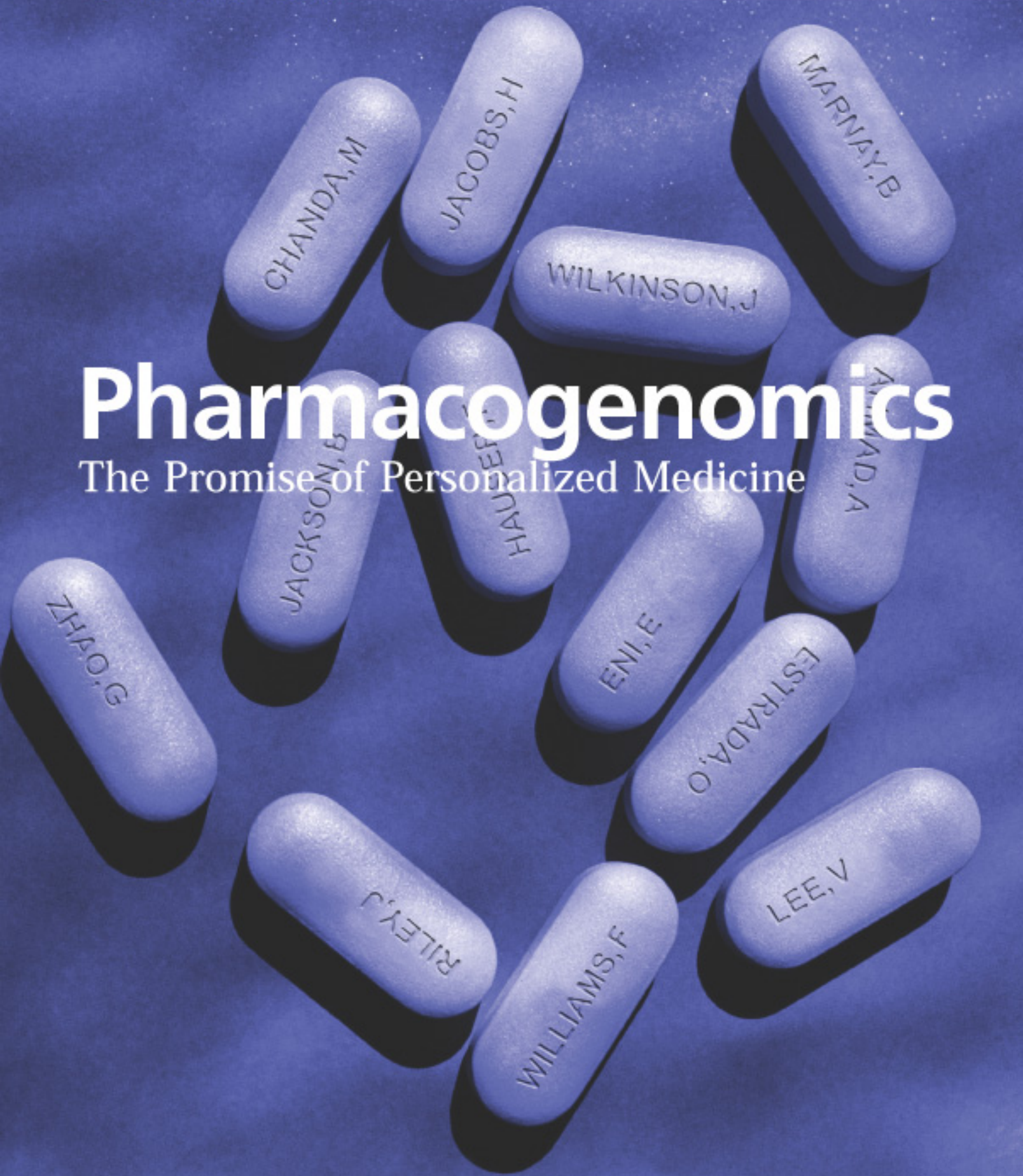


Pharmacogenomics

The Promise of Personalized Medicine

Imagine being able to walk into your doctor's office and present a "smart card" encoded either with the sequence of your genome itself or with an access code granting permission to log on to a secure database containing your genomic information. Armed with a complete and accurate understanding of your unique genome, your physician would be able to prescribe the right drug in the right dosage at the right time to effectively treat your condition, with little or no concern that the therapy won't work or that you will suffer adverse side effects. That day of truly personalized medicine is still just a gleam in the eyes of the scientists engaged in pharmacogenomics, but they are unanimous in their belief that it is achievable and that it will arrive.

Just as genomics is the study of the entire genome while genetics is the study of individual genes, pharmacogenomics looks at inheritable response to drugs over the entire genome while pharmacogenetics identifies interactions between drugs and individual genes. Pharmacogenomics seeks to uncover significant associations between genomic patterns and clinical outcomes—correlations that produce useful predictive knowledge, allowing clinical treatment decision making to be based upon more rational criteria than today's probabilistic approach, which is largely based upon educated guesswork.

Drug treatment is fundamentally a well-controlled environmental challenge to the individual, says Gualberto Ruaño, vice chairman and chief scientific officer of Genaissance Pharmaceuticals in New Haven, Connecticut. "What we learn from pharmacogenomics will also apply to envirogenomics," he says, "as relates to exposures to other challenges relevant to environmental health, such as pollution, toxins, radiation, heat and cold, and even food."

Although the enormous variability in people's responses to drugs cannot be attributed solely to their genotype, scientists believe that by understanding the genetic underpinnings of how people absorb and metabolize drugs, they will eventually quantify a great deal of that variability and be able to tailor therapies accordingly in order to optimize treatment and avoid adverse effects. The influential physician Sir William Osler summarized the problem aptly in 1892: "If it were not for the great variability among individuals, medicine might as well be a science and not an art." By solving much of the riddle of variability, pharmacogenomics may contribute to swinging the balance of medicine much further toward science.

Why Pharmacogenomics?

If pharmacogenomics can do nothing more than help reduce the frequency of adverse drug reactions (ADRs), it will have a tremendously positive impact on morbidity and mortality. According to a landmark meta-analysis appearing in the 15 April 1998 issue of the *Journal of the American Medical Association*, more than 2.2 million hospitalized patients in the United States had serious ADRs in 1994, resulting in more than 100,000 deaths and making ADRs the fifth leading cause of death in the nation. If a patient is genetically predisposed to be a poor metabolizer of a particular drug or class of drugs, when that drug is administered, even at normal dosages, amounts of the agent retained in the system can quickly build to toxic concentrations, leading to an ADR.

Experts believe that ADRs are likely to be the first area in which pharmacogenomics will benefit patients. "The first advancement

Photodisc, Chris Reuther/EHP

Favism

The advice of Greek philosopher Pythagoras to avoid fava beans was prescient, as later scientists discovered a genetic deficiency that causes acute hemolytic anemia in certain people who consume the legumes.

that's already taking place is that we will understand better what people will have a high drug level if we give them a drug, versus a low drug level," says David Hein, Peter K. Knoefel Professor and Chairman of the Department of Pharmacology and Toxicology at the University of Louisville.

Today's trial-and-error, one-drug-fits-all approach to prescribing also means that all too often a medicine is ineffective, resulting in wasted treatment time, high health care and drug costs, and, most importantly, therapeutic failures. Pharmacogenomic analysis can help identify patients who are abnormally high metabolizers of certain drugs. These people metabolize so much of the agent that it passes through their system without its intended effect.

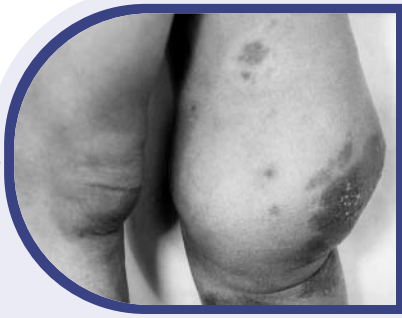
Like ADRs, ineffective drug therapy is a widespread problem in clinical practice, and it can have serious consequences, particularly in the treatment of diseases in which delays in determining effective therapy can be disastrous, such as psychiatric disorders, hypertension, and cancer. "There's an element of time in which patients are taking a drug, and it takes some period of time for that drug to become efficacious," says Michael Murphy, president and chief executive officer of Gentris, a Morrisville, North Carolina, company offering pharmacogenetic laboratory services and diagnostic tests. "Depending on the illness, that could be pretty devastating, to be taking a drug and waiting for something to happen, only to find out that it doesn't."

Penelope Manasco, chief medical officer and executive vice president of First Genetic Trust, a Deerfield, Illinois–based company involved with genetic data handling and bioinformatics, agrees. "Now most drugs are between thirty and fifty percent effective," she says. "That's a really big deal when it's something like a drug for depression. It can take people six months to a year to get on the right drug. And with pharmacogenomics, they'll be able to have a test that will say instead of having a thirty or forty percent chance, they'll have a seventy or eighty percent chance that this medicine will work."

Scientists in pursuit of personalized medicine believe that although pharmacogenomics has already begun reaping benefits, the field is still in its infancy, and change will come gradually. "In the short term," says Hein, "we're going to have less drug toxicity. In the long term, we're going to have much better drug effectiveness."

Roger Ulrich, senior scientific director of Rosetta Inpharmatics, a subsidiary of Merck engaged in the application of pharmacogenomics to the drug discovery process, feels that it's going to be a while until there's a practical, everyday application of pharmacogenomics approaches. Clinical trial data already show there's variation in response for almost any agent, he says. "I think over the next several years, we'll understand why we see variation in response. . . . And there will be a sort of gradual assimilation of that data into practice," he adds. "I don't think any of us are going to wake up one morning and go, 'Wow, we've finally entered the era of individualized medicine.' However, within research, the impact of pharmacogenomics has already been positively felt, from the way we discover and validate therapeutic targets to the way we explore drug safety and design clinical trials."

Rochelle Long, chief of the Pharmacological and Physiological Sciences Branch of the National Institute of General Medical Sciences (NIGMS), foresees a similar pattern of steady development in knowledge and implementation of pharmacogenomics: "I think progress will be incremental. . . . Within the next one to five years, we're simply going to understand enough to, in a systematic way, better use some of the drugs that are already on the market." Within 5–10 years



Alkaptonuria

In 1902, while investigating alkaptonuria, a rare inherited enzyme deficiency that results in joint disease, physician Archibald Garrod suggested that genetic differences in metabolism may be responsible for adverse drug reactions.

Top to bottom: Alamy; CDC

Taste Blindness

In 1931, in what is regarded as the first pharmacogenetic findings, chemist Arthur L. Fox reported on "taste blindness," an inherited difference in subjects' ability to taste phenylthiocarbamide.

after that, she says, there should be a little more progress in the area not of drug metabolism, but of variants in target receptors themselves; within the period after that, people are going to start better understanding the genetic basis of complex diseases such as hypertension, and drugs will be designed based on that understanding.

Pharmacogenetics Begat Pharmacogenomics

Pharmacogenomics may be in its infancy, having only recently come into its own on the heels of the advances in knowledge, method, and technologies generated by the Human Genome Project. But the discipline has deeper roots in pharmacogenetics, a field of study that has been formally recognized for more than 50 years, and that existed in practice much earlier.

"Avoid fava beans." So Greek philosopher Pythagoras instructed his followers in the sixth century B.C., supposedly because he noticed that consumption of fava beans made some people sick. Pythagoras may or may not deserve to be called the father of pharmacogenetics, but his observation was on the money—in the twentieth century, scientists discovered that ingestion of uncooked fava beans can cause acute hemolytic anemia, a serious red blood cell disorder, in certain populations. In the 1950s, it emerged that an inherited deficiency of glucose-6-phosphate dehydrogenase, a red blood cell enzyme, caused this reaction, known as favism. Today, this enzyme deficiency is known to be a relatively common disorder among certain populations, and has subsequently been linked to sensitivity to a variety of drugs, particularly antimalarial agents and sulfa antibiotics.

The emergence of pharmacogenetics in the twentieth century followed a path forged by advances in molecular biology and genetics. In the mid–nineteenth century, scientists learned that ingested substances were excreted in different forms, establishing the concept of metabolism. In 1902, the physician Sir Archibald Garrod, investigating alkaptonuria, a rare inherited enzyme deficiency, suggested that enzymes were important in the detoxification of foreign substances, and that genetically determined differences in the operation of enzymes (characterized by Garrod as "inborn errors of metabolism") could be responsible for ADRs. The year 1931 saw what is regarded as the first pharmacogenetic findings, when chemist Arthur L. Fox reported on "taste blindness," an inherited difference in subjects' ability to taste phenylthiocarbamide.

Before technology allowed the study of individual genetic variation, the field concentrated on identifying racial and ethnic variations in response to drugs. Most notable among several landmark studies, perhaps, was University of Toronto professor emeritus Werner Kalow's investigation in the 1950s of the occurrence of prolonged paralysis and rare, unexplained deaths in surgical patients receiving succinylcholine, a neuromuscular blocker tolerated well by most patients. Kalow discovered that a genetically based deficiency in the metabolizing enzyme pseudocholinesterase was responsible, and proceeded to describe the population incidence of the various alleles responsible for the deficiency. Similar studies confirmed the genetic basis of the variability, seen in response to a wide variety of drugs.

As the wider fields of genetics and molecular biology progressed, so did pharmacogenetics. Now essentially folded into the burgeoning science of pharmacogenomics, the discoveries that have emerged from the progenitor field are today available and in use in the diagnostic arena, helping to screen patients who fall into broad populations that, due to their metabolic genotypes, should not receive specific drugs. As Murphy states it, "The reality is that for a lot of genes that we've known about for the last twenty or thirty years, the need is to have a clinical test that defines two or three patient populations [i.e., normal, high, and low metabolizers], and we can do that now."

SNPs and Haplotypes

The remarkable innovations that led to the sequencing of the human genome spawned a great leap forward, as pharmacogenetics spawned pharmacogenomics. Technological breakthroughs such as polymerase chain reaction, high-throughput robotic sequencing, and DNA microarrays, as well as simultaneous advances in bioinformatics—which brought the ability to mine the mountains of data produced for nuggets of useful knowledge—have allowed the field to move forward quickly, as the genome begins to reveal some of its age-old secrets. Perhaps most significant to pharmacogenomics has been the relatively

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Succinylcholine-Induced Paralysis

In one of the first descriptions of the genetic basis of variability in drug response, professor Werner Kalow reported that paralysis after receiving the neuromuscular blocker succinylcholine was due to a genetically based deficiency in pseudocholinesterase.

recent discovery of two related genetic phenomena—single-nucleotide polymorphisms, or SNPs, and haplotypes. They have transformed the notion of personalized medicine from fond fantasy to realistic goal.

SNPs are single-letter variations in DNA sequence that happen in at least 1% of the population (lower-frequency variations are considered to be mutations). They occur every 100–300 bases along the 3 billion base pairs making up the human genome. By collecting and analyzing the DNA of a diverse group of many individuals, researchers are working toward identifying SNPs that are relevant markers of drug response and disease susceptibility, an endeavor they hope will ultimately yield diagnostic tests and targeted drugs based on genotype.

The discovery that SNPs tend to occur in patterns or blocks called haplotypes may help speed the process of squeezing clinically relevant information out of the human genome. Haplotypes are inherited groups of SNPs that occur within a defined region of the chromosome, and some of them may influence drug response more than individual SNPs do. Some experts believe that identifying haplotypes of interest will yield more useful biomarkers of response by accounting for genomic variation in the multiple genes often involved in drug response.

Genaissance Pharmaceuticals is one biotechnology company banking heavily on the value of haplotypes. "The haplotype is composed of multiple SNPs, but it has the advantage and the power that it has the SNPs grouped into an alignment as to how they occur in the chromosome and code for different versions of the gene," says Ruaño. "Because of that resolution and symmetry with the physiology and the function, the haplotype is therefore a much higher-resolution technique for looking at genetic associations."

Murphy agrees to a point: "Sometimes when we don't know how mutations segregate—that is, the pattern of how they fall on the two copies of every gene that we get from our parents—then we have to do haplotyping. Where we do know [how mutations segregate] . . . haplotyping would just be overkill. So sometimes it's needed, but sometimes it's not, and you just have to take it on a case-by-case basis. Whether it be SNP analysis or haplotyping, the most important thing is that we can predict phenotype, or clinical outcome."

Pharmacogenomics Initiatives

The rapid development of pharmacogenomics has led to an encouraging amount of scientific cooperation and collaboration among government, industry, and academia. "There's always some competition, but actually I think people have been very collaborative," says Manasco. "One of the key things that's going to be needed is more money for this translational research . . . so that the people who actually win are the patients."

Ulrich voices similar sentiments. "It's a whole different approach to science, this large-scale international consortium approach," he says. "There are pockets of opportunity for each individually, but because of the size of the challenge, it's going to take a continued joint effort."

Large-scale collaborative initiatives are making significant contributions to the effort to eventually bring the benefits of pharmacogenomics to the bedside. One such effort, the Pharmacogenetics Research Network (PGRN), was established in 2000 and currently funds 13 academic research groups conducting basic research describing pharmacogenetic phenotypes and relating them to genetic and genomic information. The PGRN is spearheaded by the NIGMS, with the participation of the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Human Genome Research Institute, the National Library of Medicine, and the NIEHS, making it a true trans-NIH effort.

Long, the NIH program director for the PGRN project, says the network stresses high-quality research. "We want interdisciplinary groups of researchers," she says, "who are coming together and putting their brains and expertise together to design the very best pharmacogenetic projects, and then execute them, collect the data, and put it in the database."

The database she refers to is the Pharmacogenetics and Pharmacogenomics Knowledge Base, or PharmGKB (**http://www.pharmgkb.org/**), developed by and based at the PGRN grantee group at Stanford University. Long emphasizes that although the data from PGRN members are the core resource of the PharmGKB, the database is open to access and contributions by one and all. "These data are all made public: the tools and resources that [PGRN members are] generating, primers, or any sort of chips they're

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developing, or reagents," Long says. "The intention also is to make [these resources] available to the community at large. . . . So we're impacting all pharmacogenetics researchers, whether or not they're presently a member of this network." [For more information on both of these efforts, see "The Pharmacogenetics Research Network and the Pharmacogenetics and Pharmacogenomics Knowledge Base," p. A575 this issue.]

In 1999, the International Life Sciences Institute Committee on the Application of Genomics in Mechanism Based Risk Assessment was formed. This international consortium, with participants from industry, government, and academia, evaluates experimental methodologies for measuring alterations in gene expression, and, in collaboration with the European Bioinformatics Institute, is building an extensive database of microarray assays and analyses, which is scheduled to be made public in 2004. A March 2003 white paper reporting on the committee's status and recent findings is publicly available at **http://rsi.ilsi.org/file/ACF539D.pdf**.

Also formed in 1999, The SNP Consortium (TSC) is a nonprofit collaborative effort among several major pharmaceutical companies, technological companies, and academic research centers, along with the Wellcome Trust, with the target of identifying 300,000 SNPs of biomedical interest. The discovery phase of the project, which is now essentially complete, in the end identified 1.8 million SNPs. The group viewed this high-density SNP map, which is publicly available online at **http://snp.cshl.org/**, as an important resource for defining haplotype variation across the genome, and a rich source of new genomic information about disease susceptibility, drug response, and novel therapeutic targets.

The SNPs identified by TSC contributed a major source of data for another extensive public library of variations, this one hosted by the National Center for Biotechnology Information. This library, dbSNP, located online at **http://www.ncbi.nlm.nih.gov/SNP/**, now contains more than 4.1 million human SNPs, a significant portion of the estimated 10 million common SNPs in the human genome.

More recently, a $100 million public–private research consortium called the International HapMap Project was launched in October 2002. Expected to take three years to complete, the HapMap will map the haplotypes in the human genome, obviating the need to study all 10 million SNPs. With the abundant information embedded in haplotypes and their variation across populations, the HapMap is expected to be a powerful new tool for researchers to conduct association studies. This will allow them to precisely identify significant genetic variations in disease susceptibility, drug response, and even infectious disease resistance and longevity [also see "HapMap: Building a Database with Blocks." *EHP* 111(1T):A16 (2003)].

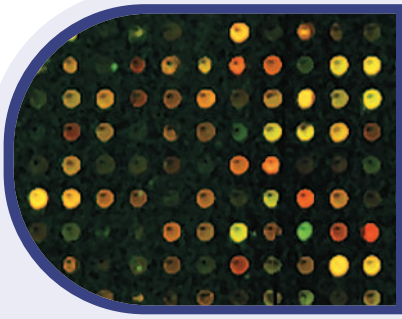
SNPs and Haplotypes

The analysis of two genetic phenomena—SNPs (single-letter variations in DNA) and the patterns that they occur in, known as haplotypes—allows researchers to identify biomarkers of drug response and disease susceptibility.

Pharmacogenomics and the Pharmaceutical Industry

The pharmaceutical industry has seen the future. In a 9 April 2003 presentation to a U.S. Food and Drug Administration (FDA) Science Board Advisory Committee meeting, Brian Spear, director of pharmacogenomics at Abbott Laboratories in Abbott Park, Illinois, put it succinctly: "[Pharmacogenomics] is not something that a company here and a company there have taken a chance on. This is now a standard part of the drug discovery and development process in every one of the drug discovery and research companies."

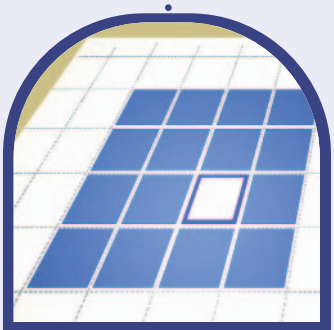
The industry's avid pursuit of pharmacogenomics, as evidenced by a recent spate of acquisitions of pharmacogenomically oriented biotechnology firms by the major pharmaceutical companies, runs the gamut from drug discovery to enhancing the safety and efficacy of drugs that have been on the



Gene Technologies

Breakthroughs such as polymerase chain reaction, high-throughput robotic sequencing, bioinformatics, and DNA microarrays have enabled great leaps forward in the ability to quantify and analyze genetic data.

Top to bottom: Chris Reuther/EHP; Steve McCaw/Image Associates



The SNP Consortium and HapMap

A nonprofit collaborative organized in 1999, The SNP Consortium has identified 1.8 million SNPs of biomedical interest and arranged them in a publicly available high-density SNP map. In 2002, the private–public $100 million HapMap research initiative was launched to map all of the haplotypes in the human genome.

market for many years. Just as the days of the one-drug-fits-all treatment approach may be numbered, so too may be those of the present pharmaceutical industry business model, which relies heavily on the periodic introduction of blockbuster drugs (typically defined as products with annual revenues in excess of $1 billion) to generate profits and fund research and development. The hope is that the application of pharmacogenomics and other genomics technologies will enable a new paradigm to emerge, with lower development costs, fewer candidate drug failures, revitalized existing products, the possible resuscitation of withdrawn drugs, and a "portfolio" approach to the introduction of new agents, with drugs available in different formulations to maximize safety and efficacy in specific phenotypic populations.

According to *A Revolution in R&D: How Genomics and Genetics Are Transforming the Biopharmaceutical Industry*, a 2001 report by The Boston Consulting Group, it currently takes on average $880 million and 15 years to bring a new drug to market. Failed candidate compounds represent a large proportion of that development cost—right now, only about 10% of compounds that enter clinical development make it to the marketplace. The Boston Consulting Group estimates that the effective application of genomics technologies could reduce that staggering investment by as much as $300 million and two years.

Ulrich is optimistic that pharmacogenomics can play a major role in increasing drug development productivity. "The real cost savings will be that we have fewer failures going into development," he says, adding, "Making better choices is really what it's all about. In the end, you might develop just as many compounds, but you're going to have more successes. You'll spend just as much money, but you'll get a greater return on investment."

Ruaño anticipates that pharmacogenomics will contribute to all pharmaceutical products, from new candidates to old warhorses. "The bottom line is that if you match the chemical and pharmacological properties of the drug to a target population that benefits from that drug, you have a new product," he says. "I believe that can be applied to old, new, and in-the-middle drugs, in-the-middle being the ones that are in clinical design and trials, the new being early-discovery ones from genomic targets, and the old, the ones that we have already on the market."

Many pharmaceutical companies are already using pharmacogenomics to screen participants in clinical trials. Murphy, whose company provides such screening services to the major pharmaceutical companies, has seen this concept evolve from novel idea to accepted necessity. "We have a number of clients now who routinely screen every single volunteer at Phase I for the important drug metabolism genes," he says. "That's a big paradigm shift. And then they consider those same inclusion/exclusion criteria, or stratification as they call it, as they continue to develop that same drug in Phases II through IV."

The FDA appears to be solidly on board the pharmacogenomics bandwagon as well. The agency has reportedly been working hard recently to acquire the necessary in-house expertise to facilitate the submission, interpretation, and implementation of pharmacogenomics data. "These studies are being widely done, and they may have tremendous progress," said Janet Woodcock, director of the FDA Center for Drug Evaluation and Research, at the agency's 9 April 2003 Science Board Advisory Committee meeting. "We need to find a way to get the information in, develop our policies, develop a regulatory framework, . . . and help to move this field

Pharmacogenetics Research Network

Formed in 2000 by the NIH, this network funds 13 academic research groups to describe pharmacogenetic phenotypes and relate them to genetic and genomic information.

Top to bottom: TSC; PGRN

Clinical Trials

Pharmacogenomics is already being used to screen participants for drug clinical trials, thereby saving money, time, and effort.

along." Later this year, the FDA is expected to issue guidelines designed to enable the free exchange of information between the industry and its regulators, with the goal of bringing the benefits of pharmacogenomics to the bedside as soon as possible.

Applied Pharmacogenetics

Most of the promise of pharmacogenomics remains to be fulfilled. However, the concept of using known genetic associations to prevent patients from taking drugs that would likely be ineffective or harmful is already available and used in clinical practice in certain specific arenas, thanks mainly to the steady progress made in pharmacogenetics over the past several decades.

Cancer therapy today includes two shining examples of applied pharmacogenetics. First, there is now a commercially available diagnostic test measuring a patient's ability to produce the metabolic enzyme thiopurine *S*-methyltransferase (TPMT), which is essential for the metabolism of thiopurine medications used to treat acute lymphoblastic leukemia (ALL), the most common form of childhood cancer. Genetic testing gives clinicians the ability to classify ALL patients according to their TPMT genotype, which allows optimized dosing. Doses in patients with alleles rendering them deficient in TPMT (who are thus less tolerant of thiopurine medications) are reduced by as much as 95%. This means TPMT-deficient patients can tolerate the drug, yet enough is still metabolized to retain efficacy.

Second, the breast cancer drug trastuzumab (trade name Herceptin), which is marketed in tandem with a diagnostic test, is often cited as an early indicator of the value of the concept. Trastuzumab is effective only sin the 25–30% of breast cancer patients whose tumors overexpress the human epidermal growth factor receptor (HER2) protein. The drug was developed specifically to exploit that characteristic; it binds to HER2, which slows tumor growth. The diagnostic test measures HER2 expression in the tumor and is thus predictive of the potential efficacy of the drug; patients who do not overexpress HER2 are not given the drug, because it will not work.

This is a unique combination today. But such diagnostic–agent pairings will become more commonplace as pharmacogenomics progresses and strides are made in disease genetics, in which a variety of diseases (particularly cancer) are being genetically subclassified, often significantly redefining treatment strategies.

An intermediate step toward such pairings is illustrated by work being done with the cytochrome P450 (CYP450) family of enzymes, which is responsible for a large segment of human drug metabolism. It is the metabolic pathway of choice for about 60% of the drugs on the market today. It has also been the focus of a great deal of research attention through the years, and the numerous CYP450 subtypes are well characterized, as are the important phenotypes of variation in response. Several companies now offer CYP450 genotyping tests to the pharmaceutical industry for clinical trial subject inclusion/exclusion based upon metabolic profile, and now such tests are making their way into the clinical diagnostic marketplace. Gentris, for example, soon expects to market five kits to physicians for pharmacogenetic testing of their patients. Genelex Corporation of Seattle, Washington, has taken the concept one step further, marketing tests directly to the public for three of the major CYP450 pathways—CYP2D6, CYP2C9, and CYP2C19. Once a consumer has placed an order for the test, Genelex sends them a blood collection kit, and the consumer either sees their own doctor or Genelex will refer them to a phlebotomist in their area.

Pharmacogenomic tests appear to be just over the horizon. In March 2003, at the 52nd Annual Scientific Session of the American College of Cardiology, Genaissance presented results from its STRENGTH (Statin Response Examined by Genetic Haplotype Markers) prospective clinical study, which showed that haplotype variations are associated with response to treatment with the statin class of cholesterol-lowering drugs. The associations discovered in the study were strongly predictive of efficacy. Genaissance plans to eventually develop the information into a point-of-care diagnostic test that will help physicians choose the safest and most effective drug for individual patients, maximizing the prevention of cardiovascular disease afforded by the statins. The company has performed similar studies of response to asthma drugs, and other researchers in industry, academia, and government are making substantial progress in establishing variability associations for drugs used to treat hypertension, depression, HIV, cancer, and several other conditions whose patients

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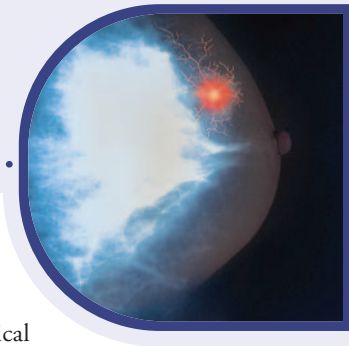


Cancer Therapies

Screening a patient's ability to produce the enzyme TPMT helps doctors determine optimal doses of medicines used to treat acute lymphoblastic leukemia in children. And the breast cancer drug trastuzumab is now marketed with a test to measure overexpression of the drug's target protein, HER2. The drug is ineffective in women who do not overexpress HER2.

stand to benefit from optimized prescribing.

Ethical Concerns

On one level, the ethical issues involved with pharmacogenomics are similar to those raised by genomics in general—broad concerns about research integrity, privacy, confidentiality, informed consent, the specter of genetic discrimination or stigmatization, and access to information or to specialized care. "There are certainly inherent problems that will not go away with pharmacogenomics research," says Patrick Terry, president of PXE International, a patient advocacy and research support group for victims of pseudoxanthoma elasticum, a rare genetic disorder that affects connective tissues. "They're certainly not new and different for pharmacogenomics research. Privacy, confidentiality, and misuse or misappropriation of data were the same twenty years ago as they are today."

Alan Combs, Johnson & Johnson Professor of Pharmacology at the University of Texas at Austin, is excited about the potential benefits of pharmacogenomics but worried about how people will apply the science. "It's the goose that laid the golden egg in potential," he says, "but you have to be very careful with that goose. I don't see where the line is going to be drawn between using it for good and abusing it. The advances are inevitable, and they're neutral—it's how we use them."

Many observers, however, feel that the ethical issues specific to pharmacogenomics are actually somewhat less problematic than the ethical lightning rods attached to genetics or even to pharmacogenetics. One crucial difference lies in the nature of the information itself, which typically applies to individual patients as opposed to larger groups. Says Combs, "The beneficial decisions you make on an individual basis are almost always good. The decisions you make based on populations are not nearly so likely to be good."

Ulrich draws another ethical distinction between pharmacogenomics and pharmacogenetics. "When you evaluate phenotype and use phenotype to stratify a patient population, it isn't necessarily linked to genotype, so you haven't actually put a label on the individual," he says. "So I think there's plenty of room for pharmacogenomics without the ethical concerns that go along with pharmacogenetics; there's a difference."

Ruaño agrees that the ethical issues connected to pharmacogenomics are perhaps less urgent. "The reason is that the core of pharmacogenomics is pharmaceutical intervention," he says. "The fact that we're talking about genomics that has a 'pharmaco-' attached to it means that the purpose is treatment, not primarily diagnosis of the disease."

Of course, such distinctions could be lost on patients without the appropriate educational efforts and informed-consent safeguards in place, in both research and clinical settings. "I don't know why anybody wouldn't want to know whether what their doctor is prescribing will actually work for them," says Carol Isaacson Barash, founder and principal of Genetics, Ethics & Policy Consulting, a Boston company that consults to medical and technology groups. "But I think the public is still a bit fearful of what genetic testing is and what it isn't, and how it could help and how it could hurt them."

Terry voices similar concerns: "I think there are certainly misunderstandings in both the professional and patient communities, both fears and emotional issues on these technologies that may be real or may not be real, but that nonetheless touch on some kind of organic or intuitive fear of the technology and what's being sold."

Today, pharmacogenomics is still predominantly a research endeavor, and the nature of informed consent is presently the most prominent ethical consideration for investigators. Manasco, whose company offers itself as a repository for and gatekeeper of access to patients' genetic data, sees an evolution in the concept of informed consent. "It's one of the big issues, making sure that people understand what their samples will be used for," she says. "We're actually at a turning point from when people gave consent for whatever researchers wanted to do with their samples, to the point now where the ethics community is becoming more restrictive in what they will allow, because in fact you truly cannot give informed consent if you're saying, 'You can use my sample for whatever research you want in the future.'" She adds, "I expect over time multiple approaches will be used to make sure people are really informed, that they don't just get a five-page sheet; . . . that

Image Source

they really understand what they're being involved in."

Achieving the appropriate level of informed consent could prove to be a major challenge, as participants will need to comprehend that their DNA could be used for multiple experiments over a long period of time, and that in many cases, their samples will not be anonymous. In many pharmacogenomics studies, anonymization of samples defeats the purpose of drawing associations between drug response and populations.

On the other hand, participants' access to the information discovered about their genomes is also a thorny issue for researchers. Obligations need to be negotiated in advance during the informed-consent process, and must be in place in situations when an individual is found to have a particular abnormality in his or her response to certain drugs, or perhaps an increased risk of disease due to a genetic susceptibility.

"These are really difficult issues, and you've got to come up with solutions," says Manasco. "You can have the best science in the world, but if your ethics aren't sound as well, and you haven't carefully thought about and addressed those issues, it doesn't matter. It isn't something that is a bother. This is the right thing to do."

Impact on Health Care Costs

With pharmacogenomics innovations just now starting to emerge, the jury is still out on what effect they will ultimately have on health care costs. However, most observers are cautiously optimistic that pharmacogenomics eventually will reduce costs. Initially it may cost more to run additional tests, but as the practice becomes more commonplace, the actual benefits of pharmacogenomics will come into play, says Long. "There's up-front investment," she says, "but ultimately, if applied correctly, in the right sort of legal–social framework, medical costs might not necessarily go up, but may even go down."

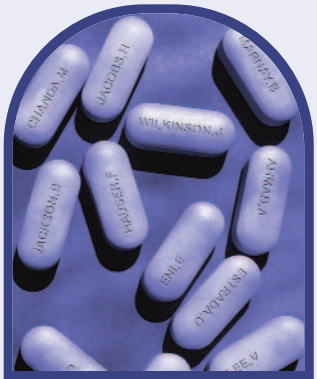
Ruaño echoes that view. "I do believe that the cost issue is going to be a challenge. However, it is really no different from any innovation in medical technology," he says. "Initially, it is going to be expensive because it's a first-generation product. The costs will decline, and it will pay for itself in terms of efficacy to the patient and reductions in side effects."

Hein is more sanguine on the issue. "There's no question in my mind that ultimately you are going to save money through pharmacogenetics," he says. "It makes perfect sense to me that health care costs are going to come down—and hopefully rather substantially—with this type of technology, because there's a lot of drug toxicity and a lot of drug failure out there that we hope in the future can be minimized."

The issue will be decided only when answers to important open questions are found as events play out in the coming years. Will payers embrace pharmacogenomic testing and customized drugs? Will drug companies charge a premium for new, targeted therapies? Will patients demand access to this information and these products, or will they be leery? Will clinicians, who are notably slow to adopt innovations, educate themselves enough to appreciate and effectively apply the new decision-making tools of pharmacogenomics? Will those of us alive today live to see the dream of truly personalized medicine for everyone come true?

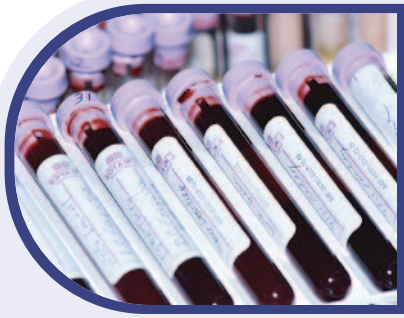
Ruaño is optimistic that we will. "I think the history of technology has shown us that many things we never expected to be real really have moved very quickly," he says. "So watch for the data that are coming out, watch out for publications and associations of drugs. Once those are established, the technology and the approval and the acceptance will take care of itself."

Ernie Hood



The Future?

Pharmacogenomics offers the hope of using genetic profiling to personalize—and thereby improve—medical treatment of a variety of diseases, including hypertension, depression, cancer, and HIV.



CYP450 Tests

The CYP450 family of enzymes is the target of 60% of drugs today. Companies are now marketing CYP450 genotyping tests to physicians and the public to help predict optimal dose and drug efficacy.

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