International Journal of Medicine and Medical Sciences Vol 2. (4) pp. 091-096, April, 2009
Available online http://www.academicjournals.org/ijmms

Review

Pharmacogenomics: Benefits of personalized medicines

Avinash Puri

Post Graduate Institute of Medical Education and Research, Chandigarh, 160012, India. E-mail: avinash_puri@hotmail.com.

Accepted 26 February, 2009

Pharmacogenomics is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good, bad, or no response at all to a drug. It refers to the general study of all of the many different genes that determine drug behavior. It could also guide companies in designing clinical trials that would more definitively prove drug efficacy, in turn decreasing the time, costs, and risks of drug development. In the clinical setting, pharmacogenomics will help physicians to better define the long-term health risks that patients face, diagnose the stage of patient's diseases more precisely and predict patients' responsiveness to specific drugs more accurately or the likelihood for adverse events.

Key words: Pharmacogenomics, biomarkers, gene variations.

INTRODUCTION

Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. The term pharmacogenomics comes from the words pharmacology and genomics and is thus the intersection of pharmaceuticals and genetics. Pharmacogenomics has the potential to personalize medical therapies because it is based on genetic testing for predisposition to disease or response to therapeutic intervention (that is, a medication, or radiation therapy) (Evans and Johnson, 2001).

Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with knowledge of genes, proteins, an understanding of common DNA variations in the human genome (Evans and Relling, 1999). The concept underlying pharmacogenomics is that response to drug therapy is variable, in part because of genetic variation. The commonest genetic variations in the human genome (occurring in at least 1% of the population) are known as polymorphisms, and mutations of a single nucleotide are known as single nucleotide polymorphisms (SNPs). There are estimated approximately 11 million SNPs in the human population, with an average of one every 1,300 base pairs (Brookes, 1999).

More than one-third of human genes have been found to be polymorphic (Gelehrter et al., 1998). A change in the nucleotide sequence of a gene can lead to a change in the amino acid sequence of the protein and altered enzymatic activity, protein stability, and binding affinities (McCarthy and Hilfiker, 2000; Veenstra and Kollman, 1997). Genetic variation can thus affect drug efficacy and safety when the mutations occur in proteins that are drug targets (e.g., receptors), involved in drug transport mechanisms (e.g., ion channels), or are drug-metabolizing enzymes (Sadee, 1999). Pharmacogenomics utilizes knowledge of the patient genetic profile to influence decisions on treatment. It is considered by many to hold the key to the future of drug research, but some remain skeptical of its immediate impact. The use of pharmacogenomics will create medical, ethical, legal, and regulatory pressures that will cause diagnostic companies to develop rapid high throughput assays to optimize patient diagnosis. The impact of these changes will inevitably require the pharmaceutical and diagnostics industries to collaborate to meet future demands (Murphy, 2000).

Since Pharmacogenomics is the study of the variability in drug handling or response due to hereditary factors in different populations, the subjects' genotype may impact pharmacodynamics (drug concentration versus time versus pharmacological effect), pharmacokinetics (absorption, distribution, metabolism, and excretion) and/or the incidence of adverse events (Ma et al., 2002). The use of pharmacogenetic tests to determine this genetic variation can facilitate correct drug selection for treatment efficacy and minimize adverse events. A pharmacogenetic test is basically an assay intended to study individual variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, halotype markers, and alterations in gene expression or inactivation that may be cor-

related with pharmacological function and therapeutic response (Ingelman-Sundberg, 2001).

An individual's response to a drug is often linked to these common DNA variations. In a similar manner, susceptibility to certain diseases is also influenced by common DNA variations. Currently, much of the research in the field of pharmacogenomics is focused on genes encoding either metabolic enzymes that can alter a drug's activity or defective structural proteins that result in increased susceptibility to disease.

ROLE OF PHARMACOGENOMICS IN MEDICINES

Clinicians prescribe medicines through a trial-and-error method of matching patients with the right drugs. If the prescribed medication does not work for the patient initially, the clinician will try a different drug or dosage, repeating the process until the patient improves. As pharmacogenomics advances, clinicians will be able to prescribe medicines based on an individual patient's genotype, maximizing effectiveness while minimizing side effects.

The potential benefits of pharmacogenomics are considerable. Applying knowledge about an individual's inherited response to drugs to the design and development of commercial pharmaceuticals holds the promise that drugs may one day be tailor-made to each person's genetic makeup (Ingelman-Sundberg, 2001). The products of this "rational drug design" technology would replace current drugs that are intended to serve the entire patient population. Some of the advantages are listed below.

Useful medicines

With the help of pharmacogenomics we will be able to get benefit of medicines by pharmaceutical companies which can create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will help in drug discovery and allow drug makers to produce a therapy more targeted to specific diseases. This accuracy will maximize therapeutic effects and it can decrease damage to nearby healthy cells.

An example of a genetically specific drug has been introduced in the form of Herceptin (trastuzumab), which is used in the treatment of breast cancer. Herceptin is only effective in women with a genetic defect which results in the overproduction of a molecule known as the HER2 receptor. When present in excessive numbers on the surface of certain breast cells, these receptors promote cellular growth, leading to tumours. Herceptin is directed against the receptor; it therefore only helps women who have an increased number of copies of the relevant gene. In all other women this highly specific drug is much less effective (Lindpaintner, 2001).

Better and safer drugs

Instead of the standard trial-and-error method of matching patients with the right drugs, clinicians 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 reduce deaths as a result of adverse drug response (Lazarou et al., 1998).

Accuracy of drug dosages

Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics means 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.

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 particular disease susceptibility will allow careful monitoring, and treatments can be introduced at the most appropriate stage to maximize their therapy (Pharmacogenomics, 2003).

Pharmacogenomics into DNA/RNA vaccines and drugs

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 (McLeod and Evans, 2001).

In recent years, researchers have been keenly aware of the increasing demand for new medicines, vaccines, and biologicals to meet the needs of patients. They have focused on both pediatric indications and diseases of the elderly. Diseases involving metabolic syndrome, osteoporosis, osteoarthritis, rheumatoid arthritis, and multiple myeloma are just a few that require comprehensive treatment, including ongoing diagnostic assessments and drug therapy to manage patients' well being.

Metabolic syndrome: Metabolic syndrome plays a critical role in a large number of illnesses ranging from pediatric disorders to diseases of the elderly. Complications from this condition lead to hardening of the arteries and an increased risk for cardiovascular and kidney disease. A combination of interrelated metabolic risk factors that occur in one person defines metabolic syndrome, e.g., physical inactivity, obesity, atherogenic dyslipidemia

(unhealthy lipid levels), elevated blood pressure, abnormal blood sugar, prothrombotic state (high fibrinogen or plasminogen activator inhibitor [-1] in the blood), and proinflammatory state (elevated high-sensitivity C-reactive protein in the blood). Therefore, metabolic syndrome frequently results in type-2 diabetes, coronary heart disease, stroke, and other diseases related to plaque build-ups in artery walls. Furthermore, researchers are investigating genetic factors that contribute to the development of metabolic syndrome. A comprehensive approach to the treatment of many of these diseases offers the best chance for enhancing quality of life. Long-term patient monitoring, drug therapy, and dietary control can prolong the onset of complications such as kidney failure, heart attack, paralysis, and coma. Although recent discoveries show progress in diseases related to metabolic syndrome, pharmaceutical and diagnostic companies will continue to invest in improving diagnostic tests and drug treatment options for many diseases related to metabolic syndrome.

Osteoporosis: Osteoporosis has been an underdiagnosed disease affecting elderly women, but diagnosis and treatment have improved significantly during the past decade. Technology for bone mineral density measurements have improved diagnoses, while new drugs (alendronate, risedronate, raloxifene, calcitonin, cyclical etidronate) have augmented or replaced traditional calcium and vitamin D supplementation therapy. Unfortunately, calcium therapy declined from 43% in 1994 to 24% in 2003, although clinicians agree that it remains a necessary part of therapy for this disease (Hetherington et al., 2002). Furthermore, in 2002, the Women's Health Initiative (WHI) published a study that showed that long-term use of hormone replacement therapy increases the risk of cancer and cardiovascular disease. These developments underscore the need for a comprehensive approach to the treatment of osteoporosis that takes into account diagnostic assessments, drug therapy, quality of life, and potential long-term risks (IMS Health, 2003).

Multiple myeloma: Multiple myeloma is an incurable bone marrow cancer that has a devastating effect on the elderly; however, recent clinical trials have shown that combination drug therapy is showing positive results and Increasing survival. The use of thalidomide and the steroid dexamethasone reduces antibody-like proteins that are an indicator of the disease. Diagnostic tests used to detect an elevation in these proteins include routine blood tests and the monochromal or myeloma protein test. Thalidomide is used "off label" for multiple myeloma while a new drug that works through an entirely different mechanism, Velcade (bortezomib) is available. Both drug therapies have improved patient outcomes, while stem cell research shows promise as a potential cure. Some Institutes of Health trial are evaluating the use of "tandem" stem cell transplants to destroy the cancer. Another innovative approach being studied uses high doses of drugs first, followed by one stem cell transplant from a donor where the donor's immune system is the source of the immune therapy.

Drug discovery

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. Targeting only those persons capable of responding to a drug will reduce the cost and risk of clinical trials

Reduction in the cost of health care

There will be decrease in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the duration of medication for effective therapy, and an increase in the range of possible drug targets will promote a net decrease in the cost of health care.

PRESENT SCENERAIO

The cytochrome P450 (CYP), family of liver enzymes is responsible for breaking down more than 30 different classes of drugs. Cytochrome P450 enzyme group which exists in many forms among individuals because of genetic differences (Tucker, 1994). The substrate specificites of the P450 enzymes appear to be due to the nature of the aminoacid residues, size of the aminoacid side chain, polarity and charge of the amino acids (Neigishi et al., 1996). For example Cytochrome P450IA2 is involved in the oxidation of Caffeine and cytochrome P450IID6 is involved in the oxidation of drugs, such as codeine, propanol and dextromethorphan. The well known cytochrome P450IID6 is responsible for debrisoquine metabolism among individuals showing genetic polymorphism (Rahmani et al., 1993).-

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. 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 (Hodgson and Marshall, 1998).

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, clinicians can use a genetic test to screen patients for this deficiency, and the TMPT activity is monitored to determine appropriate thiopurine dosage levels (Pistoi, 2002).

One of the first examples of genetic variations is in genes encoding cytochrome P450 enzymes. Some drugs which are metabolized by CYP2D6 (P-450IID6) are codeine, flecainidr, dextromethorphan, imipramine and other cyclic antidepressants that undergo ring hydroxyllation. The CYP2D6 gene, which is well characterized for controlling key pathways of drug metabolism, is expected to be important to clinical medicine (McLeod et al., 2000). Mutations of the CYP2D6 gene are responsible for varying degrees of metabolism; the most clinically significant are ultra- rapid and poor metabolizer phenotypes. Two examples during drug treatment include a slowing in progression of coronary atherosclerosis in B1/B1 homozygotes receiving pravastatin compared with B2/B2 homozygotes, (Kuivenhoven et al., 1998) and caucasian males with HLA b57 variant were at increased risk for experiencing hypersensitivity to abacavir. Genotyping of this kind has shown value in a few specific cases. Many researchers suggest that it will play a more vital role in drug metabolism, seen as the most likely areas for exploration.

The key to the most significant advances that might affect clinical diagnosis will be the pharmacodynamic effects of drug therapy, and the potential reduction of adverse events. Challenges to routine adoption of this approach include cost of genotyping to the patient and technical feasibility. Nevertheless, the potential for an influx of drug-diagnostic combinations in the pipeline is significant. For example, researchers in the area of psychiatry have largely exhausted traditional pathways for discovery, and will likely pursue broad searches of the human genome for new development targets. It is hoped that advances in technology will facilitate the search for new targets across the genome, resulting in clinical studies aimed at identifying pharmacodynamic markers of drug response. These specific areas of medicine are where pharmacogenomics should have a profound impact on mainstream clinical practice versus traditional drug discovery techniques (Hetherington et al., 2002).

Other experts are focused on the socioeconomic impact regarding the availability and use of genetic information. Some experts provide an advice on specific issues related to the development and regulation of medicines and the provision of tests and medicines as well as the use and storage of genetic information. The handling of this information might impact pharmaceutical and diagnostic companies.

The application of subject-specific genetic information goes beyond whether a subject is a "responder" or "non-responder." In fact, the available data could predict the degree to which a subject will actually respond. Diagnostic tests may therefore play an integral role in selecting an ideal drug therapy or combination therapy, and help predict the therapeutic outcome.

i.) The use and storage of genetic information will be controlled more closely through government regulation. Diagnostic companies will have to validate processes associated with managing this information to protect patient confidentiality.
ii.) If an argument can be made for genotyping subjects prior to enrollment in a clinical trial to reduce screening failures, the FDA may expect sponsors of clinical trials to incorporate pharmacogenetics testing in protocols.

For diagnostic testing to be fully accepted in this area, it must provide an economical, rapid, and accurate solution. Advances in molecular technology must lead to the development of equipment which has a high samples throughout. Additionally, it is preferable to analyze multiple SNPs in one sample, and this will be possible with the advancement of multiplex and chip technology. However, regulatory authorities will require thorough validation of these tools, to demonstrate both standardized manufacture and clinical efficacy.

Biomarkers

A biomarker is defined as a characteristic that is objecttively measured or evaluated as an indicator of a normal biologic process, a pathogenic process, or a pharmacological response to a therapeutic intervention. The development pipeline shows an increasing number of compounds that rely on biomarker evaluations in their decision process. Drugs will be developed in concert with simple and reliable tests for molecular markers, which demonstrate continuing efficacy. Given these observations, the impact of newly discovered biomarkers on clinical diagnostics is likely to evolve toward an inter-dependent dynamic between new drugs and new diagnostics.

There is a high level of interest among pharmaceutical and diagnostic companies in biomarker research. One of the most important areas where biomarkers can impact the drug development process is in clinical trials (Biomarkers Definitions Working Group, 2001).

The pharmaceutical industry typically develops 10 drugs through various stages of clinical development for every one that enters the marketplace. For years, researchers have worked toward improving those odds. The use of biomarkers in early phase clinical trials potentially improves the odds by providing definitive information regarding safety and efficacy leading to informed go/no-go decisions. Biomarkers help to reveal disease targets, show biochemical pathways, and confirm mechanisms of drug action. For example, oncology researchers incorporate biomarkers such as CA 125 (ovarian cancer), CA 15-3, and 27-29 (breast cancer), CEA (ovarian, lung, breast, pancreas, and gastro-intestinal tract cancers), and PSA (prostate cancer) in many clinical trial protocols.

Therefore, drugs with the highest probability of success are developed further while other compounds are discontinued. Increasingly, FDA is encouraging pharmaceutical companies to utilize bio-markers as surrogate endpoints to predict clinical benefit/harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. Much attention is now focused on biomarkers present at the cellular level, such as cytokines.

As new drug candidates advance through the phases of clinical development, newly discovered esoteric biomarkers demonstrate their value as sensitive indicators of both efficacy and, occasionally, safety. However, in late-phase development only the most valuable biomarkers become surrogate endpoints in clinical trials. The challenge faced by drug developers is to identify "high value" biomarkers for specific disease indications and incorporate them into early phase protocols. Diagnostic companies are partnering with pharmaceutical companies to develop and validate comprehensive menus of esoteric and nonesoteric biomarker assays to support their drug development programs.

Again, as with pharmacogenetic testing, the diagnostic challenge for biomarkers is an economical, accurate, and rapid testing solution. The advent of proteomics will no doubt provide an increasing spectrum of biomarker candidates. The move to multiplexing will allow multiple biomarkers to be analyzed in one sample. When this develops into a fully automated technology, multiple markers will be screened in thousands of patients. For example, one leading pharmaceutical company is currently researching a biomarker that has the potential to characterize the action of their drug in the treatment of atherosclerosis. Individuals who are at risk for coronary artery disease may benefit from a newly discovered breakthrough involving the enzyme Lp-PLA2. Lp-PLA2 usually binds to LDL cholesterol in the blood and has been found to be present in atherosclerotic plaque. Lp-PLA2 is believed to sequester inflammatory mediators leading to coronary heart disease. A drug is being developed that will block this mechanism, resulting in improvement of the patient's condition (Kuivenhoven et al., 1998).

Major markets where biomarkers are being widely used and developed include oncology, hematology, HIV/AIDS, diabetes, and heart disease. Pharmaceutical and diagnostics companies are investing hundreds of millions of dollars in biomarker research, with the hopes of developing drugs that effectively treat many challenging diseases.

Hurdles in pharmacogenomics

Pharmacogenomics is a developing research field that is still in its infancy. Several of the following barriers will have to be overcome before benefits of pharmacogenomics can be realized.

Gene variations: Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered. SNPs occur every 100 to 300 bases along the 3-billion-base human genome, therefore millions of SNPs must be identified and analyzed to determine their involvement (if any) in drug response.

Further complicating the process is our limited knowledge of which genes are involved with each drug response. Since many genes are likely to influence responses, obtaining the big picture on the impact of gene variations is highly time-consuming and complicated.

Drug alternatives: Only one or two approved drugs may be available for treatment of a particular condition. If patients have gene variations that prevent them using these drugs, they may be left without any alternatives for treatment.

Education: Introducing multiple pharmacogenomic products to treat the same condition for different population subsets undoubtedly will complicate the process of prescribing and dispensing drugs. Physicians must execute an extra diagnostic step to determine which drug is best suited to each patient. To interpret the diagnostic accurately and recommend the best course of treatment for each patient, all prescribing physicians, regardless of specialty, will need a better understanding of genetics.

PERSPECTIVE

The newly emerging genomic technologies enable the search for relevant genes and their variants to include the entire genome and help in the search for candidate genes. Moreover pharmacogenomic analysis can identify the disease susceptibility genes representing potential new drug targets. The current concept of drug therapy is to apply treatment for a large population group whereas application of pharmacogenomic will help individual application of drug therapy or on smaller patient sub population. But whether this individualized medicine will lead to improved and economically feasible therapy is yet to be seen. These new approaches to drug discovery and treatment will steer the pharmaceutical and diagnostic industries closer together. It holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety.

In the future, researchers have the potential to subdivide each disease according to genetics, not symptoms. Specific diagnoses may be based on the molecular mechanisms involved rather than clinical presentation. Molecular mechanism differences will subdivide patient groups with common diseases like hypertension, diabetes, and cancer. Health care professionals will use genetic tests to predict how a disease will progress and the therapeutic response to anticipate.

Drug development will be based on understanding of molecular pathogenesis. The role of genes in determining disease susceptibility, progression, complications and response to treatment could all be potentially mapped. Pharmacogenomics will yield drugs targeted to act at or near the cause of a disease. Genetically defining patient populations will help improve outcomes and genetic prognostics will revolutionize treatment and improve cost effectiveness. Pharmacogenomics is already making an impact in a wide array of disease states and drug therapy; it will eventually become part of standard patient management in selecting and monitoring drug therapy. Pharmacogenomics will definitely help us to sharpen our medical and pharmaceuticals tools. Drugs will become more precise and efficient and the risk of toxic side effects will be reduced. But at the same time increasing amounts of information and databases will be collected, which may be put to a variety of uses.

REFERENCES

Evans WE, Johnson JA (2001). Pharmacogenomics: the inherited basis for interindividual differences in drug response. Annu. Rev. Genomics. Hum. Genet. 2:9-39.

Evans WE, Relling MV (1999). Pharmacogenomics: translating functional genomics into rational therapeutics. Sci. 286:487-491.

Brookes AJ (1999). The essence of SNPs. Gene. 234:177-186

Gelehrter TD, Collins FS, Ginsburg D (1998). Principles of Medical Genetics. 2nd ed. Baltimore, Md: Williams, Wilkins. pp.431-436

McCarthy JJ, Hilfiker R (2000). The use of single-nucleotide polymorphism maps in pharmacogenomics. Nat. Biotechnol. 18: 05-508.

Veenstra DL, Kollman PA (1997). Modeling protein stability: a theoretical analysis of the stability of T4 lysozyme mutants. Protein Eng. 10: 789-807.

Sadee W (1999). Pharmacogenomics. BMJ. 319:1-4.

Murphy MP (2000). Current pharmacogenomic approaches to drug development. Pharmacogenomics. 1(2):115-123.

Ma MK Gustafson Jk, Eric C (2002). Genetic basis of drug metabolism. Am. J. Health. Syst. Pharm. 59(21): 2061-2069.

Ingelman-Sundberg M (2001). Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy. J. Int. Med. 250:186.

Ingelman-Sundberg M (2001). Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy. J. Int. Med. 250:186.

Lindpaintner K (2001). Pharmacogenetics and the future of medical practice: conceptual considerations. Pharmacogenomics 1: 23-26.

J Lazarou, BH Pomeranz, PN Corey (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 279(15):1200-1205.

Pharmacogenomics (2003). Social, Ethical, and Clinical Dimensions, edited by Mark Rothstein. p. 384.

McLeod HL, Evans WE (2001). Pharmacogenomics: unlocking the human genome for better drug therapy. Annu. Rev. Pharmacol. Toxicol. 41: 101-121.

S Hetherington, AR Hughes, M Mosteller, D Shortino, KL Baker, W Spreen, E Lai, K Davies, A Handley, DJ Dow, ME Fling, M Stocum, C. Bowman LM Thurmond, AD Roses (2002). Genetic Variations in HLA-B Region and Hypersensitivity Reactions to Abacavir, Lancet. 359- 1121.

The Global Pharmaceutical Market? (2003). Current and future trends (IMS Health: MIDAS, MAT, Dorfplatz 4 T6330 Cham, Switzerland,

Tucker GT (1994). Clinical applications of genetic polymorphism in drug metabolism. J. Pharm. Pharmacol. 46(Suppl): 417-424.

Neigishi M, Tomohide U, Darden TA, Sueyoshi T, Pedersen LG (1996). Structural flexibility and functional versatility of mammalian P450 enzymes. FASEB J. 10:683-689.

Rahmani R, Zhou XJ (1993). Pharmacokinetics and metabolism of vinca alkaloids. Cancer surv. 17:269-281.

J Hodgson, Marshall A (1998). Pharmacogenomics: will the regulators approve? Nat. Biotechnol. 16: 243-246.

S Pistoi (2002). Facing your genetic destiny, part II. Sci. Am.

HL McLeod, EY Krynetski, MV Relling, WE Evans (2000). "Genetic Polymorphism of Thiopurine Methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia," Leukemia. 14 (4): 567-572.

JA Kuivenhoven, JW Jukema, AH Zwinderman, P de Knijff, R McPherson, AVG. Bruschke, KI Lie, JJP Kastelein (1998). The Role of a Common Variant of Cholesteryl Ester Transfer Protein Gene in the Progression of Coronary Atherosclerosis, New Engl. J Med. 338: 86-93.

Biomarkers Definitions Working Group (2001). Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin. Pharmacol. Therap. 69(3): 89-95.