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Review On Pharmacological Outcomes For Pharmacogenomics Targeted Therapy

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Abstract

Pharmacogenomics, which examines the influence of genetic variations on drug reactions, has transformed personalized medicine. By customizing treatment to a person's distinct genetic profile, and pharmacogenetic data to fingerprint the pharmacological treatment of neuropsychiatric late-life conditions throughout the analysis of metabolizing enzymes and transporters of psychotropic drugs, mainly those of the cytochrome P450 (CYP) family. Pharmacodynamic response measures as treatment effects mediated through targets (i.e., receptors in the brain) may also contribute to this image. Drug treatment outcome represents a complex phenotype, encoded by dozens, if not hundreds, of genes, and affected by many environmental factors; therefore, we will almost always see a gradient of response. Phenotyping assays of blood enzyme activities (if feasible) are generally more successful than DNA genotyping for predicting unequivocal outcomes of drug therapy in each and every patient. Genotyping to predict drug disposition, efficacy, toxicity, and clinical outcome has been proposed, but the success of genotyping in individualized drug therapy currently appears unlikely because of the many shortcomings (frequency of DNA variant sites, ethnic difference differences, admixture), Genomics is an important tool in basic research; yet, it is unrealistic to include genotyping within the realm of tests available to the practicing clinician in the foreseeable future. Personalized medicine involves the selection of the safest and most effective pharmacological treatment based on the molecular characteristics of the patient. In the case of anticancer drugs, tumour cell alterations can have a great impact on drug activity and, in fact, most Pharmacogenomics studies how genetic affect drug responses and has revolutionized personalized medicine. Pharmacogenomics into clinical practice allows healthcare professionals to make better informed treatment choices, resulting in enhanced patient outcomes. according to a person's specific genetic makeup, pharmacogenomic targeted therapy seeks to enhance treatment effectiveness and reduce negative side effects. This review offers an extensive summary of the pharmacological results related to pharmacogenomic targeted therapy, emphasizing its advantages, obstacles, and future prospects.

Keywords

Adverse Drug Reaction, Bio Markers, Chemotherapeutic and Targeted Therapies, Polyploidy, Mutation, Pharmacogenetics, Personalized Medicine

Introduction

Pharmacogenomics has become an essential resource for enhancing drug treatments. By discovering genetic variations that affect drug responses, healthcare professionals can choose the best treatment approach for each patient. Pharmacogenomic directed therapy has demonstrated potential in numerous therapeutic fields, such as oncology, psychiatry, and cardiovascular medicine. Both lack of efficacy and toxicity of therapeutic agents are among the major obstacles to improving survival and quality of life of cancer patients. These are critical problems for all therapies but particularly for cancer treatment because most anticancer drugs are only effective in a minority of patients and have a narrow therapeutic index that frequently leads to severe toxicities and even death. By providing customized treatment plans based on each patient's own genetic profile, pharmacogenomics is transforming the medical industry. The development of targeted medicines for a number of illnesses, most notably cancer, has resulted from this strategy. Here are a few instances of recently developed targeted medications and illness treatments. Everything from human behavior to health is influenced by genetics. Variation in genetics is another factor contributing to the observed disparities among humans. Individual differences in the drug's pharmacokinetic and pharmacodynamic characteristics can also be attributed to genetic variances. In certain people, these genetic differences may be the cause of negative medication responses. By linking a medicine's toxicity or efficacy to gene expression or polymorphism, pharmacogenomics examines how genetic diversity affects pharmacological response.

a. Anaplastic lymphoma kinase (ALK) Inhibitors: Non-small-cell lung cancer is treated with ALK inhibitors, which include Crizotinib, Ceritinib, and Alectinib. These medications target certain genetic alterations, such as the EML4-ALK fusion gene, which affects 3-7% of patients with non-small-cell lung cancer.
b. EGFR Inhibitors: Non-small-cell lung cancer is treated with epidermal growth factor receptor (EGFR) inhibitors, including gefitinib, erlotinib, and Osimertinib. These medications target certain EGFR mutations, which are prevalent in individuals with non-small-cell lung cancer.
c. PD-1 Inhibitors: Non-small-cell lung cancer is one of the cancers that can be treated with PD-1 inhibitors, such as pembrolizumab and nivolumab. These medications function by releasing the immune system's brakes, which enables it to target cancer cells.
d. HER-2 Inhibitors: Breast cancer and other HER-2 positive malignancies are treated with human epidermal growth factor receptor 2 (HER-2) inhibitors, such as trastuzumab, deruxtecan, and tutatinib.
a. Key Stages of Pharmacogenomics in Drug Development
b. Phase I Clinical Trials: Pharmacogenetic testing informs patient selection, inclusion/exclusion criteria, and Dose range selection.
c. Phase II and III Clinical Trials: Pharmacogenetic test results inform dose modification and trial result interpretation;
d. Phase IV Clinical Trials: Analysis of reported adverse events with pharmacogenetic tests.
e. Target Identification: Pharmacogenomics aids in the identification and characterization of genes coding for drug targets, evaluating variability and potential impact on drug response.

Gene Variability in Drug Transporters:

Drug Transporter Genetic Polymorphism Drug transporters are membrane-spanning proteins that let drugs pass through the gastrointestinal tract, be excreted into bile and urine, and pass across the blood-brain barrier. Drug concentrations at the site of action and drug dispersion are impacted by genetic variations in the drug transport proteins. One transport protein that demonstrates genetic variation is P-GP (P-glycoprotein).

Function:

a. Anti-cancer substances are exported from cancer cells. encouraging chemotherapeutic resistance to many drugs protective function by the removal of harmful substrates from cells due to their position in hepatocytes, intestinal enterocytes, etc.

b. There are many polymorphisms in the MDRI gene. Exons 12, 21, and 26 of the MDR1 gene have common SNPs that result in polymorphism, for example. Patients with heart failure, cardiac arrhythmias, and digoxin dosage are affected by the polymorphisms in MDRI exons 21 and 26. This results in a higher concentration of digoxin in the body, which contributes to ADR.

Genetic Variability and Drug Metabolizer Mutations

Different subgroups within the population are created by genetic variations in drug-metabolizing enzymes, which vary in their capacity to carry out certain drug biotransformation activities. Genetic variations in drug metabolism are caused by variations in alleles for genes encoding the enzymes involved in drug metabolism. For instance, CYP2D6 genetic variation results in reduced metoprolol excretion. ADR results from this.

Phenotype

A phenotype is any of an organism's physical, physiological, biochemical, or behavioral traits. Any specific characteristic seen following medication administration is referred to as a phenotype in clinical pharmacology (Fig-I). But how simple is it to detect a phenotypic with certainty Phenocopy, or the same phenotype occurring in two people due to distinct genes or environmental variables contributing to that feature, is one issue. Many pharmacogenomics researchers are looking for phenotype-genotype associations in order to prevent the majority of serious adverse drug reactions (ADRs). If a phenotype (trait) is consistently linked to a particular genotype (an individual's genetic sequence), then a DNA test conducted prior to drug administration should prevent nearly all serious ADRs.

Genotype

The late 1990s saw the introduction of high throughput resequencing of every given gene, which sparked the discovery of an incredibly high number of DNA variant sites As a result, our entire understanding of "mutation" has evolved. The phrase "nucleotide substitution" has mostly been superseded by the word "single nucleotide polymorphism" (SNP). SNPs make about 90 to95% of all variation sites, whereas the remaining portion is made up of insertions or deletions (indels) of any number of bases, ranging from one to more than one million. The section of DNA that codes for a functional product is called a gene; it runs from the 5′ most regulatory element to the 3′ most regulatory element that surrounds the actual area that has been transcribed. Consequently, certain genes overlap, a gene may even be found inside another gene, and one gene may have many SNPs that are different from those found in the reference (consensus) allele of the same gene.

Table I Phenotypic Issues That Impact Research of Medication Phenotype-Genotype Associations

Issues	Example
Drug substrate specificity overlap	Enzymes that break down drugs, transporters of drugs, chaperones, receptors, ion channels, and transcription factors
Drug-drug interactions, many arising from pharmacogenetic differences	Drugs or other external substances that induce or inhibit enzymes
Developmental And environmental factors that can affect each step in drug disposition	Nutrition, age, sex, health and illness conditions, smoking, renal tubular excretion, exposure to chemicals, and over-the-counter natural items.
medications with many enzymes that are processed by genes that show functional Variations	The enzymes that bio-transform benzene [C6H6] are at least 14 and are encoded by as many genes as possible.

Illustrations of Pharmacogenomics in Practice

a. An anti-HER2: monoclonal antibody that only works in women who overexpress the HER2 protein is trastuzumab.
b. Warfarin: Pharmacogenetic testing helps determine dose changes by identifying genetic variants that impact warfarin metabolism.
c. Irinotecan: Genetic testing allows for dosage modifications by forecasting toxicity risk.

Instruction For Analysis:

Absence of Pharmacogenomics Education: It might be challenging to interpret and apply PGx testing since many healthcare professionals lack sufficient pharmacogenomics training.

Algorithms for Limited Dosage: Clinical practice must be guided by precise dose recommendations based on PGx findings.

Information Complexity: Patients and medical professionals may find the intricacy of pharmacogenomics data to be daunting.

Infrastructure and Data Analysis

a. Absence of Trustworthy Clinical-Genomic: Databases to direct PGx testing and interpretation, trustworthy databases and clinical practice standards are required.
b. Insufficient Information on Patient Awareness and Acceptance: Further study is required to determine whether PGx testing is acceptable to patients.

Expensive: The price of PGx testing may prevent its broad use, particularly in primary care settings.

d. Absence of Standardized Tests and Reports: In order to facilitate the integration and understanding of PGx data, standardized tests and reports are required.

Inadequate Integration with Current EHRs: Electronic health records must smoothly incorporate PGx data.

Pharmacogenetics

Exciting studies of gene-drug and gene-environment interactions have appeared over the past seven decades. Each of these apparent success stories represents a predominantly mono-genic trait in which the functional consequence of the gene was recognized, e.g. phenylthiol-urea nontaster, atypical serum cholinesterase, glucose-6-phosphate dehydrogenase deficiency, isoniazid slow N-acetylation, debrisoquine oxidation poor metabolizer, paraoxons low activity and thiopurine methyltransferase (TPMT) deficiency. Except for the first example (taste test), all the others represent a trait described as high versus low (to nil) drug- metabolizing enzyme (DME) activity (thereby clearing any drug substrate more slowly), with the high activity designated as the wild-type (reference, consensus) normally-occurring trait.

Pharmacogenetics And Psychotropic Medications Disorders

Almost one in five elderly people living in the community in the United States took psychotropic medicines, mostly antidepressants and then antianxiety drugs. Almost 2.5 million (7.5%) and almost 3 million (9.1%) of the elderly took antidepressants. Among these, people affected by dementia assumed greater number of CNS-active medications including anti- psychotics, anxiolytics, and antidepressants. The CYP2D6 metabolized the great number of CNS drugs including 80% of antidepressants.

Biomarkers Compound:

Biomarkers are biological molecules that indicate a normal or aberrant process, a condition, or a disease and can be discovered in blood, other bodily fluids, or tissues. They are employed to diagnose, track, and forecast the course of a disease or the effectiveness of a therapy.

A. Ensuring the accuracy and consistency of biomarkers through validation and standardization.
B. Integrating biomarkers into standard clinical treatment is the second step in the integration process.
C. Emerging Technologies: Finding novel biomarkers by utilizing proteomics, imaging, and genomics advancements.

Types:

1. Diagnostic biomarkers: These tell us if a disease or condition is present or not.
2. Prognostic biomarkers: Tell us how an illness or condition will probably turn out, no matter how it is treated.
3. Predictive biomarkers: Estimate the probability that a certain treatment will be effective.
4. Pharmacodynamic Biomarkers: Assess how a medication affects a biological mechanism.
5. Surrogate Biomarkers: These serve as stand-ins for endpoints with clinical significance.

Examples:

1. Genetic Biomarkers:

- Disease-related genetic alterations or changes.
- Abnormal amounts of particular proteins in blood or tissues are known as protein biomarkers.
- Modifications to metabolic pathways or metabolites are known as metabolic biomarkers.

Imaging Biomarkers: Imaging methods, such PET or MRI scans, can track the course of a disease or the effectiveness of a treatment.

Uses for Biomarkers:

1. Disease Diagnosis: Biomarkers help in early diagnosis and detection.
2. Personalized Medicine: Biomarkers predict response and help guide therapy choices.
3. Drug Development: Clinical trial design is informed by biomarkers, which also track the effectiveness of treatments.
4. Disease Monitoring: Biomarkers monitor how a disease develops and how well a therapy works.

Necessity Of Biomarkers for Individualized Care in The Elderly Population

In modern physical medicine, personalized treatment is quickly becoming a reality. The development of pharmacogenetically tailored treatment regimens that account for interindividual genetic differences is ongoing, even in older subjects, given the substantial advancements in our understanding of the biochemical, genetic, and neurobiological processes underlying major mental disorders. The avoidance of the start or progression of sickness and the reduction of the risk of harm associated with more complicated treatment regimens are thus added to the specific goals of therapeutic intervention. In psychiatry, there are currently no biomarkers measurable biological traits that indicate pathogenic processes or treatment responses or other risk markers that can be used to develop profiles that improve therapy selection and prediction.

Novel predictive biomarkers

The challenge of precisely determining the usefulness of the discovered markers or tactics for patients and healthcare systems is a significant constraint in pharmacogenomics. General recommendations have been proposed with a focus on omics-based markers, and the amount of evidence needed to prove that a marker is clinically valuable and should be adopted for routine usage has been examined. Drug selection and dosage for the majority of cancer treatments still adhere to standard operating procedures based on the general population, ignoring the unique traits of individual patients and tumor types. A common standard dose is administered to all patients for many targeted medications, and for many cytotoxic drugs, dose modifications are solely made by considering the patient's body surface area, which is frequently an incorrect dose indication. Finding biomarkers that predict the fate of anticancer drugs could significantly alter the situation, but there are significant obstacles to overcome and the work is not straightforward.

Personalized Medicine

Adapting Healthcare to Meet Individual Requirements Personalized medicine, referred to as precision medicine, is a healthcare approach that considers an individual's distinct traits, including genetic makeup, medical background, lifestyle choices, and environmental influences, to deliver customized treatment and prevention methods.

Key Aspects of Tailored Medicine

a. Genetic information: Examining a person's genetic data to discover variations that could influence disease vulnerability or treatment efficacy.
b. Medical background: Taking into account a person's medical background, including past diagnoses, therapies, and results.
c. Lifestyle and environmental elements: Considering a person's lifestyle, nutrition, and environmental exposures that could affect health
d. Biomarkers and diagnostic assessments: Utilizing biomarkers and diagnostic assessments to pinpoint specific disease features or treatment reactions.

Research on Populations and Customized Drug Treatment

Many of the hundreds of phenotype-genotype association studies of large populations that look into pharmacogenetic disorders or other complex diseases in humans have found that a certain trait is statistically significantly correlated with one or more SNPs. The results are shown as odds ratios (ORs) and confidence intervals (CIs). Consequently, it is evident that a single nucleotide site will practically never be effectively used clinically to predict and reduce each person's risk of ADRs for the reasons already mentioned. The average individual risk in the entire population can be inferred from large research, but the exact risk estimate for a given patient cannot. These outliers have been uncovered by the field of pharmacogenetics, and they are indeed a major factor driving the demand for individualized treatment.

Beyond the Genes

The study of heritable differences in medication response is known as pharmacogenetics. Pharmacogenomics, one of the Human Genome Project's byproducts, was just acknowledged as a field of study that is marginally distinct from pharmacogenetics. Pharmacogenomics describes how medications affect biological pathways and processes by interacting with the entire expression output of the genome; it has frequently been said that this field will aid in the development of new medications. A variety of recently developed "omics" disciplines of study are included in Table II.

Research on Populations and Customized Drug Treatment

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Table: II

New Phrase	Method	Research tool	Customized treatment
Genomics[a]	SNP analysis	Yes	Unlikely
Transcriptomics[b]	cDNA, microarray	Yes	Limited
Proteomics[c]	Protein analysis	Yes	Limited
Metabolomics	Metabolic profiling	Yes	Shows promise
Phenomics	Trait analysis	Yes	Shows promise

- The complexity of attempts at genotyping is revealed by DNA variant sites in the roughly 40,000 genes that make up the human genome.

- cDNA expression microarrays show what seems to be occurring in the specific tissue or cell type under investigation. C It is made possible by the proteome, which is made up of over 100,000 proteins that are produced by the genome.
- The metabonome displays the past and present. The best chance of realizing the long-term objective of genuinely "personalized medicine" may therefore lie in metabolite profiling, which appears to be the most accurate representation of each person's true phenotype, which is constantly changing with age, nutrition, illness, and drug therapy or chemical exposure.
- The whole range of biochemical, physiological, morphological, and behavioral traits that an organism can have is represented by its phenome.

Benefits of Pharmacogenomics Targeted Therapies:

a. Enhanced effectiveness: Pharmacogenomic targeted therapy can increase treatment effectiveness by recognizing patients who are most likely to benefit from a specific medication.
b. Decreased negative responses: By steering clear of drugs that may trigger adverse effects due to genetic predisposition, pharmacogenomic targeted therapy can reduce harm.
c. Improved efficacy: Pharmacogenomic targeted therapy can enhance treatment efficacy by identifying patients most likely to respond to a particular medication.
d. Reduced adverse reactions: By avoiding medications that are likely to cause adverse reactions based on genetic predisposition, pharmacogenomic targeted therapy can minimize harm.
e. Personalized medicine: Pharmacogenomics allows healthcare professionals to customize treatment approaches for each patient, resulting in more efficient and focused care.
f. Enhanced patient empowerment: Custom medicine motivates patients to engage actively in their health management.

2. Prospective Pathways:

a. Enhanced accessibility: Initiatives to improve access to genetic testing and pharmacogenomic knowledge are crucial for broad acceptance
b. Incorporating: pharmacogenomic information into electronic health records can enhance treatment decision-making.
c. Continued investigation: Further study is required to enhance our understanding of the intricate connections among genetic variants, medication response, and disease mechanisms.

Ethical Challenges:

Pharmacogenomics has a number of significant obstacles that fall into the general categories of practical execution, public policy, and ethical concerns.

- Informed permission: Since extensive genomic research necessitates a large volume of data, patient permission and possible genetic identification become issues.
- Genetic Data Ownership: Debates surround public vs corporate ownership of genetic information, influencing accessibility and study.
- Duty to Warn: Direct patient disclosure of genetic risks related to therapies is becoming more and more necessary.
- Regulatory systems: Rare genetic variations and customized therapies are difficult for current regulatory systems to handle.
- Affordability and Accessibility: The high expenses of genetic testing and developing customized drugs restrict the use of genomic technology. Legislators must strike a balance between the necessity of providing rare therapies to people who need them and the expense of developing them.
- Protection of Data Privacy and Security: It is essential to protect sensitive genetic data.
- Ownership and Access to Genetic Information: It is important to address the issues of who owns and benefits from genetic samples and data.
- Issues with Real-World Implementation
- The potential advantages of pharmacogenomics are achieved, these difficulties underscore the necessity of constant debate and innovation in the field.

a. The intricacy of analysing genetic data: incorporating genetic data into clinical practice calls for sophisticated equipment and knowledge.
b. Limited Clinical usefulness: Many medicines have little direct clinical usefulness, even with FDA- approved pharmacogenomic biomarkers, because of complicated genetic interactions or a lack of evidence
c. Developing therapies: uncommon genetic variations necessitate the use of cutting-edge techniques, such as transgenic animal models or patient-specific stem cells.

Pharmacological implementation in clinical changes:

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have authorized 190 and 155 medications, respectively, with labels that discuss the significance of genetic diversity and the growing clinical use of pharmacogenomic biomarkers. seven clinical facilities in Europe to examine how pharmacogenomic testing affects treatment results. 8100 individuals will be recruited in total, and 40 clinically significant PGx indicators from 13 significant pharmacogenes will be examined. Pharmacokinetically guided therapy will be administered to patients in one arm of the experiment, while traditional physiological and clinical measures will be used to treat patients in the other arm.

Limitations

1. Complexity of genetic variations: The intricacy of genetic variations and their interactions with environmental elements can create difficulties in interpreting pharmacogenomic information and Offering patients precise and useful insights regarding their genetic findings.
2. Restricted access to genetic testing: The availability of genetic testing and pharmacogenomic specialists may be constrained in some areas or healthcare facilities.
3. Expenses and reimbursement: The expenses associated with genetic testing and pharmacogenomic services may hinder widespread acceptance.
4. Data amalgamation and examination: Combining and scrutinizing extensive datasets from multiple origins.
5. Regulatory structures: Establishing regulatory structures to guarantee the safe and effective application of personalized medicine.

Result and Outcomes

a. Pharmacological Results

1. Oncology: Targeted therapy based on pharmacogenomics has enhanced treatment results in specific genetic mutations in cancer cells, multiple cancers, such as breast, lung, and colorectal cancer.
2. Psychiatric disease: Pharmacogenomics has aided in refining treatment approaches for mental health conditions, including depression and schizophrenia and Genetic testing to guide antidepressant selection.
3. Cardiovascular medicine: Pharmacogenomic targeted therapy has reduced adverse reactions and improved treatment efficacy in patients with cardiovascular disease.
4. Lifestyle and well-being: Offering tailored suggestions for nutrition, physical activity, and stress reduction and Genetic testing to guide anticoagulant dosing

Pharmacogenomics Enhances Treatment Results in various ways:

1. Personalized medicine: Examining a person's genetic makeup, pharmacogenomics allows healthcare professionals to customize treatment plans to fit their specific genetic traits.
2. Enhanced medication choice: Pharmacogenomics aids in determining the most suitable treatment for an individual patient, minimizing the need for trial-and-error methods.
3. Dose modification: Genetic data can inform ideal dosing, reducing side effects and enhancing effectiveness.
4. Minimized negative effects: By recognizing genetic variations liked to a higher likelihood of adverse reactions, pharmacogenomics can assist in preventing potentially harmful drugs.
5. Enhanced effectiveness: Pharmacogenomics can boost treatment effectiveness by pinpointing genetic variations that affect drug response.
6. Targeted therapy: Pharmacogenomics facilitates targeted therapy, allowing medications to be chosen according to the specific genetic traits of the patient's illness.
7. Minimized polypharmacy: Through improved medication choices, pharmacogenomics can lessen the necessity for various drugs, reducing possible interactions and negative side effects.

CONCLUSION

Personalized medication therapy is a primary goal of pharmacogenomics, and this article has explored why it appears unlikely to be successful in assisting the practicing physician in for the foreseeable future. The doctor wants to be able to confidently predict the phenotype (efficacy, toxicity, or therapeutic failure) in each of the patients treated with medication. The best genotyping and phenotyping assays now on the market may provide two or three false-negative results and two or three false-positive results for some patients; this is insufficient for the clinician. The decision-making process for choosing drugs represents a greater level of sophistication based on more technological discoveries and improvements, including CYP and drug transporter polymorphisms. In general, phenotyping using probe medicines to identify phenotype-genotype relationships has not been successful. It has been suggested that genotyping can predict medication disposition, efficacy, toxicity, and clinical outcome. However, due to the numerous drawbacks and complications discussed here, the success of genotyping in customized drug therapy currently seems doubtful. Despite being a valuable tool in fundamental research, genotyping is not likely to be included in the range of tests that practicing clinicians can use in the near future. The domains of proteomics and transcriptomics are comparable. There may be ways to predict and reduce each patient's risk for adverse drug reactions (ADRs) as well as the beginning and course of their illness using the recently developed domains of metabonomic and phenomics.

REFERENCES

1. Machado-Vieira R. Tracking the impact of translational research in psychiatry: state of the art and perspectives. J Transl Med. 2012;10:175.
2. Biomarkers definitions working group [corporate author]: biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.
3. Seripa D, Paroni G, Urbano M, et al. Pharmacogenetics in older people: what we know and what we need to know. J Nephrol 2012;25(Suppl 19):S38–S47
4. Christensen M, Andersson K, Dalen P, et al. The Karolinska cocktail for phenotyping of five human cytochrome P450 enzymes. Cli Pharmocol Ther 2003;73: 517-28
5. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther. 2007;32:113–121.
6. Brandl EJ, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotics. Can J Psychiatry. 2014;59:76.88.
7. Kirchheiner J, Nick Chen K, Bauer M, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry. 2004;9:442–473.
8. Nebert DW. Suggestions for the nomenclature of human alleles: relevance to ecogenetics, pharmacogenetics and molecular epidemiology pharmacognostic tics 2000; 10: 279-90
9. Roses AD. Genome-based pharmacogenetics and the pharmaceutical industry. Nat Rev Drug Discover 2002; 1: 541-9
10. Nebert DW. Transcription factors and cancer: an overview. Toxicology 2002; 181-182: 131-41
11. Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. UGT1A1*28 genotype and irinotecan- induced neutropenia: dose matters. J Natl Cancer Inst 2007; 99: 1290-5.
12. Ingelman-Sundberg M. Pharmacogenomic biomarkers for prediction of severe adverse drug reactions. N Engl J Med 2008; 358: 637-9
13. Cherkaoui-Malki M, Meyer K, Cao WQ, et al. Identification of novel peroxisome proliferator- receptor alpha (PPAR) target genes in mouse lives using cDNA microarray analysis Gene Expersion 2001; 9: 291-304 7
14. Greil W, Häberle A, Schuhmann T, et al. Age and adverse drugreactions from psychopharmacological data from the AMSP drug surveillance programme in Switzerland. Swiss Med Wkly.2013;143 13772.
15. Seripa D, Panza F, Daragjati J, et al. Measuring pharmacogenetics inspecial groups: geriatrics. Expert Opin Drug MetabToxicol. 2015;11:1073–1088
16. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies JAMA 1998; 279: 1200-5
17. Evans WE, McLeod HL. Pharmacogenomics: drug disposition, drug targets, 1
18. Goldstein DB. Pharmacogenetics in the laboratory and the clinic. N Engl J Med 2003; 348: 553-6

19. Ingelman-Sundberg M, Oscarson M, McLellan RA. Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. Pharmacol Sci. 1999;20(8):342–9. https://doi.org/10.1016/S0165- 6147(99)01363-2.
20. MacIntyre RJ, Fogleman JC. Molecular cloning of a family of xenobiotic-inducible drosophilid cytochrome p450s: evidence for involvement in host-plant allelochemical resistance. Proc Natl Acad Sci. 1997;94(20):10797–802. https:// doi.org/10.1073/pnas.94.20.10797
21. Kalow W, Meyer UA, Tyndale RF. Pharmacogenomics. New York: Marcel Dekker. 2001. 3 Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007; 370: 2020-9. 4 Keefe DM, Bateman EH. Tumor control versus adverse events with targeted anticancer therapies. Nat Rev Clin Oncol 2012; 9: 98-109.
22. Sim SC, Kacevska M, Ingelman-Sundberg M. Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects. Pharmacogenomics J 2013; 13: 1-11.
23. Reo NV. NMR-based metabolomics. Drug Chem Toxicol 2002; 25: 375-82
24. Freimer N, Sabatti C. The human phenome project. Nat Genet 2003; 34: 15-21
25. eripa D, Bizzarro A, Pilotto A, et al. Role of cytochrome P4502D6 functional polymorphisms inthe efficacy of donepezil in patients with Alzheimer's disease. Pharmacogenet Genomics. 2011;21:225–230.
26. Pilotto A, Franceschi M, D'Onofrio G, et al. Effect of a CYP2D6 polymorphism on the efficacy of donepezil in Alzheimer's disease patients. Neurology. 2009;73:761–767.