# Pharming the Genome

## IMPLICATIONS OF PHARMACOGENOMICS FOR HUMAN HEALTH AND PUBLIC POLICY

### Conference Report

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# INTRODUCTION

At the crossroad of genomics and medicine, pharmacogenomics is sometimes presented as getting the right medicine at the right dosage to the right patient. It is often referred to as personalized genetic medicine. Pharmacogenomics aims to define the genetic determinants of drug effects. It has the potential to translate knowledge of human genome variability into better therapeutics and to yield a new set of molecular diagnostic tools that can be used to individualize and optimize drug therapy.

Pharmacogenomics has tremendous commercial potential with an expected market of $10 billion by next year. It could bring numerous benefits to patients and the health care industry by increasing the number of new drugs and reducing the costs of drug development. The application of pharmacogenomics could reduce adverse drug reactions by up to 25%, saving the health care industry more than $1 billion per year by 2010.

To exploit the opportunities in genetic medicine, novel technologies will be needed, legal and ethical questions must be clarified, health care professionals must be educated, and the public must be informed about the implications of genetic testing in drug therapy and disease management. For a country with a universal health care policy, such as Canada, there is also the question of weighing the medical and economic benefits offered by targeted interventions against the cost of genotyping all individuals in order to direct an intervention to only a few.

On Thursday, November 4, 2004, the Canadian Biotechnology Strategy community (with the Canadian Biotechnology Secretariat, Health Canada, Industry Canada, the Canadian Institutes of Health Research, Institute of Genetics and Genome Canada) held a one-day event to examine the implications of pharmacogenomics for human health and public policy. The objectives were to:

- improve understanding of the implications of advances in pharmacogenomic research for the practice of medicine in diagnosis and treatment; healthcare costs, roles of health service providers, and patient confidentiality and protection of information;
- provide an opportunity for high-level policy discussions among leading researchers, industry representatives, academics, NGOs, and senior government officials; and
- lay the groundwork for engaging the Canadian public in a broader discussion of the public policy issues raised by advances in pharmacogenomics.

The conference included panel sessions on innovation, health, and ethics, as well as keynote presentations on the application of pharmacogenomics by the pharmaceutical industry, and the Canadian Biotechnology Advisory Committee's proposed policy framework for biotechnology-based health innovation.

# Plenary Speaker

## IMPLICATIONS OF PHARMACOGENOMICS FOR HUMAN HEALTH AND PUBLIC POLICY

**Dr. Kevin Cheeseman,**
**Director, Pharmacogenomics Development, AstraZeneca**

***Summary:*** *Dr. Cheeseman discussed how drug companies use pharmacogenomics (or pharmacogenetics) in efficacy and safety testing, and the ethical issues surrounding this field.*

### Applying pharmacogenomics

Drug development is lengthy, expensive and inefficient. The average time to identify a target for drug development, obtain regulatory approval, and market it is 11 years. The average cost is about a billion dollars. Only one compound in nine tested in the clinic reaches the market.

Pharmaceutical companies want to increase the efficiency and speed of throughput along the pipeline. New drugs may fail for various reasons: because of inappropriate pharmacokinetics (PK), because of lack of efficacy – i.e., they don't work – or due to problems with toxicology and safety. The earlier problems can be identified, the more money can be saved.

AstraZeneca uses pharmacogenomics to address all of the above issues. The most well established area of pharmacogenetics is using it to understand PK. This involves identifying the genes for enzymes involved in metabolizing a compound of interest, and then analysing patients' DNA samples to find out if a genetic variant can explain any inter-individual variability in PK.

Using pharmacogenetics to study variability in drug efficacy is less routine because it involves studying genetic variation in drug targets (receptors, enzymes, etc.) that, in contrast to drug metabolizing-enzymes, tend to be unique for each drug (or drug class). The pharmacogenetics of adverse drug reactions is the most problematic because it is seldom obvious which gene or genes to study. Nevertheless, successful examples of this approach do exist.

## Efficacy testing

In any patient population, there are responders who benefit from a drug, super-responders who benefit more, and non-responders who get no clinical benefit. If there is variability in efficacy results from phase two studies, a drug company can search for an association between genotype and clinical outcomes. If there is a real genetic basis to the variability, they can design phase three trials on the basis of genetic screening. When non-responders are excluded, phase three trials can be smaller, faster and cheaper. However, a company will need a diagnostic test to identify the responders from the non-responders. It must decide:

- Should it continue clinical development by developing a diagnostic?
- How to develop the diagnostic?
- Can the diagnostic be approved at the same time as the drug?

For now, however, most of the pharmacogenetics research done by pharmaceutical companies is still based on retrospective analysis of traditionally designed trials.

## Reclassifying diseases

Pharmacogenomics may allow diseases to be classified based on molecular biology rather than superficial symptoms. Some patients may share similar symptoms, but the underlying biological mechanisms may be different. Some patients may be classified as having different diseases based on symptoms, but may share the same molecular mechanisms. This means doctors could use one therapy to treat both groups and one diagnostic to identify them.

## Improving safety

Drug companies now collect DNA samples from most patients in clinical trials, some of whom will experience side effects or adverse drug reactions (ADRs). If they can identify the genetic basis of ADRs, they can feed this information into the drug development process.

Typically, side effects or ADRs become evident in phase three or phase four studies (after the launch of a drug). Serious ADRs are generally rare, and pharmacogenetics research is difficult because of the problems of obtaining sufficient samples and of identifying candidate genes for investigation.

## Ethical issues

AstraZeneca has translated its ethics policy into standard operating procedures for human genetic research:

- Written informed consent is always obtained. The duration of storage is defined as part of the consent process.
- DNA samples can only be used after proper authorization that the use is within the scope of consent.
- Patient samples and data are stored securely with restricted access.
- Special coding processes protect confidentiality.
- Patients retain the right to withdraw their samples if they want to.
- Patient data are never transferred outside of the company.
- An electronic audit trail keeps tabs on how DNA samples are used.

Drug companies have made strenuous efforts to respond to concerns about the ethical issues associated with genetics research, but are worried about ethical/legal overload. Consider the person who is trying to organize a multicentre clinical trial in 30 countries, each one with different ethics guidelines and laws on biobanking, genetic research and data protection. It is a heavy burden to understand and apply all of these rules in research. Ethics oversight and debate is healthy but current ethics guidelines and legislation may already provide adequate protection for research subjects. Further legislation would act as a disincentive for a promising field of research.

## Conclusion

In the recent past, there has been a great deal of hyperbole on the anticipated impact of pharmacogenomics. Some genomicists had said that pharmacogenomics would solve everything, while others said it would not make economic sense and was too difficult. There is now a sense of measured pragmatism in the pharmaceutical industry. The full impact of pharmacogenomics will take time, but it is starting to happen. However, pharmacogenomics will not solve all the problems associated with drug development and it will not impact all medicines.

Health care systems need to start planning for pharmacogenomics, as it will have some impact at the level of the prescribing physician. There is a need for greater education and training in this field. There also needs to be more investment and more research in the public sector to balance the research being done in the pharmaceutical industry and to increase the evidence base.

# Innovation Session

*The Innovation Session looked at the key advantages of commercialized pharmacogenomic applications including enhanced accessibility, cost savings and patient benefits, as well as some challenges such as information management, trained personnel and high development costs. The three speakers included representatives from the health care sector (BC Cancer Agency), the federal government (NRC), and the private sector (Tm Bioscience).*

*Topics included:*

- *Trends in pharmacogenomic innovation;*
- *Predictions for future growth of the pharmacogenomics industry; and*
- *Marketplace issues relevant to the emerging industry.*

# APPLYING GENOMICS TO HEALTH CARE

**Dr. Samuel Abraham,**
**Director of Technology Development, BC Cancer Agency**

***Summary:*** *Dr. Abraham discussed the promise of pharmacogenomics in health care and Canada's advantages in this field.*

## Cancer outcomes

Individual outcomes of cancer patients are unpredictable. Some patients could benefit dramatically from a treatment but are not being identified and some are being over-treated or under-treated. 20-40% of patients on medication receive no benefit.

In the U.S., about 100,000 people die every year from adverse drug reactions (ADR). If 40% of patients receive no benefit from a billion-dollar drug, the waste is about $400 million per year just on one drug, excluding the hospitalization costs and care that goes with it.

The B.C. Cancer Agency has the best cancer outcomes in Canada – on average, 12% lower mortality rates for both men and women. But it sees more cancer patients every year. The Agency now spends around $80-million per year for the therapeutic delivery of cancer care in B.C., compared with only $15 million in 1995/96. By 2010, the annual drug budget could equal the Agency's entire budget for salaries and operations.

## Future of medicine

The goal of medicine in the 21st century is to introduce diagnostic and predictive genomics and proteomics, based on longitudinal patient assessments. Physicians want to see patients earlier, so they can look at the worried well and not wait for ill people to come in.

The best example is lung cancer. A typical patient who sees a physician is normally at stage three and four. About 90% of these patients are dead within a year. If their cancer is detected at stage one, it can be surgically removed with an 85% cure rate. In economic terms, 80% of all the health care dollars spent on these patients are spent in their last year of life. We need better screening methods for an earlier stage of the disease.

## The promise of personalized medicine

Personalized medicine involves the interpretation of both individual variation at the allele level (pharmacogenetics) and the study of the multiple effects of different genes bearing on our drug response. Personalized medicine or pharmacogenomics may help increase efficacy, reduce toxicity, and enable more accurate dosing. It could help drug companies revive failed drugs, by identifying which people should not receive a particular therapy. The industry hopes to develop drugs less expensively. Personalized medicine could help physicians select the right patients for the right drugs, which will reduce the costs of therapy.

Pharmacogenomics drugs that receive FDA approval are more likely to work in selected sub-sets of patients and have fewer side effects. FDA approval may happen faster as a result.

## Treating breast cancer

Physicians now look at the lymph node status and histological grade of breast cancer patients. Out of every 100 lymph-node-negative patients, perhaps 70-80 will not need further treatment. But it's not known which people, so all individuals within this cohort get treated. A 2002 Netherlands study argued that these people can now be identified. The study isolated and identified genes that regulate cell cycles, invasion metastasis and angiogenesis. Such information could help physicians determine what therapeutic strategies work depending on a particular patient's profile.

A crude estimation: if we take the 80% of breast cancer patients that don't need any further chemotherapy and give them surgical treatment, it would save Canada $120 million per year just for drug costs, and save developed countries a total of $3.3 billion.

## The Canadian advantage

- The B.C. Cancer Agency currently collaborates with U.S. researchers at NIH and Stanford, not just because the Agency is renowned for cancer research but also because it has longitudinal patient outcome data that they don't have access to – in particular, patient outcome data on a population-wide basis.
- The Agency collects longitudinal outcome data on a heterogeneous population, administered via standard outcome-based protocols – the only body in British Columbia that delivers cancer health care to the whole province. Someone in the northeast corner of B.C. with prostate cancer gets the same treatment as someone in Vancouver Centre. The Agency can compare patient outcomes based on different treatment regimens, and assess whether a particular treatment makes sense.
- Marker studies suffer from poor validation. Canada can do multi-centre validation across standardized protocols to determine whether a particular treatment is useful.

# INNOVATION IN PHARMACOGENOMICS – AN NRC PERSPECTIVE

**Dr. Richard Isnor,**
**Director Biotechnology Horizontal Initiatives and Interdepartmental Relations, National Research Council**

***Summary:*** *Dr. Isnor discussed the NRC Genomics and Health Initiative, the role of emerging technologies, database mining, nanobiotechnology, market forecasts, and marketplace issues.*

## Genomics and Health Initiative

The NRC Genomics and Health Initiative builds research teams from different research institutes and disciplines to work together in new areas. Pharmacogenomics is an opportunity to do that.

Single nucleotide polymorphisms (SNPs) are a source of genomic variability. There are an estimated three million SNPs in a typical human genome. We have about 30,000 genes, of which perhaps 5,000 play a key role in causing disease. A key interest is trying to determine what role SNPs play with respect to those 5,000 genes involved in disease.

## Emerging technologies

Technologies that could play a key role in pharmacogenomics include gene expression analysis, genetic variation studies, whole-genome analysis, protein expression, metabolomics, bioinformatics, combinatorial chemistry and high-throughput screening. One factor in their development is the race to characterize the SNPs involved in disease. DNA microarray and chip technology will play a key role. Someday, single microarrays or biochips may be used to screen 100,000 SNPs at once, possibly in a doctor's office. The end goal is to provide testing right at the point of care.

Bioinformatics combines biology, computer science and information technology to form a single discipline. Another emerging field is computational biology. Scientists who have traditionally worked on the development of algorithms and mathematical formulae are now working side by side with biologists. Last year, Genome Canada ran a national workshop on computational biology.

## Database mining

In 2000 alone, life sciences companies spent $10 billion on information technology (IT). It is estimated that by 2006, they will spend up to $38 billion. IT is becoming integral to the drug development/drug discovery process.

NRC has developed two software tools to ride the wave of technology convergence between biology, math and IT. BioMiner processes and analyses vast amounts of information captured in the study of genes and protein functions. Litminer compares published gene sequence information and how it might relate to experimental information. NRC has used these tools for gene expression analysis, the analysis of regulatory gene expression networks, Alzheimer's disease research, and plant disease research. NRC has also worked with the Children's Hospital of Eastern Ontario on disease modeling in Hepatitis C virus transgenic mice.

## Nanobiotechnology

Nanobiotechnology may provide novel tools and materials that could lead to significant advances in both medicine and life science research. NRC has established the National Institute for Nanotechnology at the University of Alberta in Edmonton, but nanobiotechnology cuts across other NRC institutes. NRC is trying to use nanoparticulate drug delivery to cross the blood-brain barrier, for example, to treat brain-related diseases.

The market demand for nanobiotechnology-based drug delivery technologies, imaging agents and biosensors is expected to grow from $930 million in 2003 to over $3 billion in 2008. Twelve different NRC research institutes are interested in this field, including materials institutes and institutes that have traditionally worked in the telecommunications sector.

NRC's Genomics and Health Initiative programs include:

- Linking molecular imaging and diagnosis with molecular therapy: The aim is to understand protein/protein interactions in the intracellular environment, the regulatory factors involved, and how those factors can be controlled through therapeutic delivery.
- Structure/function characterization of kinase signalling networks: Led by Dr. Mirek Cigler of the NRC Biotechnology Research Institute, the aim is to understand and interrupt protein/protein interaction signals that act as regulatory mechanisms for biological processes underlying different diseases.

## Predictions for growth

The pharmacogenomics market is predicted to expand at a compounded annual growth rate of 22% worldwide between 2003 and 2008. According to the *U.S. Genetic Testing Markets* report, genetic testing generated revenues of about $320 million in 2000, and is estimated to reach $877 million by 2006. Emerging market segments include tests for cardiovascular disease, neurological disease and respiratory disease.

The FDA recently announced that it will soon release a pharmacogenomics guideline.

## Marketplace issues

- Major hurdles to pharmacogenomics include high costs, an unclear regulatory pathway, and uncertain levels of payoff.
- Traditional mass marketing is ineffective for pharmacogenomic interventions.
- Pharmacogenomics technologies are at various stages of maturity. Most require high levels of expertise to generate reproducible data.
- The interplay between diagnostics companies and drug discovery companies is triggering mergers, acquisitions and strategic partnerships, as firms realize that their research offshoots will produce profitable applications elsewhere.
- Inter-company partnering is becoming more important to success in the life sciences/health care industry. Information technology can facilitate collaborations by helping companies to identify optimal partners and then plan, manage and evaluate projects, and facilitate information transfer.

# PHARMING THE GENOME

**Gregory Hines, President and CEO, Tm Bioscience**

***Summary:*** *Mr. Hines discussed the microarray technology developed by Tm Bioscience, its commercialization strategy, the drivers for DNA testing, and marketplace policy issues.*

## A universal operating system

When Tm Bioscience first looked at how to deliver DNA diagnostic testing to the general population in 2000, there were about 18 biotech companies that all thought they had the best machine and the ideal technology. Very few of those companies survived, mainly because it costs approximately US$125 million to build a machine to a regulatory standard and commercialize it worldwide. Hines believed that diagnostic tests would never succeed commercially if testing labs are expected to pay for new infrastructure for every few tests that they want to run. Tm Bioscience built a universal array operating system that runs on any instrument – a microscope slide, a 96-well lab plate, a biochip, a flow-through chip, etc.

Traditional methods of DNA testing involved single-tube assays. Using these methods at a reference lab, if you wanted to look for 100 mutations in one patient, you had to set up 100 test tubes, take 100 aliquots of the patient's sample, use 100 aliquots of reagents, and then run your assay. This was too slow a process. Microarrays were the answer, but they needed to fit into current laboratory processes.

Tm's strategy was to focus on the fact that every lab in the world uses a 96-well plate format, many with automated liquid handling systems. With the Tm Bioscience microarray technology, each spot in the 96-well plate can run almost 1,200 mutations at one time to 100% accuracy. This means the laboratory technician can assess over ten times as many patients each day. The technology then is capable of reducing the cost of DNA testing to less than $100, rather than $1,000 or $3,000 per test, which we sometimes see today.

## Penetrating the U.S. market

The U.S. leads the DNA test market in terms of the number of genetic tests being run. Two labs – Quest Diagnostics and Labcorp of America – perform approximately 50% of all the DNA testing in the U.S. Six other labs perform about 20%. These include institutions like Genzyme Genetics, the Center for Disease Control, and the Mayo Clinic. The other 30% is performed by about 700 laboratories, of which 50 to 60 are larger state labs. This is a small consumer base; however a company must succeed with the major customers to succeed. Out of the top ten U.S. reference labs, six are currently converting to Tm's microarray technology.

Tm Bioscience has three product portfolios: human genetics, pharmacogenetics and infectious diseases. In pharmacogenetics, the company is currently focused on cytochrome P450 tests.

## Cytochrome P450

The average North American over the age of 60 takes at least eight different medications, many of which are metabolized by cytochrome P450 (e.g. statins for cholesterol problems, blood thinners for heart attack or stroke, Tylenol or codeine for pain relief, SSRI's lsuch as Paxil or Proxac for depression, and erythromycin for lower respiratory tract infections). Patients with an abnormal genotype for cytochrome P450 enzymes are at risk of adverse drug events or poor drug efficacy. Do prescribing doctors have the information they need to know if a patient can metabolize all of these drugs effectively? Does the drug company or the regulator know what patient will experience a life threatening adverse drug reaction (ADR)?

Over the past few years, we have seen more and more drug recalls due to adverse drug reactions: Dexfenfluramine (Redux), Terfenadine (Seldane), Cisapride (Propulsid), Cerivastatin (Baycol), Bromfenac (Duract), Miberfradil (Posicor) and Troglitazone (Rezulin) are examples. One might ask, for example, if a diagnostic test could have prevented Bayer from losing Baycol, and some patients from morbidity and mortality. More and more studies have linked cytochrome P450 to ADRs in Warfarin, Omeprazole, mercaptopurines, tricyclic antidepressants and neuroleptics.

## DNA testing: key drivers

The **Food and Drugs Administration** (FDA) will be a key driver. It will soon release pharmacogenomic guidelines that should specifically mention cytochrome P450 testing. The draft guidance documents suggest that cytochrome P450 and other drug metabolism enzymes are valid biomarkers and should be included in drug development studies. The regulatory infrastructure at the FDA is now in place to review molecular diagnostic tests, and the FDA commissioner has expressed a desire to decrease adverse drug reactions. Of the top 27 drugs that are often prescribed and cited in U.S. ADR reports, 59% are due to a drug being a poor metabolizer of one of the P450s.

The **pharmaceutical industry** will become a significant driver of pharmacogenomic testing and companion diagnostics. If a drug is ideal for 25-30% of patients in a therapeutic class, and these patients can be identified early using a proven diagnostic assay, a company can reduce the number of patients needed to reach statistical significance in clinical trials. This should lower their costs and shorten the clinical trial program. However, for regulatory reasons, the assay used must be manufactured to a current Good Manufacturing Practices (cGMP) specification.

Another consideration is that when drug companies market these medicines, they will need an IVD (FDA-approved) assay that is commercially available to the full population. For example, if a pharmaceutical company launches a $300-million drug, and a physician wants to order it but must first order a diagnostic test, the testing lab must have the test reagents in stock, the instrumentation and a technician able to run it. This means that the testing technology must meet regulatory requirements, and it must be installed with trained technicians throughout the geography. This is the goal of diagnostic companies like Tm Bioscience.

The **diagnostic industry** is also a driver of pharmacogenetic testing. The challenge within the diagnostic industry is that many genes and their respective mutations are well understood, but others are not. A lot of data has been generated that makes associations between genetic mutations and a disease. The industry needs to study the data to identify prospective mutations (biomarkers), put the appropriate biomarkers into a cGMP assay, and do medical validation studies prior to a regulatory submission. All of this work must be performed on a validated platform with a commercial cGMP manufacturing facility in place. Very few diagnostic companies have this infrastructure.

## Marketplace policy issues

***Media focus***: Adverse drug reactions are the fourth leading cause of death in the U.S. There were more than 100,000 deaths last year, versus 43,000 deaths in traffic accidents. ADRs are the fifth leading cause of illness with 2.2 million hospitalizations. The media is just beginning to focus on this.

***Legal and ethical issues***: Pharmacogenetic testing offers benefits to health care in terms of reduced morbidity and mortality. As the FDA approves these tests in the U.S., there will be legal liability and ethical issues if a test is not provided when it's available and on the market.

***Other issues***: Physicians may not want the responsibility of ordering and managing the extra burden. The pharmaceutical industry may not want to assess old drugs with little life left in their patents. Infrastructure is required to train physicians and genetic counselling. Who will pay? The regulatory process is still weak. Multiple doctors are now prescribing multiple drugs to a single patient, so they need to share information more. Laboratories need to be standardized. We need trained and certified lab technicians.

# Luncheon Speaker

**Dr. Arnold Naimark,**
**Chair, Canadian Biotechnology Advisory Committee**

***Summary:*** *Dr. Naimark provided an overview of the Canadian Biotechnology Advisory Committee's new public policy framework on biotechnology and health innovation.*

## Public policy framework

The Canadian Biotechnology Advisory Committee (CBAC) recently developed a paper on biotechnology and health innovation, which offers a framework for developing policy in areas that are important to pharmacogenomics.

The framework is three dimensional, consisting of:

- Two major pillars of public policy: "Innovation" and "Stewardship"
- Four sectors: "Research and Development"; "Regulation and Commercialization"; "Health Technology Assessment"; and "Health Technology Uptake and Assimilation"
- Five facilitation strategies: "Collaboration"; "Capacity Development"; "Citizen Engagement"; "Education"; and "Evidence-Based Decision-Making"

## Challenges

Pharmacogenomics presents significant challenges in strengthening innovation and stewardship. For example:

- In terms of research and development, we need to develop platform technologies and support major thrusts in systems biology. Although genomics facilitates the identification of drug targets, there are challenges in determining the causal relationships between genes or gene products and pathogenesis, while strengthening research ethics oversight and reformulating good practice guidelines as new approaches to clinical trials evolve.
- In terms of regulation and commercialization, we need to expand public-private partnerships; promote innovation clusters, create commercialization platforms that can better integrate industry with the public institutions involved in clinical evaluation, and mobilize investment pools, while building the capacity to implement timely and effective regulation informed by new methodology.
- In terms of health technology assessment (HTA), we need new, more comprehensive structures and methods and linkages to promote the effective use of HTA information in decision-making, while developing robust national standards and inter-jurisdictional cooperation to support portability.

- In terms of health technology uptake and assimilation, we need new and more effective methods for ensuring timely access to innovations. Our health care system has limited resources. We need to figure out how to make room for new technologies and how to sunset those that are no longer best suited to diagnosis, treatment and prevention, while attending to the increasing concern about issues of privacy and informed consent prompted by the "genomics revolution."

Public participation in the policy-making process is becoming more important given the power of gene-based technologies and the extent to which they intersect with social and ethical concerns about the acceptability of intrusive applications of new technology.

## Some cautions for policy makers

Policy makers need to see both the forest and the trees. They need to hear a different perspective on "the industry" by learning more about how health care products are developed and commercialized, rather than simply thinking of industry as a political sector. They need to maintain a broad perspective regarding the role of pharmacogenomics in health innovation beyond therapeutic drug design and development. Pharmacogenomics can also help in the development and design of vaccines and other biologics.

Policy makers also need to avoid being seduced by "genohype." There is a story about a young girl who received a Bible on her birthday from her grandfather. On the front he wrote: "this is a very important story, if true." Pharmacogenomics is a very important story. However, to realize its promise, Canada requires not only stronger thrusts on the commercialization front, but also enhanced investment in research on basic biological phenomena underlying the links between genomics and health.

# Health Session

*The Health session looked at the medium and long-term impact of pharmacogenomics on health and health systems. The three speakers included experts in cost effectiveness modeling for health interventions, health system management and therapeutic product regulation.*

*Topics included:*

- *Cost effectiveness analysis for pharmacogenomics treatments;*
- *Challenges and strategies related to implementing pharmacogenomics in our health care system; and*
- *Regulatory issues related to pharmacogenomics.*

# PHARMACOGENOMICS: EVALUATING COST EFFECTIVENESS

**Dr. David Veenstra,**
**Affiliate Assistant Professor, University of Washington**

***Summary:*** *Dr. Veenstra discussed the use of cost effectiveness analysis for pharmacogenomics treatments. He outlined the factors that are considered in cost effectiveness analysis, discussed guidelines for providing cost effectiveness information, and presented a five-point framework for evaluating the cost effectiveness of pharmacogenomics.*

## What is cost effectiveness analysis?

Cost effectiveness analysis includes many factors beyond the simple cost of a treatment. It looks at clinical evidence, patient outcomes, quality of life, and other factors. An expensive technology can still be cost effective, and an inexpensive technology is not necessarily cost effective.

Cost-effectiveness analysis aids decision makers by providing a quantitative framework for decisions, highlighting data needs, and identifying the important clinical, economic and patient parameters. However, cost effectiveness is just one piece of the puzzle for decision makers. There are other factors to consider, such as equity, efficacy and safety.

Cost effectiveness analysis is most useful in two situations:

- Comparing multiple similar products, such as various statin drugs for high cholesterol. Cost effectiveness analysis can help in selecting a technology and negotiating pricing.
- Assessing expensive and new technologies, such as Enteracept for rheumatoid arthritis. A treatment may be more effective than existing treatments, but managed care payers still need to know whether the cost is reasonable.

## Guidelines for providing cost effectiveness information

Managed care companies in the U.S. are starting to follow Academy of Managed Care Pharmacy (AMCP) guidelines for providing and utilizing cost effectiveness information. Under these guidelines, the managed care company asks the drug manufacturer to provide all available data on the drug.

Because this request is unsolicited by the manufacturer, the manufacturer can provide more information (as opposed to the standard marketing brochure), including information that is not necessarily included in the label or approved by the FDA. The manufacturer can now talk directly with the payer about cost effectiveness.

The next version of the AMCP guidelines will address pharmacogenomics, focusing on four types of information:

- Analytic validity: Does the test measure what it's supposed to measure?
- Clinical validity: Is there an association between the test result and a clinical outcome?
- Clinical utility: What can a practicing clinician do with this information? Can the patient use this information to improve their health?
- Cost effectiveness: What are the differences in costs and outcomes compared with usual care?

## Framework for evaluating the cost effectiveness of pharmacogenomics

1. How severe and frequent are the outcomes of interest? Are you trying to reduce the number of people receiving a drug that doesn't have any side effects? Is there value in that? Or are you reducing the number of people receiving an expensive drug? How severe are the side effects (e.g. dry mouth, bleeding)?

2. What is the alternative? Many drugs are already individualized - dosages are adjusted regularly to improve response or reduce side effects. What does that cost the health care system? How much better is the new intervention?

3. What is the strength of the genotype-phenotype association? What is the association between the biomarker and a valid clinical outcome?

4. What does the test include? In addition to the test itself, there are other costs, such as additional clinic visits or genetic counselling. A test may also provide information that can be used throughout the lifetime of the patient, or used in relation to other diseases or drugs.

5. What is the prevalence of the genetic variant? For example, if a genetic marker exists for a side effect, how many of these side effects have ever occurred? Is the number very low, or the variant very rare in the population?

## Cost effectiveness analysis of genetic technologies

Genetic technologies hold unique challenges, such as the extensive data needed for evaluation, and the complex interaction among these components. In order to make informed decisions, clinicians and payers will need decision-analytic modellings, systematic evidence-based reviews and cost effectiveness analyses that include evaluation of patients' quality of life, preferences, etc.

## Future issues

- Reimbursement decisions: Who will make decisions about pharmacogenomic tests? The people who handle drugs, or the people who handle diagnostics?
- Genetic testing: Will there be guidelines for use of drugs? Will people be required to have a test before the can get a drug? What if they don't want genetic testing?
- Ethnic and racial issues: Certain markers are more prevalent in specific ethnic and racial populations. How do you handle that?
- Privacy issues: Should genetic information be included in medical records?

# PLANNING FOR THE PRACTICAL ASPECTS OF IMPLEMENTATION

**Dr. Ronald Carter,**
**Chair, Ontario Advisory Committee on Genetics**

***Summary:*** *Dr. Carter presented challenges and strategies related to implementing pharmacogenomics in Canada's health care system. He discussed the problems posed by budget constraints and the rise of proprietary technologies. He then outlined three possible applications of pharmacogenomics and described the very different health care infrastructure required for each.*

## The promise and the challenge

Two major challenges limit the health care system's ability to respond to pharmacogenomics:

- Cost pressure: The budgets of Ontario's nine diagnostic genetic services are in effect frozen for the next three years, while workloads continue to increase.
- Changes in genetic testing: Proprietary technologies are emerging that will not be accessible to not-for-profit publicly funded labs.

In theory, the promise of pharmacogenomics is a better form of individualized therapy than exists now. In practical terms, there are many hurdles, including lack of exact correlations between genotype and phenotype, technical accuracy, modifying medical practice and public behaviour, and many ethical, legal and intellectual property issues.

## Infrastructure requirements for three types of applications

Below are three hypothetical applications of pharmacogenomics. Each one presents different infrastructure requirements.

| | **Situation A: Avoiding toxicity** | **Situation B: Preferential selection for response** | **Situation C: Creating a drug for a patient** |
|---|---|---|---|
| **Goal** | Identify the rare patients who will have toxic reactions | Identify patients who will respond well to a particular drug | Enhance efficacy by fabricating a drug specific to the patient |

| | Situation A: Avoiding toxicity | Situation B: Preferential selection for response | Situation C: Creating a drug for a patient |
|---|---|---|---|
| **Benefits** | • reduced morbidity and mortality<br>• possibility of higher dosage levels<br>• availability of drugs not previously approved due to unpredictable reactions | • improves response to therapy<br>• avoids unnecessary use of drugs<br>• identifies patients who cannot be effectively treated, stimulating research into alternatives | • increased efficacy and specificity, reduced toxicity<br>• increased therapeutic range, offering treatment for diseases that are currently untreatable |
| **What do you need to know?** | • what is the toxic effect? i.e. which drug, which mutation)<br>• who has the mutation (who is at risk and who actually carries it)<br>• are family members at risk?<br>• what is the alternative treatment? | • pharmacological profile of the drug activities, toxicities, application<br>• genetic basis of response<br>• what is the benefit in selecting for the patient on that particular drug? need to know outcomes for a variety of drugs in a given situation. | • technical issues: which patient, what defect, what augmentation, what technology, what efficacy |
| **When do you need to know it?** | Before you start treatment, anywhere you start treatment | Just before or during initial stages of treatment. | Before treatment and during treatment, as in situation B. However, this will initially be a highly selected population of patients. |

| | Situation A: Avoiding toxicity | Situation B: Preferential selection for response | Situation C: Creating a drug for a patient |
|---|---|---|---|
| **Infrastructure requirements** | Two options, each with different infrastructure requirements. Each will be limited by cost, technical ability, and legal and ethical database concerns.<br><br>1. Rapid, accurate, multi-site cheap testing on demand.<br><br>Issues: technology; cost (molecular diagnostic tests cost $50 to $100); informed consent; education/counselling; database storage<br><br>2. Pre-screening of the whole population<br><br>Issues: Logistics of public health screening. When to do it? How to do it? How does the data follow the patient around (database)? | A more feasible situation. The number being tested is smaller, because they are selected for a given disease.<br><br>• patients are identified by clinical criteria<br>• provides enhanced clinical management - an extension of what we do now<br><br>This approach is in progress in many applications. Speed of uptake is limited by cost and by how quickly the resources can be developed<br><br>Issues: Who can do it? How do we educate patients and providers? As with situation A, need a database of data that will follow the patient. Need practice guidelines that reflect the improvement in knowledge. | This approach might be best limited to specific centers that combine medical, research, manufacturing and regulatory expertise.<br><br>**Issues:**<br>• technical barriers<br>• oversight, monitoring of outcomes, biosafety at the individual and population levels<br>• manufacturing expertise and control<br>• medical expertise in diagnosis and therapy |

## Conclusion

There are huge differences in the infrastructure required for these three applications. With budget constraints, there will be very practical limitations on how the health care system can respond to clinical requirements for pharmacogenomic testing. The pressure for proprietary technology will be strong. Some patients will be able to find and pay for the technology, while others may not have access to it.

# REGULATORY ISSUES IN PHARMACOGENOMICS

**Dr. Agnes Klein,**
**Manager, Health Canada**

***Summary:*** *Dr. Klein provided a regulator's perspective on pharmacogenomics. She outlined the perceived benefits for medical treatment and discussed the risks and challenges of regulating pharmacogenomics. Many of these regulatory challenges relate to the complexity of pharmacogenomics, including the multiplicity of genes involved and the complexity of interactions.*

## The challenge

The regulatory challenge of pharmacogenomics stems from the multiplicity of genes governing diseases and therapeutic responses. This complexity makes it difficult to consider all factors in weighing benefits and risks. Interactions are also much more complex than they first appear. Most drugs depend on more than one pathway. Therefore, many drugs, natural health products and foods are involved in these interactions.

Health Canada must address this technology carefully, examining the most suitable approach for the Canadian setting. Canada is just beginning to systematically use pharmacogenomics and pharmacogenetics in developing drugs and other therapeutics.

Canada must also consider what is happening in other jurisdictions. The FDA has issued a proposed guidance document, which may provide some guidance for the Canadian context.

## Perceived benefits of pharmacogenomics

- Better focus in the design of clinical trials
- Better targets for drug development
- Shortened drug development processes
- Better focus on the most appropriate dose
- Increased efficacy
- Decreased toxicity
- More manageable drug interactions
- Better patient outcomes, and thus increased confidence in therapeutic interventions
- Personalized medicine (the ideal target)

## Regulatory challenges

- There is a risk of introducing pharmacogenetics and pharmacogenomics broadly and prematurely without adequate considerations for each case.
- Regulatory bodies must be proactive in encouraging drug development via pharmacogenetic and genomic approaches.
- The benefits of a drug may be limited to a narrow population, creating therapeutic orphans. Canada should consider an orphan drug regulation to address cases in which certain people cannot benefit from a treatment due to their genetic makeup.
- A re-evaluation of existing therapies in a pharmacogenetic and pharmacogenomic context may be forgotten in looking only to the future. When examined from a different point of view, old drugs may be as good as or better than new ones.
- Capacity is needed to relabel and re-assess previously marketed drugs.
- There is an urgent need to educate everyone involved in the health system to ensure that these technologies are used in the best way possible.

The regulatory system must stay flexible and open to new ways of regulating. Pharmacogenetics and pharmacogenomics must be carefully managed in order to reap the maximum regulatory and other benefits. Time and experience will help. Both will be aided by guidance documents and by Canada's participation in international endeavours.

# DISCUSSION

***Q: What are some key issues that Canada must address to realize the benefits of pharmacogenomics?***

- Our health care system must be able to respond to new demands in an organized fashion within reasonable budgets. In Ontario, 48% of the budget now is dedicated to health care. How much more is there?
- We should create a Canada-wide consortium to make decisions about particular technologies. This would give provincial health system managers a basis for decisions and allow them to avoid the inherent dis-incentives (e.g. political cost of disallowing a technology) that exist now.
- The regulatory system needs an organized educational system to allow staff to keep up with new knowledge and reap the maximum benefits.
- We must continue international cooperation in order to learn from what is happening in other jurisdictions.
- We need to create incentives for innovation. How do the technologies that you need correlate with what is being developed? How can you provide the right incentives to get what you need?

***Q: Are there any initiatives in Canada to implement the cost effectiveness methodology presented by Dr. Carter?***

B.C. and Quebec and Ontario have begun systematic approaches. The Ontario Health Technology Assessment Committee has a 14-week timeframe for assessing new applications. They release a report to the government within 14 weeks of undertaking a question. The government has 60 days to respond, then the results are posted online. Approximately 85 assessments are now publicly available.

***Q: What policy implications would affect the role of public labs as opposed to private labs in providing molecular diagnostic services?***

Historically, the government has shown that it wants to provide genetic-related services in the context of centres that link laboratory support closely with clinical centres of expertise. This policy was set up by the federal government in 1968.

Health Canada issued a position paper recommending a close link between genetic testing, genetic counselling and clinical management. This doesn't rule out private providers. However, having multiple providers creates challenges related to control of the indications for testing. This can lead to much unnecessary testing, which can lead to failure to communicate risks, benefits, and outcomes. However, as long as tests are provided for recognized indications, follow-up support is provided, and remuneration is equal for all providers, there should be no problem.

***Q: There is no single solution to the many challenges of pharmacogenomics. What first step can we take to begin to address these issues?***

We need to start by addressing questions of clinical validity, which is crucial for evidence-based decision-making and will act as a foundation for everything else.

# Ethics Session

*Pharmacogenomics raises ethical questions in areas such as drug development, commercialization, regulatory affairs and marketing. The Ethics session discussed ethics issues in these areas, and also looked at concerns related to privacy and consent.*

*Topics included:*

- *Legal and ethical challenges of pharmacogenomics;*
- *Pharmacogenetics and the regulation of pharmaceuticals; and*
- *Confidentiality and consent in pharmacogenomics research.*

# PHARMACOGENOMICS: LEGAL AND ETHICAL CHALLENGES

**Timothy Caulfield,**
**Research Director, Health Law Institute, University of Alberta**

***Summary:*** *Mr. Caulfield discussed legal and ethical challenges in the areas of development, marketing and implementation. He talked about challenges related to patenting, the potential geneticization of medicine due to aggressive marketing, and the regulatory and liability pressures that may affect implementation.*

## Patent issues

Will existing patents impair research and development? Will intellectual property be a disincentive to research for fear of patent infringement or costly licensing agreements? Can organizations such as Genome Canada and the National Research Council have commercialization of research as their goal while claiming research exemptions to patents?

Gene patenting has been the focus of a huge amount of policy development around the world. Many people have recommended changing Canada's patent system, which creates uncertainty for pharmacogenetics.

## Marketing pressures

Geneticization is the inappropriate and inaccurate emphasis of the genetic component of health to the exclusion of other factors, such as socio-economic status. Simplistic messaging is emphasizing direct relationships between genes and complex traits. The public is picking up on these messages, and starting to believe that genetic information is special. But the relationship between genes, environment and disease is complex.

## Genetics and "race"

Visible phenotypic differences, often associated with race, are being used as proxies for more complex genetic stories. This can mistakenly imply biological explanations for health disparities that have social and historical origins. There is a danger of reinforcing social stereotypes.

## Essentialism and genetic research

The public is buying into the idea of genetic essentialism. That message comes not just from the media, but also from research institutions. In a 2001 survey, 90% of Canadians said they believe that genetic information is different and that the rules governing it should be more stringent. In another recent study, 39% of Canadians said that the government should emphasize privacy over research and development. Only 37% are willing to contribute genetic information for research, down from 56%.

## Is genetic information special?

UNESCO says that genetic information is different because it's predictive: it may have significance to the family and may contain information that will be relevant in the future. As a result, UNESCO says that genetic information should have special protections.

The Nutfield Council issued a report that takes a more nuanced approach. They conclude that genetic information perhaps isn't different from medical information, but that because part of our society now believes it is special, we must take regulatory responses in order to ensure public trust.

## Research hype paradox

The public has bought into the genetic essentialist message that has been partly sold to them by the research community in an attempt to secure public and private funds. Researchers want to classify genetic information as minimal risk, which in most countries would make the consent rules much more flexible. However, because the public now views genetic information as special, privacy and consent rules are strict.

## Implementation issues

- What is the standard of care? There are estimates that 50% of clinical trials already involve a collection of DNA samples. Will this become standard of care? What are the legal implications? Will there be lawsuits against clinicians or health agencies who don't do pharmacogenetics research? There are also issues of look-back liability and recontact liability.
- What treatments should be covered by the health care system?
- Will the pharmaceutical industry want to fund research that narrows their market?

## Conclusion

There are many challenges in development, policy and implementation. There is a need for more research on the ethical, legal, and social implications. Social scientists must move beyond ethics speculation and find out how much geneticization and discrimination are happening, and what kind of policy mechanisms would really work.

# PHARMACOGENETICS AND THE REGULATION OF PHARMACEUTICALS

**Trudo Lemmens,**
**Associate Professor, Faculty of Law, University of Toronto**

***Summary:*** *Mr. Lemmens discussed ethical issues in the drug regulatory system, particularly conflict of interest in medical research. He described some of the key pressures in medical research that can raise ethical, legal and regulatory concerns, addressed the increased need for specific regulatory initiatives, and outlined some of the policy options.*

## Market developments

Clinical trials are moving from academia to contract research organizations. There is also a significant increase in the number of clinical trials. There is great pressure to get drugs on the market.

The academic research is becoming commercialized, with in the U.S. an 875% increase in industry funding from 1980 to 2000. The number of physicians involved in clinical trials increased 600% in the last 20 years. Clinical research is also becoming more international.

## Consequences of market developments

- Sponsors and contract research organizations (CROs) have increased control over clinical trials, with less input from academics.
- There is pressure to move drugs quickly to market and to expand markets.
- There is pressure to use market mechanisms for recruiting subjects, with a disadvantage for non-industry-sponsored research.
- Research is becoming part of a complex marketing process. CROs, medical communication and education firms are increasingly bought by major pharmaceutical advertising agencies, augmenting concerns about the lack of independence of scientific research and the selective promotion of research results.
- Ghost writing is increasing. According to one study published in JAMA, up to 10% of medical literature is ghost written. Many of these articles are published in the most reputable journals, giving them higher impact than non-industry-sponsored articles.
- Industry has increasing influence on policy directions.

## Recent controversies

- The Vioxx withdrawal of 2004, which *The Lancet* called a story "of blindly aggressive marketing by Merck mixed with repeated episodes of complacency by drug regulators."
- The New York lawsuit against Glaxo-Smithkline by the Attorney General of New York, which raises issues of ghost writing, hiding of important data related to the safety and efficacy of drugs, and manipulation of publication of studies.

## Current challenges in drug research

Research integrity is clearly a concern. Industry increasingly controls the design of trials, selection of subjects, collection of data, and the interpretation, analysis and publication of results. The pressure to go to market can affect the safety of research subjects.

Market pressures can affect recruitment practices and how researchers behave within clinical trials. In the U.S., researchers receive financial incentives to recruit patients quickly. The same is happening in Canada.

There is overall concern for safety of consumers and patients. Is the research that supports approval sufficiently reliable? Is there sufficient post-approval monitoring for side effects and inappropriate promotion? The lack of appropriate independent analysis of research data undermines public trust.

## Where is the counterbalance?

Market mechanisms are not a sufficient counterbalance. Industry has an interest in promoting drugs, and can't be expected to control itself to the degree that it undercuts its own interest.

Research ethics board (REB) review exists to protect research subjects. However, it is increasingly subject to financial pressures and conflict of interest. There is increasing reliance on commercial REBs, which are for-profit ventures that are part of the industry they are asked to control. Academic institutions are increasingly dependent on private funding and are also subject to conflict of interest. The same is true of academic REBs.

## Drug regulatory agencies

Drug regulatory agencies represent the biggest counterbalance that we have right now. However, they may not do enough detailed monitoring of study conduct or post-marketing surveillance. They don't determine priorities for drug development, although they do conduct priority review. They also don't compare efficacy and safety profiles of various drugs to determine which one should receive funding.

## Challenges for the regulatory system

There is an overload in the review system. There is an increase in approval applications. There are also concerns about regulatory capture. Those who believe in the need for regulatory review are critical of the use of user fees in terms of the relation it creates and the influence on the priorities. There is also a focus on reducing review times.

## Policy options

A national center for drug development could control and promote clinical trials. Trials could then be developed in academic centers or elsewhere, but under the control of this national centre. The promotion of a truly independent research sector, through appropriate governmental subsidies for research, should help compensate for the heavy emphasis on commercialized research.

# PHARMACOGENOMIC RESEARCH: CONFIDENTIALITY AND CONSENT

**Yann Joly, Research Associate, University of Montreal**

***Summary:*** *Mr. Joly discussed the confidentiality requirements of genetic information. He looked at the advantages and disadvantages of the various levels of confidentiality that are used to protect biological samples. Finally, he considered whether true anonymity of research samples is really possible.*

## Misperceptions of genetic information

Three misperceptions influence the perception that genetic information is different from other kinds of information.

- Genetic exceptionalism: the supposition that genetic research carries unique ethical risks due to its personal, familial and social nature.
- Genetic determinism: the belief that the genotype determines disease without accounting for environmental influences.
- Genetic overgeneralization: assuming that all genetic test results will have the same social and psychological consequences.

## Confidentiality issues for genetics and pharmacogenomics

Are confidentiality issues different for pharmacogenomics than for genetics? Some argue that the psychosocial risks of pharmacogenomics are lower than for other kinds of genetic testing, such as genetic testing for disease or screening of newborns. Others say that genotyping for drug compatibility causes no significant ethical concerns other than those associated with blood typing.

In 2002, the Pharmacogenomics Consortium said that pharmacogenomics research would require a sophisticated information infrastructure to protect privacy while also making information available to benefit the individual and society. They recommended that policy choices should reflect the likelihood of psychosocial harms for pharmacogenetics rather than for genetic testing in general, indicating that there may be differences in risk.

## Clinical trials

Pharmacogenomics raises privacy and confidentiality questions about informed consent for clinical trials. As a result of genotyping, some individuals could be classified as difficult to treat, less profitable to treat or more expensive to treat.

As a result of changes to the process of clinical drug trials, all subjects will be genetically screened before taking part. This screening yields information about whether the subject is a responder or a non-responder, and might even give information about disease risk.

## Is pharmacogenomics different?

Testing for pharmacogenetic and pharmacogenomic research comes in a variety of forms. Some research will look at the genotypic variation, some at the gene expression and some at the viral or tumoral genotype. Therefore, the research involves informational risks that in some circumstances could be lower than the risks associated with genetic research for disease genes.

The goal is not to make a rigid division between high-risk and low-risk genetic information. Rather, it's important to recognize that pharmacogenomics is sometimes defined very broadly to include tests that will generate different informational risks.

## Levels of confidentiality

There are several levels of confidentiality for biological samples. Each level carries its own benefits and risks.

- Identified samples: The researcher knows the identity of the source, and can go back to the subject's medical record at any time. Information can also benefit the subject's clinical management. However, potentially harmful information could enter the subject's medical record. Subjects could find out things that they don't want to know. Researchers may have ethical and legal responsibilities to protect information from third parties.
- Single coded samples: Samples are attributed a specific code for the protection of subjects. The researcher can report clinically significant personal results to subjects or their physicians. The subjects can still withdraw at any time from the research. This technique reduces the possibility of breach of confidentiality while avoiding the disadvantages of permanent anonymization.
- Double-coded samples: The sample is doubly protected via a second coding system. The code key linking samples with subject information is kept by a third party. The researcher can ask the third party holding the second key to provide information from a subject's medical record without having to access the medical record. However, this system is more expensive and time consuming.
- Anonymized samples: All personal identifiers are deleted, which offers extra security. However, this system reduces the value of patient participation in pharmacogenomics research: the subject can no longer withdraw; it is no longer possible to return individual results; regulatory authorities can't inspect the study to determine that pharmacogenetic data is accurately correlated to specific subjects.
- Anonymous samples: Samples have no link whatsoever with the subject's identity. These samples are extremely rare and only of marginal interest to science.

## Is true anonymity possible?

It is not technically feasible to protect privacy. Recent literature has stated that as few as 75 single-nucleotide polymorphisms (SNPs) could identify an anonymous subject. Research protocols should admit the limits of confidentiality protection systems to participants.

Several policy bodies have recommended that informed consent be required for any new samples collected, even if the sample is to be permanently anonymized. As long as the consent process is not unnecessarily elaborate, the requirement does not seem unduly burdensome.

While it's important to inform the participant about the level of protection, this information should be given in a clear and concise form so that subjects can truly assess the benefits and the inconveniences of the chosen method.

# DISCUSSION

***Q: Dr. Joly said it's possible to identify someone from 75 SNPs. How is this technically possible? Who would want to do this? How does this type of scare mongering help the public? This concept paints an unbalanced picture of the pharmaceutical industry. Those of us who are in the industry have deep discussions about ethics and wouldn't dream of putting patients at risk***

That statement was made in 2 recent articles (2004 Science and 2004 Nature Reviews Drug Discovery). The National Bioethic Advisory Committee has also said that there is no such thing as perfect anonymization. It may be beneficial to inform the public of the limitations of confidentiality protection techniques while also acknowledging the benefits of pharmacogenomic research.

This is not meant as a criticism of the integrity of the pharmaceutical industry. However, it is important that the relationship between industry, researchers and research subjects be based on transparency and honesty, and thus all relevant information (including information pertaining to sample confidentiality) should be disclosed to the research subject.

Greater emphasis should be placed on reasonable use rather than informed consent. Another solution would be to reinforce confidentiality protection laws or restrict third-party access to genetic information.