors have been linked to several vascular malformations and haemangiomas, also, SNPs have been associated with complex genetic disorders, such as cancer, neurodegeneration and diabetes. In addition, copy number alterations of angiogenic factors have been reported in several tumours [53].

Effective systemic drugs are increasingly used to treat patients with colorectal liver metastases. Chemotherapy can reduce the size of metastases that are unresectable rendering them resectable, and decrease postoperative recurrence rates in patients with initially resectable tumours. The increasing use of chemotherapy for colorectal liver metastases has raised awareness of the potential hepatotoxicities induced by systemic drugs and the effects of these drugs on outcome after hepatic resection [54]. Pharmacogenetics for the 3 commonly used drug classes in treating diabetes: metformin, sulphonylureas and thiazolidinediones. Metformin pharmacogenetics is focussing on drug transport with the recent finding that variation in OCT transporters might affect metformin response. In Type 2 diabetes sulphonylurea response has been shown to be associated with variants TCF7L2 associated with type 2 diabetes risk. For thiazolidinediones, focus has been on PPARgamma variants although with no consistent result. Large numbers of well phenotyped patients for response and side effect as well as similarly sized similarly phenotyped replication cohorts are required. Establishing such cohorts is a priority in diabetes pharmacogenetics research [55]. SNP-typing strategies involve an exponential amplification step, an allele discrimination reaction and detection of the products. Usually, allele discrimination is performed after amplification. Tetra-primer PCR allows allele discrimination during the amplification step, thereby avoiding additional genotyping reactions. Also, to date, electrophoresis is the only method used for detection of tetra-primer PCR products. We report a dipstick test that enables visual detection of tetra-primer PCR products within minutes without instruments. The method is applied to the genotyping of CYP2C19*2 (c.681G>A) and CYP2D6*4 (g.3465G>A) [56]. The challenge of chemotherapy of NSCLC relies on the identification of molecular markers, which are predictive of drug sensitivity and are helpful in the selection of chemotherapeutic agents best suited to the individual patient. Other intriguing issues will be the identification of the optimal drug sequence in combination regimens and the pharmacogenetics of severe toxicities. due to the developments of novel technologies to decipher genetic alterations involved in tumor progression, new agents are gaining momentum, including inhibitors of intracellular signal transduction, and a large body of research, using prospective clinical trials, should be devoted to this area [57]. Food and Drug Administration (FDA) has recognized pharmacogenomics as an opportunity to identify new biomarkers that may expedite the drug development process. There are over 50 drugs with pharmacogenetic discoveries on their labeling. Sequence variations in drug disposition

genes can alter the pharmacokinetics of a drug, while sequence variations in drug target genes can change the pharmacodynamics of the drug. The two most common strategies to test a pharmacogenetic question are the candidate-gene approach and genomewide association study. Given the complex interplay among the many factors, which influence a drug dose, determination of an appropriate dose of a particular drug for a given patient will eventually require knowledge about both genetic and nongenetic factors that affect drug disposition and pharmacodynamics. Many factors can influence the application of pharmacogenetic discoveries to patient care. Before these discoveries find widespread application in clinical practice, additional work is needed, including randomized clinical trials to evaluate the clinical utility of a pharmacogenetic test, the development of guidelines for the clinical use of various pharmacogenetic tests, and provider education on pharmacogenetics [58]. CYP oxidoreductase (POR) is an essential component of several enzyme systems, including the microsomal CYP monooxygenases. We investigated genetic and nongenetic POR variability and its impact on drug-oxidation activities in human liver microsomes [59]. Peripheral neuropathy is an important complication of antiretroviral therapy and nucleoside reverse-transcriptase inhibitor (NRTI)-associated mitochondrial dysfunction, inflammation and nutritional factors are implicated in its pathogenesis. Pharmacogenetic and genomic studies investigating NRTI neurotoxicity have only recently become possible via the linkage of HIV clinical studies to large DNA repositories [60].

Pharmacogenomics and drug resistance

Oxaliplatin is a third-generation platinum agent used in colorectal cancer treatment. Oxaliplatin resistance acquisition is a complex process mainly based on alteration of genes and pathways involved in its mechanism of action. Four colorectal cancer cell lines and their oxaliplatin-resistant derived sublines were compared. Microarray analysis was done using Human 19K Oligo Array Slides. RNA from cells were hybridized with a commercial RNA reference sample and labelled with both fluorochromes Cy3 and Cy5 [61]. Pharmacogenetics represents an exciting, new promising tool for the individualisation of therapy. Many genetic polymorphisms and haplotype have been considered in an attempt to optimise therapy with specific drugs but, up to now, their clinical applications remain limited. 5, 10 Methylene-tetra-hydrofolate reductase (MTHFR) is a key enzyme of one-carbon metabolism, catalyses the irreversible conversion of 5, 10-methylene-tetrahydrofolate to 5-

methyltetrahydrofolate. Two common non-synonymous variants, the C677T (Ala222Val) and A1298C (Glu429Ala), were described for the MTHFR gene and associated with a decreased enzymatic activity and an alteration of intracellular folate distribution [62]. Despite remarkable progress, pharmacotherapy in general, including that for the treatment of depressive conditions, has often ignored the magnitude and clinical significance of the huge interindividual variations in pharmacokinetics and pharmacodynamics, resulting in poor compliance, suboptimal therapeutic effects, and treatment resistance. Advances in pharmacogenomics and computer modeling technologies hold promise for achieving the goals of individualized (personalized) medicine. However, the challenges for realizing such goals remain substantial [63]. The distribution frequencies of four common single nucleotide polymorphisms (SNPs) of MRP1/ABCC1 in a mainland Chinese population and investigate whether these SNPs affect the expression and function of the MRP1/ABCC1 [64]. There has been an ever growing interest in the search for new anti-tumor compounds that do not interact with MDR1-Pgp and MRP1 drug transporters and so circumvent the effect of these proteins conferring multidrug resistance (MDR) and poor prognosis in AML patients. Investigated was carried out for the cytotoxic activity of the strong glutathione S-transferase (GST) inhibitor 6-(7-nitro-2, 1, 3-benzoxadiazol-4-ylthio) hexanol (NBDHEX) on AML (HL60) cell lines [65]. Drug resistance in malaria jeopardizes the most elementary objectives of malaria control--reducing suffering and eliminating mortality. Mechanism of drug resistance appears to be polymorphisms in the malaria parasite genes. Efforts to circumvent antimalarial drug resistance now range from the use of combination therapies with existing agents to genomics-based studies directed toward discovering novel targets and agents. However, the potential contribution of host genetic/molecular factors, particularly those associated with antimalarial drug metabolism, remains largely unexplored [66]. Anti-tuberculosis (anti-TB) drug sensitivity testing methods provide a dichotomous readout: isolates are reported as either drug susceptible or drug resistant. Rapid molecular methods may provide information concerning both the level of resistance and cross-resistance to other anti-TB drugs, which is important for optimal clinical management. Specific mutations detected by the Hain GenoType MTBDRplus test, recently approved by the World Health Organization (WHO) for rapid TB diagnosis and drug resistance testing, and could inform the decision of whether to include high dose isoniazid (INH) when treating patients with INH mono-resistant TB, MDR-TB or XDR-TB [67]. NSCLC is the leading cause of

cancer-related death in the US. Patients with NSCLC are mostly treated with platinum-based chemotherapy, often in combination with radiation therapy. The development of chemoresistance is a major hurdle limiting treatment success. The genetic factors modulating chemoresistance to platinum chemotherapeutics and their association with clinical outcomes for NSCLC patients were summarized. On candidate pathways responsible for drug influx and efflux, metabolism and detoxification, DNA damage repair, and other downstream cellular processes that modulate the effect of platinum-based therapy [68]. The prevalence rates of *H. pylori* are highly variable and depend greatly on the local sanitation conditions. The use of NSAIDs and aspirin is ubiquitous and increasing especially for the antiplatelet activity of aspirin in the prophylaxis of cardiovascular events. There is evidence that pharmacogenetics play a role in susceptibility to the ulcerogenic properties of NSAIDs. Prevalence of PUD parallels the risk factors, but emerging in both the East and the West is idiopathic PUD, now a substantial proportion of ulcers in areas of declining *H. pylori* infection. Genetic polymorphisms affect the efficacy of treatment using PPIs. Local *H. pylori* resistance rates also influence the eradication success rates [69]. It remains controversial whether polymorphisms of the multidrug resistance gene ABCB1 are associated with pharmacoresistance in epilepsy. A broad set of tagging SNPs was genotyped, and explored whether any associations were affected by other host factors. Correlation any association with cerebral mRNA expression of ABCB1 was done [70]. The Neuropsychiatric Inventory (NPI) was administered to determine the frequency and severity (FxS) of psychotic and other behavioural symptoms. There was a significant difference in the NPI FxS delusion score among the three variants of the 5-HT_{2a} 102T/C polymorphism, with patients carrying the TT genotype the most delusional during the follow-up period. In particular, NPI FxS delusion score was higher in TT than in CC genotype at year 2. Moreover, patients with delusion symptoms carrying the CT and TT genotypes were resistant to the treatment with antipsychotic drugs. The presence of T allele of the 102T/C polymorphism in patients with Alzheimer's disease is associated with both increased presence of delusion symptoms and treatment-resistance to second generation antipsychotic drugs [71]. The subset of patient with chronic myelogenous leukemia (CML) does not respond to the tyrosine kinase inhibitor (TKI) imatinib mesylate. Such primary imatinib resistance is distinguished from secondary resistance which reemerges after attainment of cytogenetic remission [72]. Drug resistance is an important clinical problem in epilepsy, affecting a substantial number of patients globally.

Mechanisms underlying drug resistance need to be understood to develop rational therapies. Genetics offers one route to better understanding and thus potentially treating, drug resistance. Major developments in technologies and methodologies, evolving confidence in high-throughput and genome-wide approaches and a continuing research effort into the genetics of inherited and sporadic epilepsies are beginning to uncover mechanisms that may contribute to drug resistance - there is reason for hope of better treatments to come [73].

Tumours and metastases

Analyze the effectiveness and therapeutic response of Novalis shaped beam radiosurgery for metastatic brain tumors and the prognostic factors which influence the outcome [74]. HER2-positive metastatic breast cancer (MBC) relapsing after trastuzumab-based therapy may require continued HER2 receptor inhibition to control the disease and preserve the patients' quality-of-life. Efficacy and safety of lapatinib monotherapy is evaluated in Japanese breast cancer patients after trastuzumab-based therapies [75]. Over the last two decades, oesophageal cancers, although considered among the most malignant visceral tumours, have witnessed a gradual increase in survival rates at a distance after surgery [76]. Bisdioxopiperazine compounds, including ICRF-154 and razoxane (ICRF-159, Raz), are anticancer agents developed specifically for targeting tumor metastases. Further two bisdioxopiperazine derivatives, probimane (Pro) and MST-16, have been synthesized. Anticancer activities and mechanisms of Pro and MST-16 compared with Raz, especially for antiproliferative and antimetastatic effects *in vivo* and *in vitro*, have been systematically evaluated. New novel molecular mechanisms especially relating to the inhibition of tumor metastasis between probimane and razoxane have been especially explored and explained, including pathways of inhibitions against calmodulin, sialic acid, lipoperoxidation, fibrinogen, cell-movement and the cell-cycle arrest [77]. It is unclear what role pretreatment tumor vascularity plays in determining outcomes after yttrium-90 radioembolization and hypothesis is tested that radiographic vascularity of a tumor does not affect patient survival [78]. Uveal melanoma (UM) is the most common primary intraocular tumor in adults. Disease metastasis occurs in half of the patients and is uniformly fatal despite systemic therapy. Inducible nitric oxide synthase (iNOS) is associated with disease progression in various malignancies including cutaneous melanoma [79]. Toll-like receptor (TLR)-mediated signaling is proposed as an immunotherapeutic target against tumorigenesis. Natural killer (NK) cells play a critical role in host defense against tumors.

Formation of tumor metastasis in various organs can be suppressed by the local activity of NK cells. In this study, we present a novel TLR7 agonist (termed SC-1), which induces pro-inflammatory cytokines in human blood cells, activates NK cell function and is highly efficient in preventing lung metastases in a pulmonary metastatic Renca model [80]. Surgery in gastric cancer (GC) aims to achieve resection of the primary tumor and its lymphatic drain, with a minimal adverse effect on morbidity and mortality and the best possible quality of life [81]. Cancer of unknown primary site includes metastatic tumours with different histology and behaviour. Although most of them have a poor short-term prognosis, some patients can benefit from a treatment and will achieve a longer survival. The treatable cases are: metastases of squamous carcinoma in cervical or inguinal adenopathies, metastases of adenocarcinoma in axilar adenopathies in women, malignant ascites due to adenocarcinoma in women, osteoblastic bone metastases in men with elevated serum prostatic specific antigen levels, poorly differentiated tumours with features of a germinal extragonadal tumour, poorly differentiated neuroendocrine carcinomas and patients with a single metastasis [82]. Incidence of pediatric nonrhabdomyosarcoma soft tissue sarcomas (NRSTSs) of the groin and axilla is unknown, and the optimal surgical approach to these patients is unclear [83]. Malignant peripheral nerve sheath tumors (MPNSTs) are sarcomas, which derive from peripheral nerves or from cells associated with the nerve sheath. Magnetic resonance imaging is the main diagnostic imaging modality for evaluating MPNSTs. Computed tomography (CT) of the chest is the main imaging modality used to screen for distant disease, and bone scanning is considered useful for identifying selected metastases [84]. Patients with malignant melanoma are at an increased risk of developing subsequent primary melanomas and also nonmelanoma cutaneous cancers. Several studies have reported an association between malignant melanoma and breast cancer, bladder cancer, colorectal cancer, neuroectodermal tumours, non-Hodgkin's lymphoma, leukaemia and renal cell carcinoma [85]. A set of genes related to the progression and metastasis of advanced cervical cancer after radiotherapy and to establish a predictive method [86]. There has been much development in the treatment of bone metastases using percutaneous image-guided interventional radiology procedures. They are helpful in the management of patients resulting in stabilization of bone lysis in order to achieve additional biomechanical stability and in significant symptomatic relief. Vertebroplasty consisting in an injection of acrylic cement into a structurally weakened or destructed bone plays a major role in the management of specific bone

weakening. Advances have been made also with the application of thermoablation procedures to bone tumors (radiofrequency ablation, cryotherapy) [87]. Assessment of receptors i.e., estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), is routinely carried out on primary tumour in order to select appropriate adjuvant therapy; the same analysis is not carried out on nodal metastases. Since de novo resistance to therapy is common, we quantified differences in receptor expression between primary and nodal disease in order to assess whether this might contribute to therapeutic resistance [88]. Tumor growth requires the development of independent vascular networks that are often primitive in morphology and function; whether microvessel morphology contributes to the considerable biologic heterogeneity of prostate cancer [89]. A novel imaging technique is described in which the mode conversion of longitudinal waves is used for the qualitative detection of stiff lesions within soft tissue using magnetic resonance elastography (MRE) methods. The proposed technique is shown to readily depict hard regions (mimicking tumors) present in tissue-simulating phantoms and ex vivo breast tissue. *In vivo* feasibility is demonstrated on a patient with liver metastases in whom the tumors are readily distinguished [90]. The use of pattern classification methods for distinguishing different types of brain tumors, such as primary gliomas from metastases, and also for grading of gliomas and availability of an automated computer analysis tool that is more objective than human readers can potentially lead to more reliable and reproducible brain tumor diagnostic procedures. A computer-assisted classification method combining conventional MRI and perfusion MRI is developed and used for differential diagnosis [91]. Whole-body MRI combined with a semiautomated hierarchical multispectral image analysis technique is evaluated as a method for detecting viable tumor tissue in a murine model of metastatic breast cancer (4T1 cell line). Whole-body apparent diffusion coefficient, T(2) and proton density maps are acquired in this research. The viable tumor tissue segmentation included three-stage k-means clustering of the parametric maps, morphologic operations, application of a size threshold and reader discrimination of the segmented objects [92].

Pharmacogenomics and clinical mechanism

Protein kinases represent such molecular targets; considerable research effort has been devoted to the development of targeted drugs that inhibit the action of pathogenic kinases, and clinical studies performed so far have validated the positive effects of kinase inhibitors for cancer treatment [93]. Although the pharmacokinetics of several

drugs, which are mainly eliminated by the CYP3A4 metabolism vary according to their dosing time, the mechanism of the variation remains poorly understood. In this study, we investigated how the 24-h oscillation in the expression of CYP3A4 mRNA was generated in hepatic cells [94]. Peroxisome proliferator-activated receptor gamma (PPARgamma) agonists are highly effective in the treatment of type 2 diabetes. In some patients, PPARgamma ligands are associated with fluid retention/oedema, for which the mechanism is not fully understood. A pharmacogenetic study is undertaken to investigate effects of variations in 21 candidate genes related to epithelial sodium channel (ENaC) pathways on oedema. This research used DNA samples collected from type 2 diabetes phase III clinical trials of the PPARgamma agonist farglitazar (administered alone or in combination with insulin or glyburide) and investigated oedema reported as an adverse event as phenotype [95]. Drug metabolizing enzymes and transporters are increasingly recognized as key determinants of the inter-individual variability in pharmacokinetic (PK) and pharmacodynamic (PD) outcomes of clinically important drugs. To date, most studies investigating this variability have focused on polymorphisms (e.g., SNPs) in the genes encoding metabolic enzymes and transporters; however, it has recently been reported that the expression of some of these genes is under the control of epigenetic mechanisms [96]. Pharmacogenomics can provide important insights into statins therapy through elucidation of the genetic (or genomic) contribution to variable response for these drugs. The search for genetic polymorphisms may enable us to identify novel determinants of drug responsiveness by means of the study of three candidate genes groups: (1) genes encoding proteins involved in metabolism or drug transport, or both, that influence drug pharmacokinetics; (2) genes encoding proteins involved in mechanism of action and/or metabolic pathways on which drugs operate (that influence pharmacodynamics); (3) genes encoding proteins involved in the underlying disease condition or intermediate phenotype [97]. Metabolic profiling (metabonomics/metabolomics) is the untargeted analysis of metabolic composition in a biological sample, and is principally aimed at biomarker discovery. Metabonomics can make an impact at several points in the drug-development process: target identification; lead discovery and optimization; preclinical efficacy and safety assessment; mode-of-action and mechanistic toxicology; patient stratification; and clinical pharmacological monitoring. The future goals for metabonomics are the validation of existing biomarkers, in terms of mechanism and translation to man, together with a focus on characterizing the individual personalized

healthcare [98]. Doxorubicin (DOX) is one of the most effective anti-neoplastic agents; however, its clinical use is limited by drug-induced cardiomyopathy. Molecular mechanisms responsible for this toxicity remain to be fully addressed and the involvement of atrogin-1, one of the muscle-specific ubiquitin ligases, in DOX-induced cardiotoxicity [99]. Utilization of pharmacogenomic information has the potential to significantly improve treatment outcome and markedly reduce the rate of attrition of drugs in clinical development. A major gap that limits our ability to utilize pharmacogenomic information in drug discovery, drug development or clinical practice is that the genetic variants responsible for inter-individual differences in drug metabolism or drug response. A new application of these emerging genomic technologies has the potential to significantly improve the safety of drugs, the quality of patient care and the efficiency of clinical drug development [100]. The thiopurine drugs-azathioprine (AZA), 6-mercaptopurine (6-MP), and thioguanine-are widely used to treat malignancies, dermatologic conditions, inflammatory bowel disease, rheumatic diseases and solid organ transplant rejection. The recent research in the mechanism of action as well as the molecular basis and interethnic variations of TPMT and inosine triphosphate pyrophosphatase (ITPase; EC 3.6.1.19) another enzyme implicated in thiopurine toxicity [101]. Gene expression profiling in both clinical and laboratory settings would be enhanced by better characterization of variance due to individual, environmental, and technical factors. Meta-analysis of microarray data from untreated or vehicle-treated animals within the control arm of toxicogenomics studies could yield useful information on baseline fluctuations in gene expression, although control animal data has not been available on a scale and in a form best served for data-mining [102]. Thiopurine S-methyltransferase (TPMT)*3A is degraded much more rapidly than is the 'wild-type' enzyme through an ubiquitin-proteasome-dependent process. It also forms aggregates, suggesting a possible dynamic balance between degradation and aggregation [103]. Genetic variation can impact on efficacy and risk of adverse events to commonly used oral agents in -diabetes. Metformin is not metabolized and its mechanism of action remains debated; however, several cation transporters have been identified. These pharmacokinetic genes might influence metformin response. Although the cytochrome P450 system has been implicated in sulfonylurea response in some small studies, to date variants affecting pharmacodynamics, including those in ABCC8 (SUR1) and TCF7L2, are the most promising. For thiazolidinedione response, variants in PPAR γ or ADIPOQ (adiponectin) have been variably associated with response [104].

Drug resistance mechanism

Glucocorticoids (GCs) are widely used as co-medication in therapy of solid malignant tumors to relieve some of the side effects of chemotherapy drugs. Recent research has shown that GCs could render cancer cells more resistant to cytotoxic drug-induced apoptosis, but the mechanism is largely unknown [105]. Hepatocellular carcinoma is chemoresistant to many anticancer drugs. Tunicamycin, an N-glycosylation inhibitor, causes unfolded protein response and is widely used as pharmacological inducer of endoplasmic reticulum stress. Several designs are used to investigate the resistance mechanism to camptothecin and etoposide in hepatocellular carcinoma Hep3B cells. Tunicamycin significantly inhibited apoptosis induced by camptothecin or etoposide. Tunicamycin neither modified the topoisomerase levels nor inhibited the ATM activation caused by camptothecin and etoposide [106]. Amphetamine-type stimulants (ATS) are the most widespread narcotics in the 21st century. The methamphetamine's intoxication mechanism, psychological dependence, drug resistance and therapeutic drug development are the hot spots in current research. Establishment of animal model with methamphetamine poisoning is the basic for the relative studies, the normalization and standardization of the animal model settles the foundation for methamphetamine's further research [107]. To investigate the drug-resistance of *Acinetobacter baumannii* (Ab) isolated from patients in burn ward and study the incidence of 16S rRNA methylase genes mediated high-level aminoglycoside drug-resistance and its mechanism of transfer [108]. To study the drug-resistant characteristics genetic mutation of *rpoB* in *Mycobacterium tuberculosis* L-forms among patients of pneumoconiosis complicated with pulmonary tuberculosis [109]. Overexpression of ABCG2 has been reported in cell lines selected for drug resistance and it is widely believed to be important in the clinical pharmacology of anticancer drugs. In ABCG2-overexpressing drug-resistant cells, hsa-miR-519c is unable to affect ABCG2 expression because the mRNA lacks its binding site, whereas hsa-miR-520h is sequestered and unable to limit ABCG2 expression. The recent observation that a truncated 3'UTR is also observed in ABCG2-overexpressing human embryonic stem cells, results in drug-resistant cell lines suggest, which 3'UTR truncation is a relatively common mechanism of ABCG2 regulation [110].

Drug pharmacogenomics

Antipsychotic drug development, precise mechanisms behind the action of typical and atypical antipsychotics is poorly understood.

Typical antipsychotics and atypical antipsychotics affect different genes and biological function in the liver. Typical antipsychotic phenothiazines exert robust effects on gene expression in the liver that may lead to liver toxicity. Genes found in the current study may benefit antipsychotic drug development with better therapeutic and side effect profiles [111]. The growth inhibitory effect of tamoxifen is used for the treatment of hormone receptor-positive breast cancer is mediated by its metabolites, 4-hydroxytamoxifen and endoxifen. The formation of active metabolites is catalyzed by the polymorphic cytochrome P450 2D6 (CYP2D6) enzyme. Among women with breast cancer treated with tamoxifen, there was an association between CYP2D6 variation and clinical outcomes, such that the presence of 2 functional CYP2D6 alleles is associated with better clinical outcomes and the presence of nonfunctional or reduced-function alleles with worse outcomes [112]. In recent years a number of studies on variations of DNA and RNA characteristics as related to drug response' (PGx) have in fact produced growing evidence that, besides the effects of age, sex, diseases, and different drugs interactions, genetic factors play a role in the inter-individual variability of drugs response. The increasing genomic knowledge has also raised the profile and role of the so called 'genomic biomarkers' (GBs) in drug development, approval, and clinical use [113].

Translational and functional pharmacogenomics

Serotonin (5-HT)₃ receptor antagonist relieves symptoms in women with diarrhea-predominant irritable bowel syndrome (D-IBS). 5-HT undergoes reuptake by a transporter protein (SERT). Polymorphisms in the promoter for synthesis of SERT (SERT-P) influence response to serotonergic medications in depression. Hypothesis is that polymorphisms of the promoter region for the SERT influence colonic transit in response to treatment with alosetron in D-IBS. SERT polymorphisms tended to be associated with colonic transit response; there was a greater response in those with long homozygous than heterozygous polymorphisms. Slowing of transit by >1.1 colonic region is observed in 9 women and 3 men and is more frequent in long homozygous than heterozygous patients and age, gender, and duration of IBS were not significantly different in the 3 groups [114]. Functional gastrointestinal disorders, including irritable bowel syndrome and functional dyspepsia, are highly prevalent disorders affecting approximately one in four people in Western societies. This article reviews examples of the role of pharmacogenomics in the safety and efficacy of medications used in the management of such disorders. These include

variations in the effects of medications metabolized by cytochrome P450 enzymes (e.g., 2D6 and 2C19), and the effects of genetic polymorphisms in the promoter of the serotonin transporter protein, which influence the response to alosetron in patients with diarrhea-predominant irritable bowel syndrome. These observations suggest that pharmacogenomics will introduce a new era in pharmacotherapeutics in gastroenterology [115]. Field of proteomics is taking on increased significance as the relevance of investigating and understanding protein expression in disease and drug development is appreciated. Proteomics have been driven by the availability of numerous annotated whole-genome sequences and a broad range of technological and bioinformatic developments that underscore the complexity of the proteome. The various technologies that comprise Expression Proteomics and Functional Proteomics, citing examples where these emerging approaches have been applied to pharmacology, toxicology, and the development of drugs [116].

Therapeutic and experimental strategy

Metronomic chemotherapy regimens have shown anti-tumor activity by anti-angiogenic mechanisms, however, the efficacy of metronomic topotecan in ovarian cancer is not known and the focus of the current study. Compared to controls, metronomic and maximum tolerated therapy dosing regimens reduced tumor growth in dose-finding experiments, but significant morbidity and mortality was observed with higher doses. Endothelial cells demonstrated a significantly higher sensitivity to topotecan using metronomic dosing versus MTD *in vitro*. Pro-angiogenic regulators Hif-1 α and VEGF levels were reduced *in vitro* with topotecan independent of proteasome degradation and topoisomerase I [117]. Discovery of novel targets that can be pharmacologically exploited to lead to a better disease outcome has long been an aim of biomedical research. The technology and robotisation available have pushed the search for novel molecules to a high-throughput screening (HTS) context, making it possible to screen several hundreds of compounds or genes in a single day. High-content screenings (HCS) have added a refined complexity to the screening processes, as the information drawn from an image-based assay is more complete than the monoparametric readouts obtained in classical HTS assays. The development of HCS platforms to identify molecules influencing FOXO nuclear relocation and activation as pharmacological targets their applicability and the future directions of the screening field [118].

Pharmacogenomics and biomarker in drug development

Prognosis of patients with colorectal cancer (CRC) is affected by various factors at the time of diagnosis, including location of the tumor, gender, age and overall performance status of the patient. Predicting response and limiting drug-induced toxicity for patients with CRC are also critical. Interpatient differences in tumor response and drug toxicity are common during chemotherapy. Genomic variability of key metabolic enzyme complexes, drug targets and drug transport molecules are important contributing factors. At present, there is inconsistent and rather low use of pharmacogenetic testing in the clinical setting because of a lack of robust evidence or of resources [119]. Predicting response and limiting drug-induced toxicity are 2 important challenges faced by clinicians in the treatment of colorectal cancer (CRC). Introduction of genetic testing to individualize treatment regimens will hopefully allow better response prediction and limit drug-induced toxicity leading to improved patient outcomes [120]. Elevated circulating levels of chromogranin A (CgA) are found in the neuroendocrine tumors (NETs), but diagnostic usefulness of this marker is still debatable. To assess the role of CgA for the identification and follow up of gastroenteropancreatic neuroendocrine tumors (GEP-NET), a multicenter prospective longitudinal study has been carried out in Argentina [121]. Pharmacogenetics has gradually focused on studies of whole-genome single-nucleotide-polymorphisms screening associating disease pathophysiology with potential therapeutic interventions. Transcription profiling aiming at similar objectives has also been actively pursued, known as pharmacogenomics. It has become increasingly apparent that treatment effects between different genomic patient subsets can be dissimilar and the value and need for genomic biomarkers to help predict effects, particularly in cancer clinical studies, have become issues of paramount importance. Pharmacogenomics / pharmacogenetics has thus become intensely focused on the search for genomic biomarkers for use as classifiers to select patients in randomized-controlled trials [122].

Conclusion

Most genetic variation is determined by individual variation, not racial grouping, indicating race is not adequate as a surrogate to individualized therapy. Pharmacogenetic polymorphisms in the pathway may help identify patients at risk for associated toxicities and may serve as a guide for dose individualization. The unique advantages of the proposed method are its simplicity and low cost. Contrary to electrophoresis, hybridization provides sequence confirmation of amplified

fragments. The dry-reagent dipstick format minimizes the requirements for highly qualified personnel. Pharmacogenetics has made significant progress in the past decade, and many pharmacogenetic discoveries have now been included on FDA-approved drug labeling. Pharmacogenetic discoveries may further promote safe and effective use of medications by more accurately predicting an individual's drug response.

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