

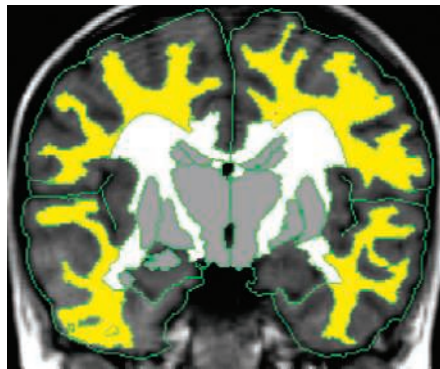
long ones, perhaps accounting for the disproportionate increase in white matter relative to gray matter in autistic brains.

And in unpublished findings from seven autistic and seven control brains, Casanova and Christoph Schmitz of the University of Maastricht in the Netherlands and their colleagues found that the autistic brains also had smaller cells in their minicolumns. Smaller cells carry shorter axons, bolstering the hypothesis that autism results from too many short-range connections and not enough long ones.

Even if a neuronal imbalance is to blame, no one knows how it arises. Courchesne and others hypothesize that it might result from a problem in the pruning, or elimination, of neurons and synapses early in life. Work from Courchesne's lab from 2003 suggests that most of the abnormal brain growth in autism occurs from birth to age 3. This may leave an unruly excess of neurons and circuitry in certain brain regions.

More questions than answers

Despite the converging evidence, not everyone is convinced that faulty connections lie at



Not too deep. Autistic brains contain an excess of surface white matter (yellow), which contains relatively short neuronal fibers, but do not show an enlargement of deeper white matter (white), where the longest fibers reside.

the heart of autism. Geraldine Dawson, an autism researcher at the University of Washington, Seattle, suggests that connectivity problems in autism might be an effect—rather than a cause—of an earlier dysfunction in the brain, such as a defect in brain systems that govern social reward and affect an infant's attention to faces and speech. Such a

defect, Dawson says, “will influence the development of speech and face perception, which ultimately will affect the development of the complex, integrated brain circuitry that underlies language and social development.”

Even if connectivity problems are at the root of autism, the theory needs fleshing out. Abnormalities in brain connectivity have also shown up in attention deficit hyperactivity disorder (ADHD), schizophrenia, and dyslexia. To get to the heart of autism, researchers now need to pinpoint which particular white matter—or gray matter—abnormalities are the problem in autism versus, say, dyslexia or ADHD, skeptics point out.


Even so, proponents argue that the theory at least points researchers in the right direction. “It's a much more valid way of looking at impairments in autism. It's where the field of autism has to go,” Müller says. And no matter where connectivity theory leads, the autism field is energized by the concept. Says Courchesne: “People smell something really exciting. They are seeing that there is a very interesting, if complex, story emerging.”

—INGRID WICKELGREN

Pharmacogenomics

Going From Genome to Pill

A new medicine for African Americans with heart failure hints at what the drug industry sees as the enormous payoff from pharmacogenomics



Last week an advisory panel to the U.S. Food and Drug Administration (FDA) took an unprecedented step in recommending approval of a drug for a single racial group. The drug, a combination pill called BiDil that contains two heart-failure medications, had failed to help patients in the general population live longer. But in a clinical trial last year, BiDil decreased the risk of death among African Americans by 43%. That was sufficient evidence to convince the panel that BiDil should be approved to treat African-American patients with heart failure. FDA was widely expected to follow the recommendation this week.

By backing BiDil, the FDA panel gave another push to pharmacogenomics, an approach that promises to revolutionize both drug discovery and patient care. African Americans have a higher likelihood of developing hypertension and other condi-

tions related to heart failure. However, whether that's due to genes, the environment, or some complex interplay isn't yet known. Still, BiDil represents the latest example of the industry's push to target drugs to subgroups of patients who, based largely on their genetic makeup, are most likely to benefit (*Science*, 24 October 2003, p. 594). In recent months studies have shown potential benefits of medicines targeted to patients with specific genotypes for treating cancer and heart disease. Other studies have helped doctors properly dose a wide variety of compounds already on the market. “I think that the use of pharmacogenomics will have a profound effect,” says Gary Peltz, head of genetics and genomics research at Roche's Palo Alto, California, lab. “It hasn't hit yet. [But] we're clearly on the road.”

To date, pharmacogenomic therapies represent a trifling portion of pharmaceutical sales, some \$3.65 billion in a \$550 billion market. That won't change unless scientists overcome an array of challenges, from untangling the genetics behind complex diseases such as diabetes to altering

practices that could disqualify patients for health insurance based on their genes. There are also concerns that approval of drugs based on race, a sociological trait, will increase racial stereotypes and bolster the discredited notion that there are fundamental genetic differences between races. But those problems, say drug industry officials, pale in comparison to the projected benefits to patients—and to the industry. “Every major pharmaceutical company is reorganizing or has reorganized their clinical paradigm” to test drugs in conjunction with tracking genes or other molecular markers of disease, says Ronald Salerno, who directs regulatory affairs for Wyeth Pharmaceuticals in Collegeville, Pennsylvania. “This is the way drugs will be developed in the future.”

Improving the odds

Although pharmacogenomics only recently entered the lexicon, the notion of treating populations based on the genes involved in health and disease dates from the 1950s. That's when researchers caught an initial glimpse that the speed at which different people metabolized drugs in their system was linked to genetics. But it took another 40 years to progress from those hints to medicines. In 1997, Genentech's Herceptin was approved to fight a form of breast cancer in which cancer cells overexpressed a protein

CREDITS (TOP TO BOTTOM): MGH/CENTER FOR MORPHOMETRIC ANALYSIS; PHOTO BY MATT INCKE

called the HER2 receptor. In 2001, Novartis won approval for Gleevec to treat a form of cancer called chronic myeloid leukemia, in which an aberrant gene triggers a proliferation of white blood cells. And last year, ImClone's Erbitux went on sale to fight colon cancer by targeting a growth factor receptor on tumor cells. Since 1996, doctors have also genotyped the HIV viruses present in AIDS patients to help them select the best combination of drugs to treat the disease. The completion of the human genome project in 2001 allowed drugmakers to scan humanity's entire genetic sequence for links to a wide swath of diseases.

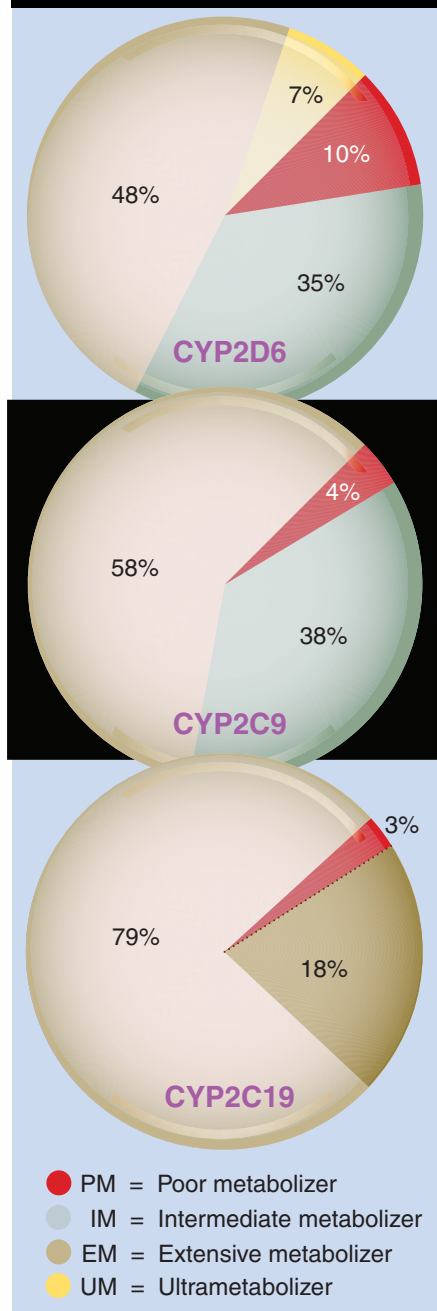
Although pharmacogenomics is expected to be useful throughout the drug development pipeline, its greatest effect at present is on how clinical trials are conducted. In particular, it's helping researchers identify which patients are most likely to benefit from a drug. Better screening of novel compounds for efficacy, toxicity, and side effects should mean fewer compounds falling by the wayside once they enter late-stage trials, the biggest component of the \$1-billion-plus cost of bringing the average drug to market. "If we can get the attrition rate down, even the most reluctant managers will shift," says Mitch Martin, who heads genomic research at Roche's Nutley, New Jersey, R&D center.

Having a better idea of the likely beneficiaries of a drug also increases the odds of identifying the best therapeutic dose. Take the example of warfarin, a blood-thinning compound used by 2.1 million Americans every year to lower the risk of heart attack and stroke. Too little of the drug can be ineffective, but too much of it can cause dangerous internal bleeding and other potentially fatal consequences. Moreover, there is a 120-fold difference in the dosages given to different patients depending on the suite of enzymes each patient carries that break down the compound. Finding the right dose depends largely on repeated blood tests and a lot of trial and error.

That may soon change. This month, researchers at the University of Washington, Seattle, and Washington University in St. Louis, Missouri, reported in the *New England Journal of Medicine* that as much as 25% of this dosage difference can be explained by variations in a gene encoding an enzyme involved in blood clotting called vitamin K epoxide reductase complex, subunit 1 (VKORC1). After examining medical records and blood samples from more than 550 patients and sequencing their *VKORC1* genes, the researchers found 10 common variants of the gene. Patients clustered into three groups requiring high, medium, or low dosages. These clusters, it turned out, were closely linked to racial heritage. African Ameri-

cans were most likely to have a genetic makeup requiring a large dose of the drug, whereas Asian Americans more often required a low dose and European Americans were split between the two groups.

People Have Different Forms of Drug-Metabolizing Enzymes



The bottom line for physicians is both obvious and subtle, Martin says: Genotyping patients can save lives, and finding the right dosage may help get a drug through clinical trials. A traditionally run clinical trial will select a dosage that ensures safety for all participants, Peltz points out. If 10% of patients can tolerate only a low dose of a particular

drug, that dosage will become the standard of care. That means 90% of patients won't receive an optimal dose, decreasing the chance that the drug will be shown to be effective. "The real value is in increasing the probability of bringing a compound to market," says Nicholas Dracopoli, a pharmacogenomics expert at Bristol-Myers Squibb in Princeton, New Jersey.

Another major role for pharmacogenomics is expected far upstream in the process: helping companies determine which among the myriad possible proteins and other compounds in the body make the best targets for drugs. Traditionally, drug target hunters would work with mice and other animals to knock out the gene for each target individually or overexpress it to determine its effect on the animal's health. But animal models often don't mimic human disease closely enough. With pharmacogenomics, however, researchers who



Breakdown. Drug-metabolizing enzymes, such as CYP2C9 (structure above), come in many versions. People who are poor metabolizers break down drugs slowly, increasing toxicity concerns. Ultrametabolizers break them down quickly, lowering the chance that the drug will work. Intermediate and extensive metabolizers fall in the middle.

identify a gene that may be involved in a disease can look to see if a common variant is shared by a large number of patients and then identify the protein involved. "It's a way for us to put all the targets on the same playing field and see which ones confer risk and rank-order them," says Martin. "We're going to use this because we think it will help us make better decisions."

Picking winners

Even so, most industry experts agree that the technology is not yet ripe for a complex disease such as diabetes, which is triggered by a wide range of genetic and environmental causes. That's also true for conditions such as hypertension, in which doctors can already get a rapid readout on the effectiveness of a drug just by performing a simple test, such as checking a patient's blood pressure.

By contrast, cancer seems a promising target. “In oncology patients, it’s very important to treat with an optimal therapy in the first cycle,” Dracopoli says. “Every time it fails, the tumor becomes more systemic, more drug-resistant, and harder to treat.”

The fact that cancer is typically initially examined with a biopsy and, in some cases, surgery gives doctors tissue samples that can be used to genotype the cells present. In theory, says Dracopoli, the next step would be to select a drug most appropriate for combating that form of cancer. Last month, for example, researchers led by Michael Heinrich of Oregon Health and Science University in Portland reported new evidence of Gleevec’s ability to treat a form of gastrointestinal cancer, abbreviated GIST. Gleevec works by inhibiting a protein called KIT, which is abnormally expressed in GIST and fuels tumor growth by signaling cancer cells to keep growing. The majority of GIST patients initially respond well to Gleevec. But after 2 years, more than half develop resistance to the drug.

In a previous study, Heinrich’s team found that patients with a mutation on a region of the KIT gene called exon 11 were far more likely to respond well to Gleevec over time than were patients with a different mutation on exon 9. In a paper he presented at the American Society for Clinical Oncology (ASCO) meeting in May, Heinrich confirmed this result with a much larger set of patients and also revealed the best dosing for GIST patients. Meanwhile, in another study at the same meeting, researchers led by George Demetri of the Dana-Farber Cancer Institute in Boston, Massachusetts, reported that a Pfizer compound called Sutent was more likely to improve the outcome among GIST patients with a KIT mutation on exon 9.

Another major push for pharmacogenomics research is deciphering the genetics behind the metabolism of different drugs in the body. A classic example is a compound known as 6-mercaptopurine, or 6-MP. The drug has long been used to treat children with a form of blood cancer known as childhood acute lymphocytic leukemia (ALL). But one in every 300 children has a variant of a gene for an enzyme called thiopurine methyltransferase that prevents 6-MP from being metabolized. In those patients, the

drug builds up and in many cases has proven fatal. Beginning in the 1980s, researchers led by Richard Weinshilboum at the Mayo Clinic in Rochester, Minnesota, flagged the genetic link to the slow metabolism of 6-MP. Now doctors increasingly run genetic tests on ALL patients before giving them 6-MP to weed out the patients who shouldn’t receive the drug.

That same strategy is also being used to unravel the genetics behind a broad range

of drug-metabolism enzymes, known as cytochrome P450s, that are present primarily in the liver and kidneys. The impact could be dramatic: Variations in just one of these enzymes, known as CYP2D6, have a broad effect on drug metabolism, according to a report this month in *Nature Reviews Drug Discovery* by health policy experts Kathryn Phillips and Stephanie Van Bebber of the University of California, San Francisco. “The most commonly used drugs metabolized by CYP2D6 account for 189 million prescriptions and \$12.8 billion annually in expenditures in the U.S., which represent approximately 5% to 10% of total utilization and expenditures for outpatient prescription drugs,” the authors conclude.

Whether researchers can tie patients’ responses to all these drugs to variations in CYP2D6 genes remains to be seen. But they have made some progress. Researchers led by Matthew Goetz, a medical oncologist at the Mayo Clinic in Rochester, Minnesota, reported at the ASCO meeting that genotyping drug-metabolism enzymes can drastically reduce the risk of toxic side effects from a standard chemotherapy regimen containing three cancer drugs, called irinotecan, oxaliplatin, and capecitabine. Despite the drugs’ antitumor benefits, their combined use can be lethal for some patients. But Goetz’s team found that genetic variants of an enzyme abbreviated UGT1A1 determined what dose of irinotecan could be tolerated, as well as whether the drug works with the others.

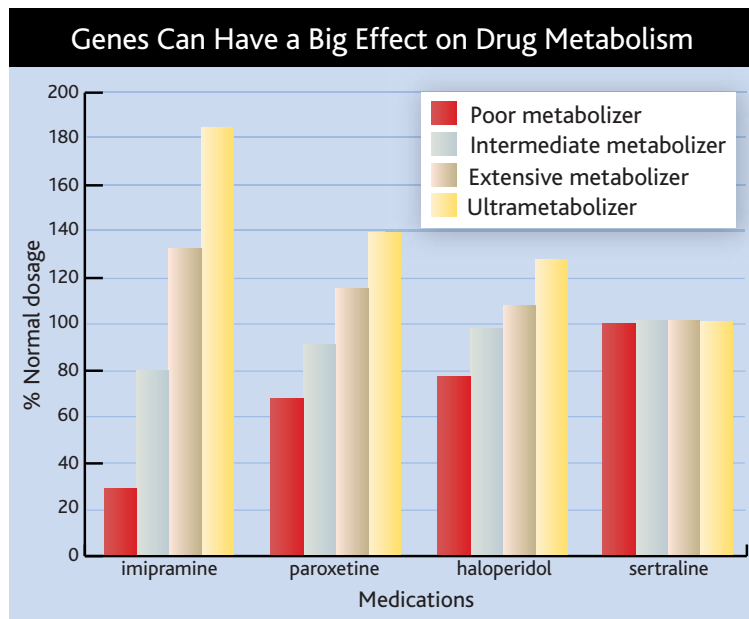
Finally, pharmacogenomics is also opening up new markets for biomarker companies with the tests needed to draw the link. Last December, for example, FDA approved a new gene chip from Roche called the AmpliChip, which tests for two important genes for drug metabolism, CYP2D6 and CYP2C19. A Seattle, Washington, company called Genelex recently started marketing an alternative test directly to consumers.

Despite these and other enticing results, even pharmacogenomics proponents warn against expecting a medical revolution. “It’s not something that’s going to change the world in 3 years,” says Scott Weiss, a pharmacogenomics researcher at Harvard Medical School in Boston. Among the hurdles, Weiss and others say, is that studies linking genes to disease outcome are time-consuming and expensive. That means higher costs in the short run.

Doctors also must be trained to use and properly interpret genetic tests. “Doctors have to buy in,” says Wyeth’s Salerno. One reason they might resist, Salerno suggests, is a fear of being second-guessed by lawyers. “If someone gets injured from an adverse event [from taking a drug], will that person ask why the doctor didn’t check my genotype?” Salerno asks. Finally, patients must become comfortable with the notion not only of having their genomes tested but also with the possibility that insurance companies might exclude coverage for a particular disease, arguing that a genetic link makes it a pre-existing condition.

Many of these changes will take time. But that’s fine, Salerno says, because the field of pharmacogenomics is still young. “This is not a fad,” Salerno says. “This is going to be a cornerstone of future medicine.”

—ROBERT F. SERVICE



Not so simple. People with different forms of the enzyme CYP2D6 respond differently to some antidepressants, such as imipramine, but similarly to others, such as sertraline. In the graph above, the normal dose is 100%. Poor metabolizers of imipramine, for example, can only tolerate 25% of that amount.