Review article

Pharmacogenomics- The Promise of Personalized Medicine

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Abstract

Introduction: Pharmacogenomics (PGx) is the study of the genetic basis of variability among individuals in response to drugs. It is the newest discipline of medicine and is becoming a very active area of research, with the pharmaceutical industry gaining experience applying it, integrating it into the drug development process, and also learning to better manage the expectations of the medical community. ***Methodology:*** A comprehensive review of the literature on the principles, applications, challenges and prospects of pharmacogenomics was performed. ***Results:*** Pharmacogenomics tailors therapies to the genetic makeup of an individual and can therefore offer treatments that are more efficacious and have fewer side effects. Despite these benefits, personalized medicine has not been embraced by large pharmaceutical companies. It is expected that the first wave of successful pharmacogenomics products will be used in acute treatments for which current therapies have and severe side effects. These products should also be good candidates for premium pricing. Personalized medicine (PM), based on the genetic makeup of a patient, may result in not only an improved therapeutic response but also a clinically important reduction in adverse drug reactions. The experience to date is mixed, with a few successes but many frustrations. ***Conclusion:*** However, for pharmacogenomics to be truly embraced, the benefits of this technology must become more widely accepted in terms of economic, public, regulatory and ethical issues.

Key Words: Pharmacogenomics, Applications, ethics, challenges, prospects

Introduction

There is an imperative need for the pharmaceutical industry to discover and market drugs that will allow patients to live longer and healthier lives. However, the pharmaceutical industry is facing a huge problem and some key challenges[1]. The outcome of drug therapy is often unpredictable, ranging from beneficial effects to lack of efficacy to serious adverse effects. Many environmental factors including genetic variation of human affects the delivery, distribution, persistence and activity of the drugs[2]. Thus the pharmaceutical industry is in desperate need of innovation, increased productivity, ways to better differentiate compounds from competitive compounds, and ways to bring better, safer, more efficient drugs to the market with lower costs of development[3]. Pharmacogenomics possess solution of all these quests.

Pharmacogenomics is the art of analyzing various genomic information (e.g. polymorphisms, gene expression, copy number, methylation and protein profiles) in assessing differential response to drugs[4]. The objective of such analyses is to detect evidence of variation in response to drug action and factors influencing the absorption, distribution, metabolism, and excretion of these chemical agents[5]. Pharmacogenomics, which is considered as an outgrowth of the Human Genome Project is the next research frontier and significant industrial investment is anticipated in this field[6].

What Is Pharmacogenomics?

Pharmacogenomics is an umbrella term that includes the use of genetics to optimize drug discovery and development. This term broadly refers to tailor-made drugs or personalized medicine-that is developing the right drug for the right people. Personalized medicine is the marriage of functional genomics and molecular pharmacology[7].

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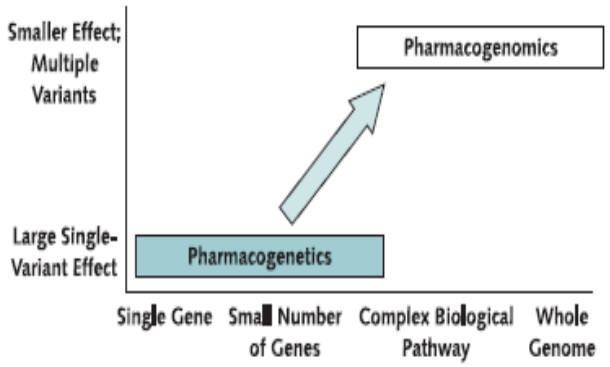
Pharmacogenomics seeks to find and decipher correlations between patient's genotypes (genetic profile) and their therapeutic responses. Pharmacogenomics uses these correlations to discover new and highly effective therapies tailored to specific genetic makeups[8]. The process involves identifying genes and their protein offspring as potential drug targets and then understanding the variations of the genes. Interest and funding in pharmacogenomics is largely fueled by growing evidence that an individual's genetic profile is and will continue to be the key predictor of how effective particular therapies are[9].

Pharmacogenomics focuses on large clinical effects of single gene variants in small numbers of patients. However, the concept of pharmacogenomics examines many genomic loci, including large biological pathways and the whole genome, to identify variants



that together determine variability in response to drug therapy (Fig 1)[10].

Fig 1: The concept of Pharmacogenomics

Personalized Medicine

Personalized medicine is the use of new methods of molecular analysis to better manage a patient's disease or predisposition toward a disease. It aims to achieve optimal medical outcomes by helping physicians and patients choose the disease management approaches likely to work best in the context of the patient's unique genetic and environmental profile[4]. Variations in human genome can influence how well a patient might respond to a particular drug. Personalized medicine hopes to use these variations to develop new safe and effective treatments for genetically defined sub-groups of patients. Treatments may include administration of drug therapy as well as recommendations for lifestyle changes that can delay onset of a disease or reduce its impact[1]. Personalized medicine also offers the possibility of improved health outcomes and has the potential to make healthcare more cost-effective. The natural variations (DNA polymorphisms) found in our genes play a role in our risk of getting or not getting certain diseases[7]. Understanding these genetic variations and their interactions with environmental factors will help researchers produce better diagnostics and drugs, and will help physicians better select treatments and dosing based on individual need[9].

Pharmacogenomics In Use

Pharmacogenomics is in use today to a limited degree. The cytochrome P450 (CYP) family of liver enzymes is responsible for breaking down more than 30 different classes of drugs. DNA variations in genes that code for these enzymes can influence their ability to metabolize certain drugs. Less active or inactive forms of CYP enzymes that are unable to break down and efficiently eliminate drugs from the body can cause drug overdose in patients[11, 12]. Today, clinical trials researchers use genetic tests for variations in cytochrome P450 genes to screen and monitor patients. In addition, many pharmaceutical companies screen their chemical compounds to see how well they are broken down by variant forms of CYP enzymes[13].

Another enzyme called TPMT (thiopurine methyltransferase) plays an important role in the chemotherapy treatment of common childhood leukemia by breaking down a class of therapeutic compounds called thiopurines. A small percentage of Caucasians have genetic variants that prevent them from producing an active form of this protein. As a result, thiopurines elevate to toxic levels in the patient because the inactive form of TMPT is unable to break down the drug. Today, doctors can use a genetic test to screen patients for this deficiency, and the TMPT activity is monitored to determine appropriate thiopurine dosage levels[14].

Market Justification

The pharmacogenomics vision includes three key goals: to increase efficacy and reduce risk to patients, to develop diagnostics that impact therapeutic decisions and improve patient care, and to improve clinical development outcomes[25]. These goals must all be accomplished while allowing for attractive economic returns. Pharmacogenomics products will remain unattractive to Big Pharma

Table 1: **Examples of clinical pharmacogenomic studies** [15]

Clinical condition or disease	Drug(s)	Genetic polymorphism (s)	Outcome	References
Alzheimer's disease	Tacrine	*APOE4*	*APOE4* homozygotes have poor responses compared with research subjects with other *APOE* alleles	16, 17, 18
Schizophrenia	Clozapine	5-HT2A receptor C102 allele	C102 homozygotes seem to respond better to the atypical antipsychotic clozapine	19, 20, 21
Coronary atherosclerosis	Pravastatin	Cholesteryl-ester transfer protein (CETP) with polymorphisms at the TaqB1 site (alleles B1 and B2); lipoprotein lipase (LDL); and β-fibrinogen	B1B1 homozygotes have a better response to pravastatin then either B1B2 heterozygotes or B2B2 homozygotes	22
Gastric or duodenal ulcers	Omeprazole and amoxicillin	*CYP2C19*	*CYP2C19* poor metabolizers responded more favourably to dual therapy than subjects with extensive metabolizer genotypes	23
Asthma	Zileuton and Montelukast	*ALOX5* genotype	Reduced response among heterozyogtes	24

(ALOX5, arachidonate 5-lipoxygenase; *APOE4*, apolipoprotein E4 allele)

unless the economic impact of having a smaller target market is offset by either decreased development costs or premium pricing[26]. Specifically, the attractiveness of pharmacogenomics to pharmaceutical companies relies on the following factors:

1. Lowered discovery and development costs through mare-targeted research efforts
2. Development of diagnostic tests those are accurate and economically justified
3. Justification for premium pricing
4. Sufficient market size
5. Payer support through adequate reimbursement
6. Surmountable marketing issues
7. Resolvable public and ethical issues

Social End Ethical Issues Regarding Pharmacogenomics

Pharmacogenomics is raising new issues in the hotbed of biotechnology. Although the toxicity model tries to maximize the population with the inclusion of as many genotypes as possible, the efficacy model of personalized medicine involves targeting patients with specific genotypes, which raises important ethical challenges. For example, in 2005, Nitro Med (Lexington, Massachusetts) launched the first "Black" drug, Bidil, specifically targeted to treat heart failure in African Americans[27]. Beyond the clear concerns of using skin color as a therapeutic category, the introduction of this drug also involves issues of fairness.

Both models (toxicity model and efficacy model) may also arouse fears about racism because, by nature, pharmacogenomics highlights the differences in genotype among individuals and populations. Certain types of genetic variations that are of importance in the metabolism of drugs are known to be more common in some ethnic groups than in others. If adverse responses are associated with a partic-

ular ethnic group, members of the group might suffer from stigmatization. Similarly, if one treatment serving an ethnic group comes to market more quickly than another, issues will certainly surface about placing greater "value" along racial lines. In adverse countries, it will be difficult to ensure that therapies for all ethnic groups are fairly addressed[28].

Personalized medicine also prompts concerns about the security and privacy of a patient's pharmacogenomics information. Among those concerns, issues relating to informed consent and secondary information are key[29].

Patients will more readily accept pharmacogenomics testing if their rights to consent to the testing are fully protected. First, the information gathered in pharmacogenomics tests, like that in many diagnostic or clinical lab tests that are now routinely administered with at most minimal informed consent, should theoretically carry no major risk of psychological harm. Second, in determining what information should be collected from patients, the benefits of diagnostic information and the costs to privacy should be balanced[30, 31].

Ethical Issues

The most important ethical issue that concerns pharmacogenomics is privacy of the study subjects [32]. Participants should be adequately informed about how their genetic material will be handled, what all tests may be done, how the data will be utilized, where the genetic material be stored and how secure the DNA banks are. They should have knowledge about the persons who will have access to their genetic material. They should also be told that their DNA may be required for future use and how that data will be maintained. Informed consent for future use should also be taken before hand. Privacy issues of family: A genomic study may need some information about subject's family, which may not be acceptable. Some critics are of the opinion that even the patient subjects should not be disclosed with their own genetic material to avoid the fear of future harm that may be predicted[33].

Better pharmacological care means better life expectancy. It may not be affordable for a common man. It is possible that only those who have money to afford the high expenses may benefit. Ethics demand equality, the cost of these pharmacogenomic techniques should be thus subsidised by the government. In countries like India where potable food is more important a public issue, is it worth allocating funds to learn how genes indicate a predisposition to disease and developing cures for the same? On the other hand in countries like USA, where adverse drug reactions account for major morbidity and hospitalisation (the fact that medicines are "a one-size fits- all", leading to adverse drug reactions can be avoided), a lot of which can be avoided if genetic profile is known and drugs given accordingly[34]. Initial high cost of technology development for genome analysis along with threat of losing one's autonomy needs to be reviewed. The interest of pharmaceutical companies in financial gains that they may have if treatment is highly specific with minimal adverse effects, could threat the valid research or threaten protection of the rights and well-being of individuals may become need of the hour. Genes are not the only thing, environment has its own role in pharmacokinetics and pharmacodynamics of drug response. Thus implicating everything on genetics and promoting drugs may not be ethically acceptable[35].

Legal Issues

With pharmacogenomics in future, some legal issues need to be discussed before full implementations occur. The person should know who owns the genetic data once he has given consent to analyse that. What is the legal liability if that data is stolen or lost or made public? Who is responsible for the damages? What is the compensation? Besides this, if he has not given consent for future use of his genomic data, and that is breached, what is the legality in such a situation? Can a person refuse for using his data without payment at any stage of drug development and use? How much is the doctor or hospital obliged to inform the person? One viewpoint is that the study subject should be informed only about the particular condition being tested and the rest should not be disclosed. i.e. person should not be told the future. What is the legal issue if discrimination is made by job providers or insurance firms[36]. In case the job providers know the person's gene data and avoids job (good for company as only best fitted individuals will be there to improve success but a loss for person who may have to face unemployement and switch over to malpractices) or insurance cover is avoided [37]. These issues need to be answered.

Social Issues

The economic burden of a new therapeutic science will be borne by the society. Knowing the genotype of the person will open the genotype of whole community of that person. Family tree can be constructed.Alot can be deduced from this family tree. This leads to breach in privacy of whole community whose consent is not taken[38]. This may also lead to formation of a group susceptible to a particular drug, having a possibility of a particular disease in future or having a predisposition to something not curable as per current standards. In one way it is good: the lifestyle modifications can be initiated early, the effective therapy can be started for prevention and treatment at the earliest and longevity can be expected. But other side is, if the person knows that someone a specific drug reaction such as interactions with other drugs and environmental factors. The influence of these factors will need to be determined before any conclusions are made about the genetic influence on how the drug is working [41].

Challenges

Pharmacogenomics is a developing research field that is still in its infancy. Several of the following barriers will have to be overcome before many phar

Limitations

Many genes are likely to be involved in how someone reacts to a drug. It means that targeting different drugs may be very complex. Everyone has small variations in their genes that do not cause any problem with the way that the gene works. Since these differences may influence drug metabolism or how the condition develops, the variations would need to be identified [40]. This process is very difficult and time consuming. In addition other factors may influ-

Table 2: Challenges of Pharmacogenomics[39]

Challenge	Potential Approaches
Establishing that drug responses are heritable	Twin studies; family studies Linkage between drug response and genomic loci in cell lines, or model Organisms
Defining candidate genes	Pharmacokinetic Pharmacodynamic Drug targets Biological milieu in which drugs act Disease genes and pathways Whole genome approaches
Defining drug responses	Biomarkers Surrogates “Hard” end points
Data management, including uniform representation of phenotypic data	Improved informatics Centralized, Web-accessible public database relating genetic variants and drug responses: www.PharmGKB.org
Reproducibility	Replication sets Large study populations
Statistical analysis of associations	New statistical methods, including consideration of haplotypes
Interrogating very large sets of polymorphisms in large numbers of patients	New platforms (e.g., chip- or bead-based)
Moving to practice	Reproducible study results Cost-effectiveness Health care provider education

time in future he will develop some cancer for which no treatment exists, he will die hundred deaths before that. Pharmacogenomic variations may lead to opening up of some constitutional issues like those of getting some special incentives or minority status[35].

Anticipated Benefits Of Pharmacogenomics

(a) More Powerful Medicines

Pharmaceutical companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases. This accuracy not only will maximize therapeutic effects but also decrease damage to nearby healthy cells [42].

(b) Better, Safer Drugs

Instead of the standard trial-and-error method of matching patients with the right drugs, doctors will be able to analyze a patient's genetic profile and prescribe the best available drug therapy from the beginning. Not only will this take the guesswork out of finding the right drug, it will speed recovery time and increase safety as the likelihood of adverse reactions is eliminated. Pharmacogenomics has the potential to dramatically reduce the the estimated 100,000 deaths and 2 million hospitalizations that occur each year in the United States as the result of adverse drug response [43].

(c) More Accurate Methods of Determining Appropriate Drug Dosages

Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics--how well the body processes the medicine and the time it takes to metabolize it. This will maximize the therapy's value and decrease the likelihood of overdose [44].

(d) Advanced Screening for Disease

Knowing one's genetic code will allow a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Likewise, advance knowledge of a particular disease susceptibility will allow careful monitoring, and treatments can be introduced at the most appropriate stage to maximize their therapy[45].

(e) Better Vaccines

Vaccines made of genetic material, either DNA or RNA, promise all the benefits of existing vaccines without all the risks. They will activate the immune system but will be unable to cause infections. They will be inexpensive, stable, easy to store, and capable of being engineered to carry several strains of a pathogen at once [46].

(f) Improvements in the Drug Discovery and Approval Process

Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. Previously failed drug candidates may be revived as they are matched with the niche population they serve. The drug approval process should be facilitated as trials are targeted for specific genetic population groups--providing greater degrees of success. The cost and risk of clinical trials will be reduced by targeting only those persons capable of responding to a drug [47].

(g) Decrease in the Overall Cost of Health Care

Decreases in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the length of time patients are on medication, the number of medications patients must take to find an effective therapy, the effects of a disease on the body (through early detection), and an increase in the range of possible drug targets will promote a net decrease in the cost of health care [48].

Expectations And Future Possibilities

Resurrecting Previously Failed Drugs

It has been reported that 10% of drugs are withdrawn in the years following FDA approval [49]. This statistic provides a great deal of motivation for resurrecting such drugs using pharmacogenomic knowledge. Most of these drugs are expected to be the ones that failed during clinical trials due to toxicity or lack of efficacy. Since the level of toxicity of a drug is confounded by the level of drug metabolism, there is a chance that by matching the drug dose to the genetic information, one can control the bounds on the toxicity and thus use such drugs for genetically selected responders. Therefore, for drugs that failed during clinical trial or at the discovery stage because of ADRs, pharmacogenomics provides hope for gaining a balance between the generality of a drug and its efficacy[50]. In other words, one could obtain an effective drug (i.e., less prone to causing ADR) by narrowing the scope of a drug to certain genetic groups [49].

Balancing Efficacy and Toxicity of Drugs

For a drug to be effective, it must be exposed to the tissue of interest at a critical concentration for a given period of time. Below this critical concentration, the drug is not expected to be effective. Above this critical concentration, there is a margin above which the drug could be toxic 51. This critical con-

centration and the associated margin (for effectiveness vs. toxicity) are functions of the drug dose and drug metabolism. Drug metabolism has been linked to genetic variation (e.g., the polymorphic cytochrome P450 enzyme). Pharmacogenomics could use such information on such polymorphisms to predict the correct dose for effectiveness of a drug [52]. In fact, many of the large companies are already considering pharmacokinetic variations [53] with the particular interest of drug effectiveness and toxicity [54]. In summary, there is great interest in fine-tuning the effective drug concentration to obtain a maximal effect and minimal toxicity. Cancer is considered to be an ideal condition for which to apply this approach, as subtle differences could account for notable differences between a particular dose of chemotherapy being toxic or effective[55].

Improved Generalization

Japanese pharmaceutical authorities require clinical trials on the Japanese population [13]. This bias toward a certain population could create a gap in the applicability of such products for other populations. Such biases are not always evident and overtly stated. For instance, similar biases do exist in drug development in the United States, where a majority of the drugs are tested on the Caucasian population. Such biases provide the basis for inefficacy of the drugs on other populations (e.g., the untested groups). Pharmacogenomics can provide guidance to those drugs being of use to other populations in two ways. The most obvious way would be to design drugs for different ethnic groups based on their genetic composition. However, this method has serious flaws. The more elegant way would be to bypass the dependency of the drug to population composition by screening for compounds that bind to all expressed variants of a target (if possible), thus eliminating the need for such a genetic test[56].

Strategic And Commercial Considerations

There are concerns in the pharmaceutical industry about generating potentially uninterpretable PGx results in a regulated environment. This has led sometimes to a "let's not generate data that we do not fully understand" attitude in relation to PGx research on pharmaceutical compounds. This attitude is gradually going away in view of the recognition that many of the PGx data generated are exploratory and probabilistic in nature, extremely difficult to replicate and to translate into clinical practice, and that in the long term more information, particularly about drug safety, is better. When thinking about the commercial attractiveness of PGx, critics often suggest that a more targeted approach to the identification of patients who might respond to therapy would "niche" those drugs, leading to a reluctance to embark on a given PGx study. In fact, utilizing a stratified approach (to identify the group of patients who might benefit from a particular therapy) may reduce new patient trials for some therapies 57. But this initial sales reduction may be offset by better compliance rates, ultimately higher product use, and pricing strategies that consider market size. One key variable is ensuring that PGx work is initiated sufficiently early to optimize a proactive approach to integration into development. Generally, the establishment of biomarker-driven endpoints within early phase clinical development may enable more efficient clinical trial design. Additionally, prospective introduction of PGx clinical endpoints can enhance the prospects for expedited drug approval, reduce development costs, and improve attractiveness to payers and prescribing physicians58. Therefore, in the short term, a PGx approach may provide a competitive advantage for pharmaceutical compounds and support better treatment practices through drug-linked diagnostics. But commercial viability may not be a question of what is gained or lost by moving forward with the development of biomarkers; rather, it may center around what is at stake by not moving forward with these approaches. While pipelines for many therapeutic areas are shrinking, a landscape review highlights the increasing infrastructure development in PGx and the initiation of product-specific work across a variety of therapeutic areas, indicating the awakening of the pharmaceutical industry [59]. So in the longer term, the utilization of biomarkers may improve prospects for significant new product development, in a time when there are fewer novel compounds in the pharmaceutical pipelines. Finally, as external groups apply more pressure on pharmaceutical companies to develop valuable new offerings, it may become a requirement to provide information that helps the regulatory agencies to ascertain which patient populations might benefit from the availability of a new drug. PGx is one means for providing such information to regulators and payers [60].

Conclusion

Pharmacogenomics is emerging as a boon for medical fraternity. Although many believe in the scientific value of pharmacogenomics, the industry still has

many skeptics. Some argue pharmacogenomics to be too complex. Other argues that although pharmacogenomics has incredible potential, people are too impatient in our desire to realize its promise. Pharmacogenomics will be an important factor in the future of medicine but cautions that the long discovery and development times in the industry means we must be patient before the benefits of pharmacogenomics are realized. There are numerous controversies concerning the utility of pharmacogenomics. While at a small scale and for a limited number of drugs, it may be possible to use genomic information to provide drugs that are more potent and have fewer side effects for certain individuals, generalizing this idea to the whole genre of medicine and treating pharmacogenomics as a panacea is the subject of much speculation and debate. However, before the full application of this branch, the higher authorities should frame and address the various social, legal, ethical issues along with incentives to overcome technical difficulties.

References

1. Cardon LR, Idury RM and Harris TJR. Testing drug response in the presence of genetic information: sampling issues for clinical trials. Pharmacogenetics 2000; 10: 503-510 http://dx.doi.org/10.1097/00008571-200008000-00003 PMid:10975604

2. Ingelman-Sundberg M. Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy. *J. Int. Med.* 2001; **250:** 186-200 http://dx.doi.org/10.1046/j.1365-2796.2001.00879.x PMid:11555122

3 Evans WE and Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999; **286:** 487-491 http://dx.doi.org/10.1126/science.286.5439.487 PMid:10521338

4. Classen DC, Pestotnik SL, Evans RS and Lloyd JF. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1997; **277:** 301-306 http://dx.doi.org/10.1001/jama.1997.03540280039031 PMid:9002492

5. McLeod HL and Evans WE. Pharmacogenomics: unlocking the human genome for better drug therapy. Annu. Rev. Pharmacol. *Toxicol.* 2001; **41:** 101-121 http://dx.doi.org/10.1146/annurev.pharmtox.41.1.101 PMid:11264452

6. March R. Pharmacogenomics: the genomics of drug response. *Yeast 2000*; **17:** 16-21 http://dx.doi.org/10.1002/(SICI)1097-0061(200004)17:1<16::AID-YEA6>3.0.CO;2-E

7. Norton RM. Clinical pharmacogenomics: applications in pharmaceutical R & D. *Drug Discov. Today 2001*; **6**: 180-185 http://dx.doi.org/10.1016/S1359-6446(00)01648-2

8. Patino CM and Martinez FD. Interactions between genes and environment in the development of asthma. *Allergy 2001*; **56**: 279-286 http://dx.doi.org/10.1034/j.1398 9995.2001.00135.xPMid:11284793

9. Persidis A. Pharmacogenomics. *Nature Biotechnol.* 2000; **18**: IT40-IT42 http://dx.doi.org/10.1038/80079

10. Rubenstein, Ken. Pharmacogenomics- Impact on drug discovery. Drug Market Development Reports, October. BioPortfolio, Frampton, Dorset, UK. 1999.

11. Lazarou J, Pomeranz BH and Corey PN. Incidence of adverse drug reactions in hospitalized patients: *a meta-analysis of prospective studies.* JAMA 1998; **279:** 1200-1205 http://dx.doi.org/10.1001/jama.279.15.1200 PMid:9555760

12. Lessard E et al. Influence of CYP2D6 activity on the disposition and cardiovascular toxicity of the antidepressant agent venlafaxine in humans. *Pharmacogenetics* 1999; **9:** 435-443 PMid:10780263

13. Hodgson J and Marshall A. Pharmacogenomics: Will the regulators approve? *Nat Biotechnol.* 1998; **16(2):** 13-21. http://dx.doi.org/10.1038/5143

14. Pistoi S. Facing your genetic destiny, part II. Scientific American. *February* 25, 2002. http://dx.doi.org/10.1038/scientificamerican0402-25

15. Issa AM. Ethical considerations in clinical pharmacogenomics research. *Trends Pharmacol. Sci.* 2000; **21:** 247-250 http://dx.doi.org/10.1016/S0165-6147(00)01493-0

16. Poirier J et al. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc. *Natl Acad. Sci. USA* 1995; **92:** 12260-12264 http://dx.doi.org/10.1073/pnas.92.26.12260 PMid:8618881 PMCid:PMC40336

17. Richard F et al. APOE genotyping and response to drug treatment in Alzheimer's disease. *Lancet.* 1997; **349:** 539-540. http://dx.doi.org/10.1016/S0140-6736(97) 80089-X

18. Rigaud S et al. The apolipoprotein E4 allele and the response to tacrine therapy in Alzheimer's disease. *Eur. J. Neurol.* 2000; **7:** 255-258. http://dx.doi.org/10.1046/j.1468-1331.2000.00073.x PMid:10886308

19. Arranz M et al. Association between clozapine response and allelic variation in 5-HT2A receptor gene. *Lancet.* 1995; **346:** 281-282 http://dx.doi.org/10.1016/S0140-6736(95)92168-0

20. Masellis M et al. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. *Neuropsychopharmacol.* 1998; **19:** 123-132 http://dx.doi.org/10 1016/S0893-133X(98)00007-4

21. Joober R et al. T102C polymorphism in the 5HT2A gene and schizophrenia: relation to phenotype and drug response variability. *J. Psych. Neurosci.* 1999; **24:** 141-146 PMid:10212557 PMCid:PMC1188995

22. Kuivenhoven JA et al. The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. New Engl. *J. Med.* 1998; **338:** 86-93 http://dx.doi.org/10.1056/NEJM199801083380203 PMid:9420339

23. Furuta T et al. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin. Pharmacol. *Ther.* 2001; **69:** 158-168 http://dx.doi.org/10.1067/mcp.2001.113959 PMid:11240980

24. Drazen JM et al. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nature Genet.* 1999; **22:** 168-170 http://dx.doi.org/10.1038/9680 PMid:10369259

25. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions. *JAMA 2001*; **286:** 2270-2279 http://dx.doi.org/10.1001/jama.286.18.2270 PMid:11710893

26. Moses H, Martin JB. Academic relationships with industry: a new model for biomedical research. *JAMA* 2001; **285:** 933-935 http://dx.doi.org/10.1001/jama.285.7.933 PMid:11180737

27. Peerson, H. 2004. First Black Drug Near Approval. Nature Online, July 23. Available at http://www.nature.com/news/2004/040719/full/040719-16.html

28. Emmanuel E, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000; **283:** 2701-2711 http://dx.doi.org/10.1001/jama.283.20.2701

29. Robertson JA. Consent and privacy in pharmacogenetic testing. *Nature Genet.* 2001; **28:** 207-209 http://dx.doi.org/10.1038/90032 PMid:11431685

30. Issa AM, Keyserlingk EW. Apolipoprotein E genotyping for pharmacogenetic purposes in Alzheimer's disease: emerging ethical issues. *Can. J. Psychiatry* 2000; **45:** 917-922 PMid:11190361

31. Albert SM, Sano M, Marder K. Participation in clinical trials and long-term outcomes in Alzheimer's disease. *Neurology* 1997; **49:** 38-43 http://dx.doi.org/10.1212/WNL.49.1.38 PMid:9222167

32. Williams-Jones B, Carriyan OP. Rheotoric and type: where's the ethics in pharmacogenomics? *Am J Pharmacogenomics.* 2003; **3(6):** 375-383. http://dx.doi.org/10.2165/00129785-200303060-00004 PMid:14672518

33. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials, Wright, Boston, 1996.

34. Kreeger KY. Scientific, ethical questions temper Pharmacogenomics. *The Scientist* 2001; **15**(12): 32

35. Bansal V, Kumar V, Medhi B. Future Challenges of Pharmacogenomics in Clinical Practice. *JK Science* 2005; **7**(3): 176-189.

36. Sterne JAC. Sifting the evidence - what's wrong with significance tests? *Br. Med. J.* 2001; **322:** 226-231 http://dx.doi.org/10.1136/ bmj.322. 7280.226 PMid:11159626 PMCid:PMC1119478

37. Lindpainter K. Pharmacogenetics and the future of medical practice. *Br J Clin Pharmacol.* 2002; **54:** 221 230. http://dx.doi.org/10.1046/j.1365-2125.2002.01630.x PMCid:PMC1874402

38. Roses AD. 2000. Pharmacogenetics and future drug development and delivery. *Lancet.* 2000; **355:** 1358-1361. http://dx.doi.org/10.1016/ S0140-6736(00)02126-7

39. Aronowitz RA. Making Sense of Illness: Science, Society and Disease. Cambridge Univ. Press, Cambridge, UK, 1998. PMCid:PMC 1496984

40. Bird TD, Jarvik GP and Wood NW. Genetic association studies: genes in search of diseases. *Neurology* 2001; **57:** 1153-1154 http://dx.doi.org/10.1212/WNL.57.7.1153 PMid:11591829

41. Bodenheimer T. Uneasy alliance: clinical investigators and the pharmaceutical industry. New Engl. *J. Med.* 2000: **342:** 1539-1544 http://dx.doi.org/10.1056/NEJM200005183422024 PMid:10816196

42. Bains W. The long-term value of genomics companies. *J. Chem. Technol. Biotechnol.* 2000; **75:** 883-900. http://dx.doi.org/10.1002/1097-4660(200010)75:10<883::AID-JCTB298>3.0.CO;2-8

43. Arledge T, Freeman A, Arbuckle J, Mosteller M and Manasco P. Applications of pharmacogenetics to drug development: the Glaxo Wellcome experience. *Drug Metab. Rev.* 1. 2000; **32:** 387-394

44. Becker RE. Modifying clinical trial designs to test treatments for clinical significance in individual patients. Clin. *Drug Invest.* 2001; **21:** 727-733 http://dx.doi.org/10.2165/00044011-200121100-00007

45. Cardon LR and Bell JL. Association study designs for complex diseases. Nature Rev. *Genet.* 2001; **2:** 91-99 http://dx.doi.org/10.1038/35052543 PMid:11253062

46. Primohamed M and Park BK. Genetic susceptibility to adverse drug reactions. Trends Pharmacol. *Sci.* 2001; **22:** 298-305 http://dx.doi.org/10.1016/S0165-6147(00)01717-X

47. Rioux PP. Clinical trials in pharmacogenetics and pharmacogenomics: methods and applications. Am. *J. Health Syst. Pharm.* 2000; **57:** 887-898 PMid:10840530

48. Roden, D. M. and George, A. L. The genetic basis of variability in drug responses. Nature Rev. *Drug Discov.* 2002; **1:** 37-44 http://dx.doi.org/10.1038/nrd705 PMid:12119608

49. Shah J. Enoconic and regulatory considerations in pharmacogenomics for drug licensing and healthcare. *Nature Biotechnol.* 2003; **21:** 747-753. http://dx.doi.org/10.1038/nbt0703-747 PMid:12833092

50. Todd JA. Interpretation of results from genetic studies of multifactorial diseases. *Lancet* 1999; 354 **(Suppl. 1):** 15-16 http://dx.doi.org/10.1016/S0140-6736(99)90243-X

51. McCarthy JJ and Hilfiker R. The use of single-nucleotide polymorphism maps in pharmacogenomics. *Nature Biotechnol.* 2000; **18:** 505-508 http://dx.doi.org/10.1038/75360 PMid:10802616

52. Ledley F. Can pharmacogenomics make a difference in drug development? *Nat Biotechnol.* 1999; **17:** 731.http://dx.doi.org/10.1038/11614 PMid:10429218

53. Marshall A. Getting the right drug into the right patient. *Nature Biotechnol.* 1998; **16(2):** 9-12. http://dx.doi.org/10.1038/5141

54. Kling J. US FDA contemplates collection of pharmacogenomic data. *Nat Biotechnol.* 2003; **21:** 590. http://dx.doi.org/10.1038/nbt0603-590aPMid:12776133

55. Smaglik P. Pharmacogenetics initiative galvanizes public and private sectors. *Nature.* 2001; **410:** 393-394. http://dx.doi.org/10.1038/35066732 PMid:11268220

56. Hodgson J and Marshall A. Pharmacogenomics: will the regulators approve? *Nature Biotechnolgy.* 1998; **16:** 243-246 http://dx.doi.org/10.1038/5143 PMid:9528002

57. Long AD and Langley CH. The power of association studies to detect the contribution of candidate genetic loci to variation in complex traits. *Genome Res.* 1999; **9:** 720-731 PMid:10447507 PMCid:PMC310800

58. Persidis A. The business of pharmacogenomics. *Nature Biotechnol.* 1998; **16:** 209-210 http://dx.doi.org/10.1038/nbt0298-209 PMid:9487533

59. Regaldo A. Inventing the pharmacogenomics business. Am. *J. Health Syst. Pharm.* 1999; **56:** 40-50

60. Butler D. Epidemiology set to get fast-track treatment. *Nature* 2001; **414:** 139 http://dx.doi.org/10.1038/35102713 PMid:11700517