MEDICINE

Developing Prescriptions With a Personal Touch

Richard Sykes, who heads one of the world's largest pharmaceutical companies, Glaxo Wellcome, made a bold assertion last fall about the future of clinical testing for new drugs. "It's going to change very, very dramatically. ... The way studies are carried out is going to be driven by genetic technology," said Sykes at an international summit on health research funding (*Science*, 25 October 1996, p. 491). And if that prediction seems daring, consider this: Many researchers now believe the way drugs are prescribed in the future is going to be driven by genetic technology, too.

The impetus for these extraordinary shifts stems from a dusty, old field called "pharmacogenetics," which attempts to understand the genetic roots of diseases so as to unravel why drugs affect different people differently. Now the boom in genomics is elevating the status of pharmacogenetics from novelty to necessity. "The field has been sort of slow for a number of years, but now, suddenly, people are seeing this [connection between genes and drugs]," says Arno Motulsky, a medical geneticist at the University of Washington, Seattle, who first published on the topic in 1957. Jay Lichter, a geneticist at Sequana Therapeutics, a genomics biotech in La Jolla, California, agrees. "Five years ago, when I was doing this at DuPont Merck, they didn't get it," says Lichter. "I was the guy with cockamamie ideas."

Grouping people according to their genetic makeup, or genotype, in clinical trials could make it easier to prove that a drug works, say Lichter and others. Rather than selecting patients at random, as is typically done, researchers theoretically could use genetic differences, such as a mutation in a gene linked to an enzyme that helps metabolize drugs, to select people who are most likely to respond. Genotyping can also help elucidate why some drugs make some people sicker, and this "ability will allow us at one point to sell a drug even though it's toxic to a subpopulation," says Roy Whitfield, chief executive officer of Incyte Pharmaceuticals in Palo Alto, California, which sells drug companies subscriptions to its genetic database. Companies additionally might use genotyping to try and rescue "dead drugs" that have failed clinical trials because of efficacy or toxicity problems.

Some researchers caution that, at this point, the impact of genotyping patients on drug testing and prescribing is still speculative. "There's a lot of hyperbole by certain individuals in the field," says U.S. National Cancer Institute chemist Frank Gonzalez, editor of the journal *Pharmacogenetics*. "That's how they get their fees," says Gonzalez, who has done pathbreaking work on how genetic differences in the liver enzyme cytochrome P-450 (CYP) can alter the way individuals metabolize drugs. Pharmacogenetics also raises thorny marketing, safety, and regulatory issues.

Still, intriguing efforts already are under way. At Georgetown University in Washington, D.C., Raymond Woosley, chair of the pharmacology department, says he and his colleagues have been working with Affymetrix of Santa Clara, California, to develop a rapid screening procedure for CYP mutant genes—some of which occur in up to 7% of the population. And Woosley's staff now routinely screens patients in clinical drug trials for these mutations. "We find it very helpful in analyzing [unusual] responses," says Woosley. In the future, says Affymetrix President Stephen Fodor, "people are going to get diagnosed and treated at the same time."

Myriad Genetics, a genomics company in Salt Lake City, is developing a diagnostic that may let physicians better customize how they treat patients for hypertension, which can be caused by many factors, including high salt intake. "Right now, it's a hit-or-miss situation to get you on the appropriate therapy," says Myriad CEO Peter Meldrum. "Frequently, physicians put all patients on a low-salt diet, which won't lower blood pressure in many." Myriad has developed a test for mutants of the angiotensinogen (AGT) gene, which codes for a protein that regulates salt retention. The test now is being evaluated in a large clinical trial at the U.S. National Institutes of Health. If patients with AGT mutants are most helped by a low-salt diet, Myriad hopes to bring the AGT test to market this year.

At the University of Toronto, psychiatric geneticist James Kennedy is aiming at an entirely different target: mutant receptors for brain chemicals. For the past year, Kennedy has been studying 180 patients with schizophrenia to see whether individuals who have a mutant gene for a dopamine receptor are less likely to be helped by the antipsychotic drug clozapine.

While these lines of research offer patients and physicians the possibility of precisely tailored treatments, they could be a mixed blessing for pharmaceutical companies. One fear is that pharmacogenetics will shrink the market for a particular drug by limiting who can take it. "They're very worried about labeling on a bottle that says, 'This [drug] only for person with genotype 87,' " says Eric Lander, co-founder of Millennium Pharmaceuticals in Cambridge, Massachusetts, and head of a genome center at the Massachusetts Institute of Technology. Geneticist J. Craig Venter, who runs The Institute for Genomic Research in Rockville, Maryland, points out that such targeting could cause harm, too. Venter is concerned about marketing drugs that are toxic to a specific genotype. "If you don't [genotype] those people before giving them the drug, you'll kill them," says Venter. "That's a real downside." Drug companies also worry that drug development might be slowed if the agencies charged with regulating new drugs begin requiring pharmacogenetic data.

Despite such concerns, several large drug companies are ramping up their pharmacogenetics programs. C. Thomas Caskey says Merck & Co., where he leads the genomics program, is genotyping patients in clinical trials—and animals in preclinical tests—but he declines to give details. George Poste, head of R&D at SmithKline Beecham, is also reluctant to provide specifics but confirms that the company is doing the same. Lee Babiss, who helps run Glaxo Wellcome's genomics program, is more forthcoming. Babiss says Glaxo now is testing patients for mutants of the apolipoprotein E gene, which is implicated in Alzheimer's, in a study of a drug to combat that disease. "Ultimately, I believe our drugs and our competitors' are going to be administered with a diagnostic in mind," says Babiss. "There's a real threat to any pharmaceutical that doesn't [incorporate pharmacogenetics]. Your market could be taken away from you."

–Jon Cohen

LINKING GENETICS TO TREATMENTS

Mutant Gene	Disease	Treatment
CFTR	Cystic fibrosis	Pulmozyme
Cytochrome P-450, CYP1A2	Cancer	Amonafide
Dopamine receptor D4	Schizophrenia	Clozapine
Angiotensinogen	Hypertension	Low-salt diet
Apolipoprotein E	Alzheimer's	Experimental Glaxo Wellcome drug