THE NEW NEW PHARMACOGENOMICS

[PART ONE OF A TWO-PART SERIES]

BY MALORYE BRANCA

One of the most seductive lures of the genomic revolution is the promise of personalized medicine. The rapid identification of tens of thousands of human genes and hundreds of thousands of DNA variations that might influence disease susceptibility has spawned a new field — pharmacogenomics. Dozens of companies have sprung up over the past few years, quantifying and cataloguing human genetic variation and using algorithms to tease out correlations among markers, genes, diseases, and drug response.

"Pharmacogenomics is the necessary beginning for the entry into personalized medicine," says Kari Stefansson, CEO of deCODE genetics in Reykjavik, Iceland.

But today, most pharmaceutical companies are more concerned with weeding potentially dangerous compounds out of their pipelines than with finding the ideal drug for the right patient. For some, this is a stunning disappointment, but for the industry as a whole, this diversion on the path to personalized medicine provides an exciting new way to combat the serious issue of toxicity-related drug failure — one of the industry's biggest problems.

Scattered throughout the human genome are millions of discrete, one-letter variations known as SNPs (single nucleotide polymorphisms). Most SNPs are benign, with absolutely no effect on gene structure or expression. But a subset of these variations provides crucial links to disease-causing genes, either because they directly alter a gene's activity or because they help pinpoint the location of such a disease-related gene.

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PHARMACOGENOMICS: The application of genomic concepts and technologies to the study of drug activity and metabolism, including gene expression, or inactivation, and SNP association studies.

Photograph by Ann Elliott Cutting

While the promise of a new era in **personalized medicine** still seems a long way off, the field of pharmacogenomics is proving its mettle in the battle against **toxicity** and late-stage **drug failure**, one of the pharmaceutical industry's worst problems.

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Their abundance and facile identification make SNPs the new markers of choice for genetic studies, particularly for those seeking to unravel complex diseases like Type 2 diabetes, caused by the interplay of multiple genes and environmental factors. SNPs are also found in genes for drug-metabolizing enzymes, influencing individuals' ability to process a drug properly.

Many companies have compiled large collections of SNPs with a view to developing diagnostic and prognostic tests, as well as to guide the development of a new generation of drugs that would target genetically determined subsets of patients. Companies including Genset SA (recently acquired by Serono SA), DNAPrint genomics, deCODE genetics, Genaissance Pharmaceuticals Inc., and Oxagen Ltd., as well as a few pharmaceutical giants such as GlaxoSmithKline and Novartis AG, invested heavily in the field. Dozens of tool companies also sprang up offering a range of technologies for SNP detection and genotyping (see "Tools of the Trade," page 55).

Although the research, clinical, and investment communities loved the idea at first, pharmacogenomics is a prime example of how new biotechnologies are often far more complicated than expected (recall monoclonal antibodies and antisense, for example). Only in this case, people underestimated both the business and the scientific issues.

FURNALD & GRAY

Variagenics' R. Mark Adams (left), vice president of bioinformatics, and Jay Mohr, president and chief business officer, have seen pharmacogenomics change as the industry struggles to come into its own.

A Bumpy Ride

"The early story was, 'We'll find genetic variation that we can relate to drug effects, whether it is toxicity or efficacy, create mechanisms for assaying that, and license that out,'" recalls R. Mark Adams, vice president of bioinformatics at Variagenics Inc., based in Cambridge, Mass. "Finding SNPs wasn't the hard part. In fact, that proved to be easier than anyone anticipated."

In 1999, The SNP Consortium Ltd., made up of pharma companies and funding organizations, began identifying and publishing on the Web more than 1 million SNPs, thus preventing any pharmacogenomic company from claiming a monopoly. The result was an "early one-two punch," says Adams. "First the data became plentiful, then it wasn't even clear if you could patent it."

Another problem was the pharmaceutical industry's concern that by subdividing patient populations, pharmacogenomics would segment the multibillion-dollar markets that they depend on. "The industry is not sure whether this is friend or foe. Will it cause people to take more of their drug or less?" says William Evans, chairman of pharmaceutical sciences at St. Jude's Children's Hospital in Memphis, Tenn.

"The early story was, 'We'll find genetic variation that we can relate to drug effects, whether it is toxicity or efficacy; create mechanisms for assaying that; and license that out.'"

R. Mark Adams, *Variagenics Inc.*

As a result, pharmacogenomics companies hoping for licensing arrangements found they were waiting much longer than anticipated. "They didn't see a value proposition, so it was much harder than we thought to get those Big Pharma deals," says Jay Mohr, Variagenics' new president and chief business officer.

"Like everyone else, we anticipated that the early demand for this would be much bigger than it turned out to be," says Richard Judson, senior vice president of informatics at New Haven, Conn.-based Genaissance.

As a result, many business plans have been hastily rewritten — some even scrapped. DNAPrint, for example, is developing forensic as well as pharmacogenomic tests, while Variagenics is focusing on their own oncology diagnostics. Genaissance is still pursuing its groundbreaking STRENGTH (Statin Response Examined by Genetic HAP Markers) study, seeking markers associated with the effects of therapy using the blockbuster cholesterol-lowering statin drugs. But the company is also diversifying, doing gene expression studies and marketing the HAP database and DecoGen informatics platform

Large pharmaceutical firms, meanwhile, are hedging their bets. Mohr cites figures from clinical research firm Covance Inc. estimating that 80 percent of Covance's large pharmaceutical clients are banking DNA samples from patients enrolled in clinical trials, even if they are not actually doing association studies. "Even companies like GlaxoSmithKline and Bristol-Myers Squibb, which are most heavily involved, are doing many fewer studies relative to the rest of the field," says Adams.

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So what are the big companies doing with all of that DNA? And how are they actually using pharmacogenomics?

Bomb Scares

A prime concern of the pharmaceutical industry is avoiding drugs that fail in clinical trials or, even worse, after approval. "The cost of drug development is shaped like the outline of a brontosaurus," says venture capitalist Jerry Karabelas of Princeton, N.J.-based Care Capital. The tip of the dinosaur's tail marks the discovery starting point, while its lofty head represents the high cost of completing clinical trials. Once the drug is on the market, the human and financial toll of unforeseen side effects becomes even greater.

The lessons of several spectacular drug withdrawals, including Fen-Phen, Rezulin, and Baycol, have fueled demand for improved means to test prospective drugs for toxicity. The mantra "Fail fast, fail cheap" was probably first coined by Michael Pavia, former chief technology officer for Millennium Pharmaceuticals Inc., in describing how the company planned to secure its pipeline. Pavia's phrase quickly caught on as more genomics firms vied to demonstrate the quality of their drug selection process.

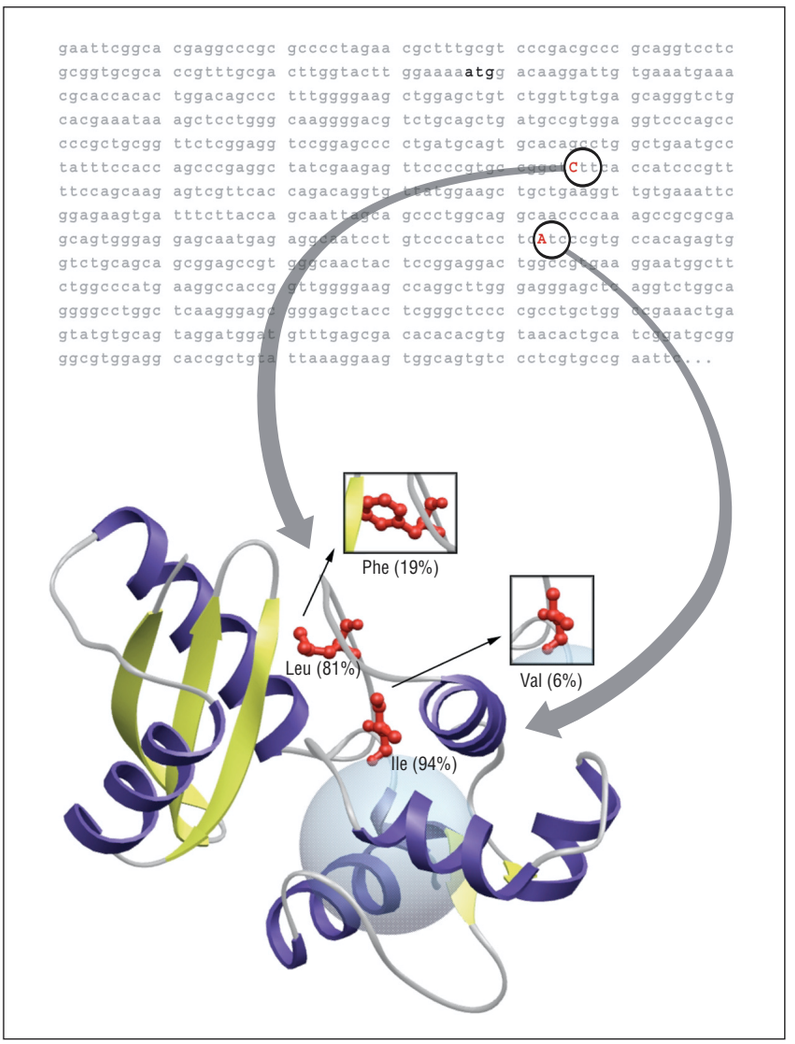
Identifying better drug candidates to begin with is good, but what about the hundreds of candidate drugs already in development, many of which have years of research invested in them and could reach the market in just a few more years? Pharma companies are desperate to pick through those or improve their chances of success. Pharmacogenomics could help with both problems by opening an early window into a compound's effects on drug metabolism and toxicity.

For example, about 60 percent of all marketed drugs are broken down in the body by the cytochrome P450 family of enzymes. Individuals vary greatly in the efficiency of their P450 enzymes: Some people are poor metabolizers, while others metabolize very quickly. An individual's CYP450 profile could thus predict if he or she will experience side effects when given a particular drug or not respond at a particular dose.

Of the 50 or so pharmacogenomics-related new drug applications and investigative new drug applications received by the FDA in recent years, two-thirds involve screening patients for drug-metabolizing enzymes. Investigators want to find out early about potential population-specific toxicities and dosing requirements.

What about the banked DNA? The FDA may someday demand genotype information as part of the drug application process, and genotyping costs are likely to decrease significantly in the coming years. But there is another possible use for these samples. "You can run your trials, bank the DNA, and then not worry about it unless something comes up," explains Colin Dykes, a consultant and former research director at Variagenics. If a cluster of patients emerges with an unusual response to the drug, the DNA can be tested retrospectively, and perhaps a new trial initiated or the labeling adjusted. By genotyping only when necessary, companies avoid doing high-cost association studies.

Financial restraint isn't the only reason for the highly selective interest in genotyping. Some researchers think that it's also scientifically sensible. "Today, people are more realistic about how genetics will impact drug development," says Brian Spear, director of pharmacogenetics at Abbott Laboratories in Abbott Park, Ill. "Previously, the idea was that we would identify the right patient population, we would create new drugs, and we would sell them specifically for those patients. People have done enough work to determine how difficult it is and how infrequently this will happen. What people are learning is that there are a lot of ways to use genetics within pre-clinical and clinical development that are turning out to be quite useful."



SNPs in action. At top, the DNA sequence of the gene for methyl guanine methyl transferase (MGMT), an important DNA repair enzyme. The start of the coding sequence is shown in bold (atg). Two non-synonymous SNPs that result in amino-acid substitutions in the MGMT protein, are highlighted in red (ctt to att; atc to gtc). Below, the resulting amino-acid changes in MGMT indicated as red amino acid residues: leucine to phenylalanine (position 84), and isoleucine to valine (position 143). Also shown are the respective frequencies of each allele. The light blue sphere shows the active site of the protein, close to the Ile-to-Val polymorphism.

Tox Screen

Toxicogenomics, a fledgling offshoot of pharmacogenomics, is proving a lot easier for the industry to swallow. It doesn't break up blockbuster markets or require a complete redesign of the pharmaceutical business model. Instead, it's a fresh new tool that could help solve one of the industry's biggest headaches.

Companies like Gene Logic Inc., Phase-1 Molecular Toxicology Inc., and Iconix Pharmaceuticals Inc. are creating gene expression databases filled with signatures of toxic responses in humans or traditional animal models. Chip manufacturers, including Affymetrix Inc., Motorola Inc., and BD Biosciences Clontech, are marketing ADME (absorption, distribution, metabolism, elimination/excretion) and toxicology chips to screen for drug toxicity or determine if patients need a dose adjustment. Although the emphasis is currently on gene expression, SNP chips are also coming into use. (Screening tests based on protein and metabolite signatures are not far off.)

"We have chips with a whole range of genes, including some that are specific for toxic responses, such as genes in the liver and kid-

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neys," says Phillip Stafford, group leader in statistical informatics at Motorola Life Sciences. The company has developed the CodeLink expression arrays including chips containing human, mouse, and rat genes. (The Codelink business line was recently acquired by Amersham Biosciences.) "Some drugs have a perfectly good response on the targets, but a latent response elsewhere," Stafford explains. "Expression chips can tell you if, two or three months down the road, you've got a latent toxic response in the kidney."

In the clinic, gene expression or SNP chips can be used to zero in on subpopulations that are at risk for either a bad response or no response. "Researchers at the Mayo Clinic used our P450 SNP chip to screen patients in a trial for a psychiatric drug. They had one patient who had an unusual response, and the chip indicated it was a metabolizing enzyme problem that was addressed by changing the dose," Stafford says. "People are using the chips in discovery, but also to decide which drugs will go into clinical trials."

Nothing to Fear but the FDA

Originally, pharmacogenomics was meant to encompass tests for drugs already on the market, new targets gleaned from studies of population subsets, and drug/diagnostic pairings for personalized prescriptions — therapeutics prescribed exclusively based on results from a particular diagnostic test. But linking drug and diagnostic development is tricky. No one wants to impede the launch of a drug because they are waiting for a partner diagnostic. Tying the two products together heightens the risk that nothing will be approved — at least not in time for the developer to profit fully.

"One reason people may think it will be difficult to get a test approved is because of what happened with Herceptin," said Lawrence Lesko, director of the FDA's office of clinical pharmacology and biopharmaceutics at the Center for Drug Evaluation and Research, in an interview with *Bio•IT World* in June (page 45). (Herceptin is the breast cancer drug from Genentech Inc. that is typically prescribed following a diagnostic test.) "That was the first time the agency ever looked at a drug and a diagnostic test together, and there may have been some rough edges. But we have learned a lot from that experience, and now, we expect some submissions will require co-review of a drug and kit." However, no one is rushing to be the second test case.

"We're very interested in how the FDA proceeds," says Variagenics' Mohr. "We are just waiting to see if they issue a guidance with a capital 'G' or a little 'g.'" Lesko told *Bio•IT World* that the agency is seeking to champion the field, launching a variety of print and educational initiatives.

"Interest in pharmacogenomics is increasing overall, primarily because the FDA is becoming interested," says Abbott Labs' Spear. "The FDA is concerned that there are identifiable populations that will respond to drugs in ways that are not currently addressed on the drug label."

Indeed, the FDA wants to know about genotype-specific effects, and it wants doctors to understand them, too. So, even if companies don't want to develop and market the diagnostic tests themselves, they may have to do the studies and fork over the information. "The role of genetics will become more prominent in the labeling of certain drugs," Spear says. "That means that there will be testing, even if no one mandates it."

If no test is available, it could be more difficult to get approval. "Once the FDA sees the technology is reliable and cheap, companies won't have a choice about it," says Michael Liebman, director of computational biology at the University of Pennsylvania and chief scientific officer for Philadelphia-based ProSanos Corp. "Companies that take a proactive position will be in a leadership role; otherwise, they'll have to respond reactively."

Labeling the drugs opens another can of worms. Perched at the tip of this information pyramid are doctors who need to interpret the test results without necessarily knowing every genetic variation associated with a drug response. "One of the big challenges for everyone is educating the physicians about the role of genetics with certain drugs," says Spear. But IT may offer a solution. "If the information is part of the label and, as a result, ends up in something like the physician's Palm Pilot, you may be able to make this kind of change even without education."

So there are signs that real pharmacogenomics could also catch on.

"There is no question you can find markers for drug response and they can be clinically useful," says consultant Dykes. "There are data already available that would allow the development of molecular diagnostics tests." He anticipates a push to find markers for some drugs already on the market. One promising example of this is the St. Jude's TPMT (Thiopurine Methyltransferase) test (see "St. Jude's Test Makes It Better," page 56).

More would help. "A big success story is always important, and that's why we are doing the STRENGTH trial," says Judson at Genaissance. The company is trying to find markers of efficacy for the highly successful cholesterol-lowering statin drugs. Despite enrolling only a few hundred patients, powerful associations have emerged from the trial. "The number of patients you need depends largely on the strength of the associations," says Judson. "Doing it this way wasn't a shot in the dark, but we could have been unlucky if the associations turned out to be much weaker than we expected."

"Today, commercializing and making pharmacogenomics real means developing molecular diagnostics," says Variagenics' Mohr. His company is betting on multiple lines of information, including gene expression, SNPs, and other factors like loss of heterozygosity. The early focus is colorectal cancer and developing a pipeline of diagnostics for the standard chemotherapies used to treat the disease.

Pharmacogenomic companies aren't the only ones looking into this. Compugen Ltd.'s Michal Preminger, vice president of new research directions, says the Tel Aviv, Israel-based company has several agreements to perform data mining and molecular analysis for firms whose "drugs are less successful than others," to determine if there are patient subpopulations who gain specific benefit from the drug.

The Rumblings of Giants

Meanwhile, companies that pay health-care bills — employers, HMOs, health insurers, and so on — are also understandably concerned about drug safety and utility, and some are starting to do something about it.

Orchid GeneShield and Merck-Medco (both based in New Jersey) recently announced a collaboration to identify genetic variations that predict

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Pharmacogenomic Suppliers

Amersham Biosciences www.amershambiosciences.com
Applied Biosystems www.appliedbiosystems.com
Beckman Coulter www.beckman.com
Compugen www.cgen.com
deCODE Genetics www.decode.com
diaDexus www.diadexus.com
DNAPrint Genomics www.dnaprint.com
Genaissance Pharmaceuticals www.genaissance.com
Illumina www.illumina.com
Interleukin Genetics www.ilgenetics.com
Lynx Therapeutics www.lynxgen.com
Luminex www.luminexcorp.com
Nanogen www.nanogen.com
Orchid BioSciences www.orchid.com
Oxagen www.oxagen.co.uk
Pyrosequencing www.pyrosequencing.com
Qiagen Genomics www.qiagengenomics.com
Sequenom www.sequenom.com
ThermoHybaid www.thermohybaid.com
Transgenomic www.transgenomic.com
Third Wave Technologies www.twt.com
U.S. Genomics www.usgenomics.com
Variagenics www.variagenics.com

Tools of the Trade: Advances in Genotyping

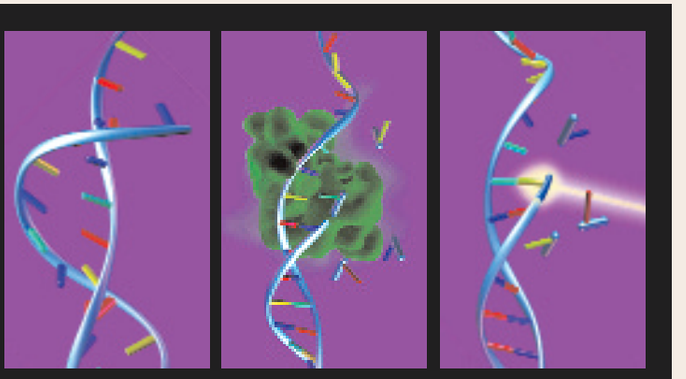
One of the major problems confounding pharmacogenomics from the beginning has been the quality and quantity of the genotyping tools.

It can take millions of genotypes (the scoring of a single nucleotide polymorphism, or SNP, in a single patient) to uncover links between SNPs and disease or drug response genes. One year ago, the average cost was $1 per genotype — beyond the reach of most companies. Now that the price is hovering around 35 cents per genotype for some systems, more candidate gene surveys are within reach. But genome-wide studies, aimed at finding all the SNPs associated with a disease, remain exorbitant.

"We estimated that you would need about 500,000 SNPs to do such studies," says Richard Judson, senior vice president of informatics at Genaissance. Other figures are much higher. "Discussions around the NIH's [haplotype] map initiative suggested it could require 1 or 2 million SNPs and about 1,000 patients," he says. This disparity results from the many uncertainties and the different assumptions people make (see July *Bio•IT World*, page 46).

A dozen or more companies offer genotyping tools and/or services. Every step — from finding a putative SNP through sample preparation and scoring the genotype — can influence the speed and accuracy of the project. Perhaps the biggest development is the number of validated SNP assays, some of which can be selected and purchased over the Web. The idea is so simple it's a wonder no one thought of it earlier. "We dramatically simplified the steps going from getting a piece of information in a database (i.e., 'this looks like a SNP') to having an assay for the SNP that works in the lab," says Dennis Gilbert, vice president of genomics for Applied Biosystems Group. The company launched its Assays-on-Demand online genotype-product store this summer.

Applied Biosystems has 90,000 validated SNP assays on hand, and is aiming for 200,000 by year's end. Sequenom Inc., which launched its RealSNP.com Web site in April, has approximately 400,000 SNP assays available, more than 200,000 of which are confirmed (common) variants. Orchid BioSciences Inc. and Third Wave Technologies Inc. each have approximately 100,000, and Illumina Inc. has about 10,000.



Orchid's SNP-IT technology uses a simple three-step process to directly analyze genetic information at the site of a SNP. First the technology identifies the precise area of DNA where the SNP is located (left). Then an enzyme called DNA polymerase catalyzes a reaction that adds a signal specific for the SNP (center). Finally, the result is read out using one of various methods commonly used by researchers (right). This flexibility gives SNP-IT a key commercial advantage. SNP-IT tag array is Orchid's next-generation technology innovation which enables unparalleled flexibility, throughput, and robustness through multiplexing, the ability to perform multiple SNP analyses at one time.

Other steps are becoming easier too. "Our Autoprimer.com Web site allows you to load a sequence and design primers for PCR and genotyping," says Michael T. Boyce-Jacino, vice president and chief technology officer at Orchid. "For us, validation means it works in your lab," says Gilbert. "And the workflow with TaqMan is simple: You take the DNA and the enzyme, mix [them] together, and it works the same way every time."

Speed and capacity have also changed dramatically thanks to multiplexing (doing multiple reactions at once). "Multiplexing is a term that is used loosely," says Bill Craumer, director of marketing communications at Illumina. "We routinely prepare samples and perform assay amplification at 1,000-target PCR multiplex levels." Each Illumina Sentrix array has up to 384 fiber-optic bundles and can interrogate up to 1,500 targets.

Several companies, including Illumina, Orchid, Third Wave, and Sequenom, are working on very large-scale projects. "Many people are looking to do genomewide scans," says Orchid's Boyce-Jacino. "Our product addresses that." Orchid also recently launched a whole genome scan mapping service. Applied Biosystems, according to Gilbert, is focused primarily on candidate gene analysis. "That customer already has a set or list of genes they want to study SNPs in," he says.

Comparing costs can be difficult. Some systems require purified oligonucleotides, others do not, and Third Wave's process does not require PCR — a key cost consideration. Accuracy also plays a part. "The denominator determines the cost of genotyping," Gilbert says. "If half the genotypes have to be redone, you are not saving money."

As projects move toward the clinic, new considerations will arise. "Pharma companies want to standardize the development of SNP assays," says Boyce-Jacino. "In case it becomes a diagnostic, they don't want to have to switch biochemistry. We have a very robust biochemistry that, thanks to our propagation efforts, is now available on several other platforms as well." — **M.B.**

Pushing the Throughput Envelope

Company	Platform	Throughput
Applied Biosystems Group	TaqMan — 5' nuclease assay with ABI Prism 7700 or 7900 HT sequence detection system	200,000 per day on 7900 HT
Illumina Inc.	BeadArray technology deployed on Sentrix array matrices	More than 1 million genotypes per day (using 7 matrices)
Luminex Corp. (with Tm Bioscience Corp.)	Universal Array platform — xMAP bead system	240,000 genotypes per day
Orchid BioSciences Inc.	SNPstream UHT — SNP-IT tag array technology	800,000 genotypes per day
Pyrosequencing AB	PSQ 96 and PTP systems — sequencing by synthesis	100,000 genotypes per day (Can be increased through multiplexing)
Qiagen Genomics Inc.	Masscode — PCR-based SNP discrimination assay	65,000 genotypes per day
Sequenom Inc.	MassARRAY 7K, 20K, and 200K systems	200,000 genotypes per day on the 200K system
Third Wave Technologies Inc.	Invader — allele-specific hybridization with novel signal-amplification technology	500,000 genotypes per day.

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response to asthma drugs. Interleukin Genetics Inc., based in Waltham, Mass., is teaming up with UnitedHealth Group's Center for Health Care Policy and Evaluation to study the influence of genetic variation in treatment of inflammatory diseases. Interleukin also has a deal with Kaiser Permanente's Center for Health Research to examine how genetic variation influences the risk of diabetes-related heart disease.

Compugen just announced several confidential agreements with health-care providers including one HMO, and more are expected (see July *Bio•IT World*, page 26). The bioinformatics company is mining the clinical information in these records and may add genotype data later.

"The reimbursers have a simple calculation to make," says Dykes. "We know how much we have to pay for this, and how often we pay it. If there is a test that cuts hospitalization in half, they can easily figure out what it's worth." Outcomes studies will therefore be necessary to encourage this trend (see "Answering the Billion-Dollar Question," page 58). Providers are one of the few groups that could power pharmacogenomics through to the clinic, so these studies will be pivotal for the future of the field.

The Public Effort

The public initiative in this field continues to thrive. By next spring, the Human Genome Project will be complete. The public/private SNP Consortium has already exceeded its goals, putting more than 1.5 million SNPs into the public domain.

Francis Collins, director of the National Human Genome Research Institute, is championing the creation of a public haplotype map — a map

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St. Jude's Test Makes It Better

Like many cancer drugs, mercaptopurine can have harsh side effects. For more than 50 years, doctors had to accept that some patients developed serious bone marrow-toxicity, leaving them at risk of infection and possibly death. But after a pair of leukemia patients at St. Jude's Children's Hospital in Memphis, Tenn., reacted badly to the drug, William Evans decided to do something about it.

"This was a profound effect," says Evans, chairman of pharmaceutical sciences at St. Jude's. "These children had to go to the ICU because they were getting so sick." As pharmacogenomics and leukemia were areas of particular interest for Evans, he initiated an National Institutes of Health (NIH)-supported study spanning five years, to the tune of approximately $1 million. One advantage St. Jude's had was direct access to patients, but they didn't have the rapid-fire genotyping tools available today.

Evans' team compared DNA sequences from patients who suffered the toxic reaction with those who did not. They found three SNPs that could cause the problem. "Those same SNPs show up in Asian populations, as well as in Europeans and others," Evans says. Any of these SNPs result in the deactivation of the enzyme thiopurine methyl transferase (TPMT), which is needed to metabolize mercaptopurine. About 10 percent of patients are heterozygous for such a mutation (that is, they carry one errant copy of the TMPT gene), which can still cause problems. But the most serious effects are seen in the 1 in 300 people who are homozygous for the faulty gene. "In these patients you have to decrease the dose down to 5 to 10 percent of what is normally given," says Evans. "That's not the kind of adjustment you'd normally start with."

As word of the St. Jude's findings spread in the late 1990s, other groups validated their results. "When we published this, people from around the country started to contact us, and we would try to help them," says Evans. "In 70 percent of the cases we saw like that, the inherited defect was the problem."

Best of all, the test made it to the clinic. "We were delighted when a couple of national reference labs decided to make it available as a clinical diagnostic so physicians could order it, just like a blood glucose test," he says. "TPMT became the first pharmacogenomic test that went all the way to CLIA [Clinical Laboratory Improvement Amendments] certification."

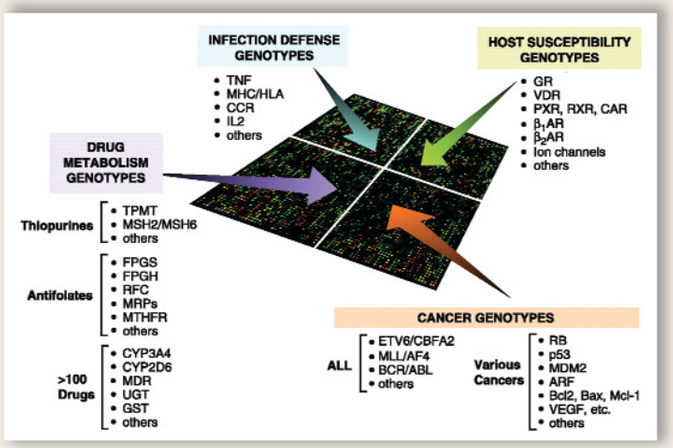
The progress of the test illustrates what many other pharmacogenomic projects are lacking, says the University of Louisville's Mark Linder. "To get momentum, the tests have to be driven by centers of excellence where they have a particular interest in the problem, like St. Jude's has."

St. Jude's is unusual in many ways. They are even building a GMP pharmaceutical manufacturing facility to make their own small molecules, vaccines, and gene therapies. More pharmacogenomic tests may also be forthcoming. For example, Variagenics has just licensed a patent application from St. Jude's that covers genotyping methods and diagnostic kits for the cytochrome CYP3A5 drug metabolizing enzyme. Variations in CYP3A can influence the metabolism of more than 50 percent of all cancer agents, including colon-cancer drug irinotecan.

Evans' group is now part of the NIH Pharmacogenetics Network. "We are doing more genome-wide investigations now," says Evans. "But our focus is on a candidate gene strategy."

— M.B.

William Evans pioneered pharmacogenomic diagnostics at St. Jude's Children's Hospital.



A potential diagnostic DNA array that would detect genes influencing a patient's response to chemotherapy for acute lymphoblastic leukemia, including genes that determine drug metabolism, disease sensitivity, and the risk of side effects (cardiac or endocrine toxicities, infections, etc.).

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including a critical mass of some 400,000 common SNPs to ensure that most genes are represented by a SNP either within its coding sequence or nearby. Such a map, costing an estimated $100 million, should accelerate association research by reducing the number of SNPs that have to be studied.

Several divisions of the National Institutes of Health (NIH) have already pledged about $32 million, and international partners say they will contribute as well. But with the U.S. government earmarking resources for biodefense, Collins is turning for help from the pharmaceutical industry. "Pharma companies are interested in seeing it generated," Collins says, "but it has not been an easy year for them, given what has happened in the stock market."

For Collins, there's also the nagging question of "whether markers for drug response will diminish the markets for widely prescribed drugs." But Collins and his team are persevering. "If there is a shortfall in funding, we can just extend the timeline," says NIH Program Officer Lisa Brooks.

The "Hap Map" doesn't have to be comprehensive; it must merely have sufficient SNP coverage to provide good markers for the most useful genes. "Considering how huge our ignorance is now," Collins says, "if we found haplotypes across 85 to 90 percent of the genome, that would be an incredible treasure of information."

Collins is unimpressed by the hubbub that has shaken the industry lately. "In some quarters there was a misunderstanding, or naivete, about how having the sequence was going to solve everything. And there were some business models built solely upon the notion of quick profits, particularly selling subscription databases."

IN PART TWO: The impact of SNPs on disease gene identification, drug discovery, and informatics, plus a Q&A with Klaus Lindpaintner of Roche.

He dismisses talk about a foundering industry. "I think that every pharmaceutical company is still expecting that genomics will be the platform upon which they will build the next generation of drugs," says Collins. Others echo Collins' perspective. "We will change the treatment of cancer," says Variagenics' Adams. And there is no hint of doubt in his voice.

But there are clearly challenges ahead. "The sequencing of the human genome was a definable milestone that was very clear-cut, and that is hard to replicate with any of the other parts of this science that are necessary to understand the genome." ●

Answering the Billion-Dollar Question

Before they start using SNPs to guide treatment, doctors will want to know that these tests are worth the necessary time and expense. A patient's age, medications, diet, exercise, and so on also contribute to his or her response to drugs. Simply linking a SNP to a response is not enough — that link must also be sufficiently strong to provide practical information.

"There is a very strong need for clinical validation," says Brian Spear, director of pharmacogenetics at Abbott Labs. Many SNPs have been linked to diseases, but few studies have demonstrated that genotyping makes a measurable difference in treatment outcome. The first examples of pharmacogenomics — TPMT and Herceptin — all involve cancer. It is easier to justify an expensive treatment that helps only a few patients if the disease (or side effects) are life-threatening.

"Everybody has been promoting the concept of genomics as a therapeutic tool, but if you could demonstrate that a genetic variation is influencing therapeutic costs, then you would have every HMO in the country saying, 'We have to start using this.'"

Peter Wedlund, *University of Kentucky's College of Pharmacy*

But there are other attractive targets, such as the anticoagulant Warfarin, which Spear cites as "a good example because there is strong evidence that genetics can be used to predict the initial dose and later dose adjustment. It's also been well demonstrated CYP2D6 variations cause poor metabolism of tricyclic antidepressants." The dosage of Warfarin is critical; dosed improperly, patients can have serious complications. Tricyclic antidepressants, meanwhile, can cause cardiovascular problems in poor metabolizers.

At least two groups have tried to tackle the issue of outcomes in exactly those cases, although funding is hard to come by. Mark Linder at the University of Louisville in Kentucky has proposed a study of the influence of genotyping on the outcomes of patients taking Warfarin. Peter Wedlund at the University of Kentucky's College of Pharmacy and Eastern State Hospital Mental Health Research Center wants to determine if genotyping can improve outcomes for patients who are candidates for tricyclic antidepressants.

Both researchers have had grant applications to the National Institutes of Health (NIH) turned down. "The study section officers ... encouraged me and said Warfarin is a problem and this is a high priority," Linder says.

Wedlund and Linder acknowledge there could be other problems with their proposals, but they are concerned that the NIH may have set up a catch-22 for researchers seeking funding for outcomes studies. "Some of the reviewers said, 'This is old hat, we don't need to prove these associations,'" says Linder. "But you can't do a proper outcomes study unless the association is proven." Wedlund received similar criticisms. "One reviewer said, 'This is so obvious,' and that's true of course," he says. "We've known for 20 years that the CYP2D6 variations influence drug response. The question is, would a test influence outcomes in a clinical setting?"

"NIH funds good research," says Rochelle M. Long, chief of the pharmacological and physiological sciences branch of the NIH and head of the National Institute of General Medical Science's Pharmacogenetics Research Network (found online at www.nigms.nih.gov/pharmacogenetics), which funds numerous studies in this field. She attributes the researchers' complaints to "sour grapes," and insists that "anyone who submits an application to the NIH must defend the approach they are taking." The NIH is interested in outcomes studies, she says, but "our primary goals were to get the molecular commonalities nailed down." She is unaware of any outcomes studies being funded by the NIH.

The underlying question is whether there is a source for funding for these studies, particularly since drug manufacturers are not interested in them. Wedlund is resubmitting his grant to the Agency for Health Research and Quality and is pursuing other sources as well. But he's worried that the NIH is sending conflicting messages to those seeking to do outcomes research. "This has nothing to do with sour grapes," he insists. "It has to do with making sure there are appropriate avenues for advancing genomics into the clinical arena."

No matter who ends up doing these studies or when they get done, the impact will be enormous. As Wedlund says, "Everybody has been promoting the concept of genomics as a therapeutic tool, but if you could demonstrate that a genetic variation is influencing therapeutic costs, then you would have every HMO in the country saying, 'We have to start using this.'"

— M.B.