cant chance of being charged more for less coverage or denied insurance altogether, she says.

The March to Drugs

Single-gene disorders are rare and even in the age of the genome won't be very compelling targets for drug developers. But in a few cases, enhanced understanding of a single-gene disease has major implications for a far more widespread condition.

One high-profile example: the search for a drug to combat low HDL cholesterol, a leading cause of cardiovascular disease, which has become "the drug race of the decade," according to Louis Lange, MD, CEO of Palo Alto-based CV Therapeutics, a company looking to develop cardiovascular therapies based on "the tremendous amount of science that hasn't been translated into treatments yet." More people have heart disease stemming from low levels of HDL — "good cholesterol" — than from high LDL, "bad" cholesterol, Lange says. But "we don't have the statin," the Lipitor or Zocor, of HDL as we do for LDL.

Enter the residents of Tangier — a tiny island in the Chesapeake Bay — many of whom suffer from a single-gene disorder that gives them "virtually undetectable" HDL levels. The disease has been under study using traditional techniques for decades. But it was not until genome data was brought to bear that the nature of Tangier disease really began to yield to science. Using gene chip technology that scans tissue for matches with around 60,000 genes, CV Therapeutics researchers found about 200 genes that are active in Tangier patients but not in healthy people, and another 200 that are active in healthy people but turned off in people who've inherited Tangier.

Previous research on inheritance patterns had not precisely located the key Tangier gene but had shown that it was somewhere on chromosome 9, says Lange. When only one of the 200 genes turned off in Tangier tissue but not in normal tissue was found to inhabit that chromosome, the gene instantly became the prime candidate as the suppressor of HDL. That gene turned out to produce a known protein whose function had not been previously understood. Experimentation showed that suppressing production of the protein blocks cholesterol transport out of cells.

Use of genome data also allowed CV Therapeutics to discover the entire genetic picture of Tangier patients "in only a few months," Lange says. Because of chip technology, "from start to finish it was a very short process," he says.

Overall, genome knowledge can shorten the path to therapies by leading drug developers more directly to a complete understanding of a disorder, and thus to all potential protein targets for a drug. Beyond that, however, it won't do much to accelerate drug development. Drugs will be sought by the same methods as before.

Gene science will change the drug industry in some ways, however. For example, it will become increasingly clear that virtually every major disease is, in fact, not one disease but several. Each variety will require a different treatment to suit the protein pathways that create it. This won't surprise pharmaceutical companies, although it means a likely slowdown in the search for blockbuster drugs that will sell to everybody. "I think the industry has accepted that this is the way things are going," says Deirdre Gillespie, MD, of the San Diego-based genomics company Vical.

Even more individualized responses to drugs are built into each person's genotype and phenotype, including individual responses to toxins. That leads some analysts to make this prediction: "It will become the norm for each drug to be bundled with a specific set of diagnostic tests for those positions in the human genome which alter drug response," as Cantor put it in the April *GeneLetter*.

The science of drug creation is itself at a "bottleneck," in need of a paradigm shift to substantially improve the way it's done, says genome venture capitalist and former science advisor to President Jimmy Carter Alan Walton of Oxford Bioscience Corp. Genome science won't help. "We need a few real breakthroughs," "a huge bio-idea" to break the bottleneck, he says.

Nevertheless, Walton does see a substantial number of new drugs coming onto the market thanks to the many new cellular targets genome studies will reveal. And that development may trigger a truly revolutionary change of paradigm in clinical therapeutics, he predicts. Even with the relatively limited number of drugs available today, adverse drug interactions are becoming a major problem, he notes, since each drug inevitably binds to sites in the body other than the disease target, triggering side effects — new, unwanted chain reactions among cellular proteins.

So what will be the end of genome science's contribution to drug development? The end of drugs as we know them, Walton says. "We can't just go on making drugs in the same old way, because when you get to the point of 20- to-30 thousand drugs, we're in a real mess with drug interactions."

Drugs' replacement?: "I think the clue, the major strategy is cloning, stem cell work," Walton says, direct manipulation of genes to switch off undesirable cell processes. "Instead of looking for drugs for individual diseases, you will look at something that will address cellular machinery gone wrong." Walton acknowledges these technologies are controversial. "I think there will be a dynamic tension between what we can do and what we're allowed to do." The result will be either an age of science where researchers locate entities inside the nuclei of cells that can switch off the processes of disease and degeneration, or "a new dark age" where public and governmental fears of such approaches see them declared unequivocally off limits, he predicts. — *MC*

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