

An individual approach

Reduced side effects and more effective therapies are some of the benefits promised by pharmacogenomics. But to reach these goals industry will have to marshal a broad range of skills, as **Ricki Lewis** explains.

It would be the ultimate in personal service: medical treatment tailored to match exactly your personal genetic make-up. Understanding how your body is likely to react to certain therapies would potentially eliminate side effects and increase the efficacy of the drugs you take. That, loosely, is the promise of pharmacogenomics — but until recently it seemed a very distant goal.

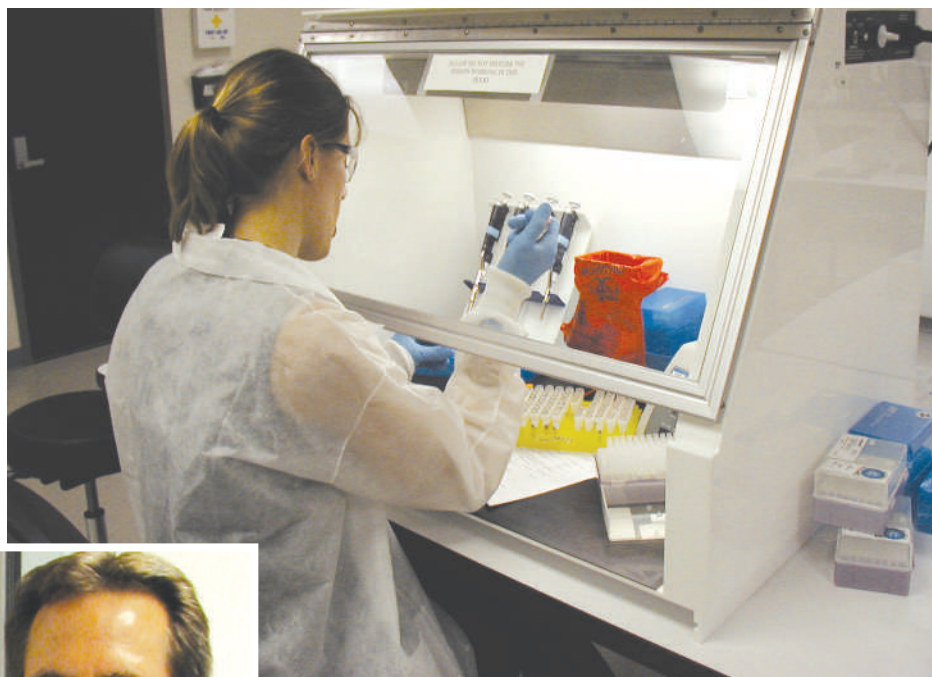
Events last autumn have changed all that. When a group of painkillers known as COX-2 inhibitors, used to treat arthritis, were linked to an increased risk of heart disease, the idea of personalized medicine gained some very public momentum (see 'A long time coming', opposite). The idea that targeting drugs to individuals can save lives has helped to boost the role of pharmacogenomics.

In March, the US Food and Drug Administration (FDA) released guidelines that encourage, but do not require, companies to provide pharmacogenomic data in new applications for drug approval. This information would predict how a patient might respond to a drug based on their genetic profile: both the gene variants they have inherited and the expression pattern of those genes. This small regulatory step will translate into jobs all along the drug discovery and development pipeline. Those who can acquire the right mix of skills now will be poised to take advantage of what some see as a complete restructuring of the pharmaceutical industry.

"The FDA guidance document has opened up a large opportunity for people with pharmacogenomics knowledge to help pharmaceutical companies navigate the path forwards," says Michael Murphy, president and chief executive of Gentriss, a pharmacogenomics company in Morrisville, North Carolina. Gentriss has already opened a consulting division to meet the growing demand for expertise in combining genomics knowledge with statistics, bioinformatics and quality assurance.

In the past five years, every large pharmaceutical company has set up a pharmacogenomics group, says John Ryan, senior vice-president of translational medicine at Wyeth Pharmaceuticals in Collegeville, Pennsylvania. "Based on the technology, the resurgence of biotech, and the fact that the drug industry is being pressed to do things differently, there will be hundreds of openings in pharmacogenomics over the next several years," he predicts.

Wolfgang Sadec, director of the pharmacogenomics programme at Ohio State University in Columbus, adds that it will be five years until drug companies fully



Michael Murphy believes that pharmacogenomics will offer many career opportunities.

Peering under the hood: a deeper understanding of gene expression will help tailor therapies to individual needs.

GENTRISS

embrace the field. "If we train people now," he says, "in five years they will be in the right position to help out."

The earlier approach of pharmacogenetics, which targets a single gene, has already scored some successes. Herceptin (trastuzumab), for example, treats breast cancer by targeting a single receptor on tumour cells that is overabundant in women who inherit a specific gene mutation. And the analysis of individual genes that affect drug metabolism has helped to improve efficacy.

With its emphasis on multiple genes and their expression patterns, pharmacogenomics extends the reach of its predecessor. For instance, researchers at the University of Toronto in Canada have identified 18 genes whose expression pattern predicts whether or not a person will respond to treatment for hepatitis C. Current treatment (interferon plus ribavirin) works for only half of them. Measuring expression of these genes could indicate who can be helped, right from the start.

A mix of skills

Pharmacogenomics requires expertise in genetics and genomics, drugs and drug interactions, bioinformatics and especially statistics, says Kelly Frazer, vice-president of genomics at Perlegen Sciences, a pharmacogenomics company in Mountain View, California. The ability to communicate is also essential, she stresses: people work in teams, at least in the short term, because not many individuals have all the necessary skills.

The field leans heavily on two techniques: analysis of SNPs (single nucleotide polymorphisms) and DNA microarrays. SNPs are sites in the genome where the DNA base differs in at least 1% of a population. Sets of SNPs along chromosomes form haplotypes, which are the chunks of information associated with specific

drug responses. DNA microarrays are used to identify inherited SNP patterns — a singly array can screen 100,000 SNPs in just hours. Microarrays that represent the mRNAs in a particular cell type are used to track gene-expression patterns that can correlate to drug response.

The real work to come will be in data-mining. “There is still a gap — but it is shrinking — in the ability to understand the data from a genomics perspective, manipulate it from a computational perspective, and analyse it from a statistical perspective,” Frazer adds. Audrey Papp, manager of the pharmacogenomics lab at Ohio State University, agrees: “We need people to look at the information and pull it all together. How do the data fit? Which data are significant?”

Learning the ropes

Several trajectories lead to the skill sets of a pharmacogenomics specialist. David Gurwitz, director of the National Laboratory for the Genetics of Israeli Populations at Tel Aviv University, suggests taking pharmacogenomics courses in medical, pharmacy or health-science schools, and seeking a mentor who is actively working on a pharmacogenomics problem.

Doctoral degrees in pharmacy or clinical pharmacology provide excellent preparation, says Murphy. Demand for Ohio State University's pharmacogenomics programme is high, adds Sadee, who directs the programme, which was set up three years ago in the department of pharmacology. The programme draws students from an integrated biomedical graduate programme, neuroscience and biomedical informatics. “Quite a number of young people are now interested in the area. I get e-mails all the time from people in academic departments requiring this type of expertise,” Sadee says.

A degree in biostatistics is another route to pharmacogenomics. “The area where most of the jobs will be is in bioinformatics, and this is where the industry is the least well-served. Biostatisticians specifically trained in pharmacogenomics is a growth area,” says Ryan.

Education can also stem from conferences — such as the Cold Spring Harbor–Wellcome Trust meeting this September in Hinxtton, Cambridge, UK — or through industry. Celera Genomics of Rockville, Maryland, for example, offers intern opportunities and recruits recent college graduates.

Job opportunities range from the basic to the applied, and from tightly focused tasks to broader responsibilities. Industry, for example, requires technicians to sequence DNA, and study directors to oversee the entire journey of correlating genotypes and expression patterns to drug responses.

“A study director has basic scientific knowledge and knows how to do quality-assurance checks on genomic data,” explains Murphy. Gentris has had to recruit externally to fill these positions, and has set up in-house training for internal promotion, where professionals with RQAP-GLP (registered quality assurance professional in good laboratory practices) certification teach traditionally trained scientists the regulatory ropes.

Another niche is in hospitals, where adverse drug reactions attest to the need for the field. It is estimated that there are about two million adverse drug events in the United States a year, of which about 100,000 are fatal. “As pharmacogenomics slowly moves into the

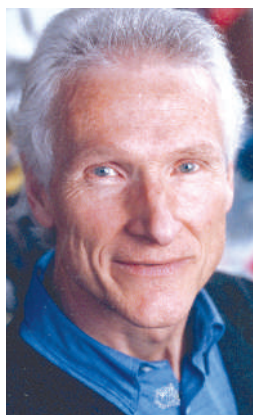
A LONG TIME COMING

The recent problems surrounding the COX-2 group of painkillers illustrate how pharmacogenomics could in future limit side effects. After revelations last year that extended use of some COX-2 inhibitors could increase the risk of heart problems, action was swift. Merck voluntarily took its COX-2 inhibitor Vioxx (rofecoxib) off the market in September 2004. The licence for Pfizer's Bextra (valdecoxib) was later withdrawn by the US Food and Drug Administration, although the company's Celebrex (celecoxib) was allowed to stay on sale subject to certain restrictions.

While Merck and Pfizer were worrying about the loss of their blockbuster drugs, a test for gene expression was offering a glimpse of the future. The test, introduced by Roche Diagnostics in 2004, detects variants of the genes that encode the proteins cytochrome P450, 2D6 and 2C19, which regulate the rate at which the liver metabolizes many drugs. Patients identified as ‘poor metabolizers’ risk overdosing on what for others would be standard doses.

Not only will pharmacogenomics become standard in future drug discovery: it is already fine-tuning use of old drugs. Consider the anticoagulant warfarin, used by millions since the 1940s to prevent blood clots after major surgery, stroke or heart attack. Matching dose to patient is notoriously tricky, and if it's misjudged a patient could either bleed to death or suffer a fatal blood clot. A team from the National Institute of General Medical Sciences' Pharmacogenetics Research Network recently identified gene variants that correlate to requiring low, moderate or high doses of this commonly prescribed drug.

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Wolfgang Sadee sees training now as the key to future success within personalized medicine.

health-care arena, more and more hospitals are going to set up teams to monitor adverse events due to drugs. Hospitals will need people to consult on what happens to those patients,” says Murphy.

Teaching opportunities will also span the lab and the clinic. “There will be an urgent need for many pharmacogenomics instructors, both for professional education and for explaining to patients the meaning of tests and their results,” Gurwitz predicts.

Government research groups and consortia offer opportunities, too, such as the Pharmacogenetics Research Network of the the National Institute of General Medical Sciences (NIGMS), and its knowledge base to handle the incoming data, PharmGKB. The International HapMap Project is linking millions of SNPs to drug responses at ten centres around the world, and introduces yet another job title: ‘community engagement and sample collection’. This involves acquiring DNA samples from populations in the United States, China, Japan and Nigeria.

The extensive partnering between big drug companies and smaller biotech firms in pharmacogenomics presents opportunities for researchers in one sector to explore the other. For example, Eli Lilly of Indianapolis and ParAllele BioScience of South San Francisco are analysing 180 genes and their 2,000 variants that affect drug metabolism, using ParAllele's microarray system. And Roche, based in Basel, Switzerland, investigates the pharmacogenomics of asthma and high blood pressure with deCODE Genetics of Iceland.

The future job market in pharmacogenomics is intimately tied to the gestation of the field. The first phase of personalized medicine, says Ryan, is already under way, with the genotyping required to prescribe Herceptin for breast-cancer patients. But there's still a long way to go.

“The end result — each individual having a genomic profile at the doctor's office for every drug — is decades away,” he adds. In the meantime, those who can read drug responses in DNA sequences will enjoy an increasingly robust job market.

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WEB LINKS

FDA pharmacogenomics guidelines

♦ www.fda.gov/cder/genomics/default.htm
Pharmacogenomics knowledge base

♦ www.pharmgkb.org
International HapMap project

♦ www.hapmap.org
SNP database

♦ www.ncbi.nlm.nih.gov/projects/SNP
Pharmacogenetics research network

♦ www.nigms.nih.gov/pharmacogenetics