

Gene tests as potential guides for treatments

By Gina Kolata *The New York Times*

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A decade or so ago, when the revolution in genetics was getting under way, the air was heady with promises. Gene tests, scientists predicted, would become an integral part of drug prescribing. No longer would patients find out too late that a drug did not work for them. No longer would they have to wait to see if they had side effects requiring them to switch to another drug.

But with the exception of a few tests for genes on some cancer cells, the genetics revolution has not happened.

There are many reasons. But the stories of two drugs - one for heart failure, the other for breast cancer - illuminate some of the difficulties, as well as the immense promise.

"We are sitting here on the edge of a very significant improvement," said Dr. David Flockhart, a professor of medicine, genetics and pharmacology at Indiana University. "It involves no new drugs, no massive drug-development program. It involves exploiting natural human variation to protect people from therapy when it will be useless."

One story begins with a drug that was wholly abandoned: bucindolol, a once-promising treatment for heart failure.

Bucindolol, one in a class of drugs known as beta blockers, was tested in a large study sponsored by the National Heart, Lung and Blood Institute and the U.S. Department of Veterans Affairs.

But the clinical trial was halted early after research on other beta blockers found that those drugs improved survival for most heart failure patients.

Soon, bucindolol was all but forgotten. But even if beta blockers help most heart failure patients, they do not help all, and Dr. Stephen Liggett, who researches heart failure at the University of Maryland School of Medicine, wanted to understand why.

Heart failure is a dire illness. It takes up to a year of beta blocker treatment before it is clear whether the drugs are helping. And with heart failure, Liggett says, a year is too long to wait. The hallmark of the illness is a damaged heart, from a heart attack, viral infection, high blood pressure or unknown causes. Struggling to pump blood, the heart grows, sometimes getting so large that it fills a patient's chest. Soon the lungs fill with fluid and patients become so short of breath that they cannot walk across a room. Half die within five years.

Those who respond to beta blockers, Liggett proposed, may have a slight variation in a gene that determines the structure of a protein on heart cells where the drugs attach.

In the meantime, Dr. Michael Bristow of the University of Colorado Health Sciences Center refused to give up on bucindolol. Poring through the clinical trial data, he was

convinced that some patients were substantially helped, even more than they were by other beta blockers. And the bucindolol trial was unique in heart disease research in that the researchers insisted that the participants' DNA be collected and stored.

Bristow and Liggett realized that they had a chance to test Liggett's hypothesis. They could go through the trial data and ask whether the gene variants identified responders and nonresponders to the drug. The gene tests succeeded, as the investigators report this week in *The Proceedings of the National Academy of Sciences*. Responders not only had a 38 percent reduction in their death rate with bucindolol, but they also did better than patients who were taking beta blockers that are already on the market.

Bristow wants to resurrect bucindolol. He has licensed it; formed a company, Arca Discovery; and hired Liggett as a consultant. He is applying to the Food and Drug Administration to market the drug along with a genetic test.

But what if the test also identified people who would do better with the beta blockers now on the market? Which drug should they take? Should nonresponders take any beta blocker at all? The only way to find out would be to do a huge clinical trial of all the drugs using the genetic test, Liggett said. But who, he asked, would pay for that? Drug companies probably would not do it, he said, because it was not in their economic interest, and the government can sponsor only so many studies.

Another drug whose fortunes may change with a genetic test is tamoxifen, which ushered in one of the greatest advances in breast-cancer treatment. By starving tumors of estrogen, tamoxifen stanches their growth and saves lives.

But tamoxifen must be activated by a liver enzyme, and Flockhart and his colleagues found that not everyone's enzymes activate the drug. As many as 7 percent of white women and a significant proportion of black women have two copies of a variant gene and are unable to activate tamoxifen. Others, with one copy of the variant gene, have a greatly reduced ability to activate it.

Flockhart wonders, he said, if tamoxifen is restricted to responders, whether it may actually be more effective than the newer drugs called aromatase inhibitors. Those drugs, unlike tamoxifen, are still under patent and are heavily marketed by their manufacturers as being 2 percent to 3 percent more effective than tamoxifen. But who will pay for such a comparative study?

The evidence that the gene test could completely determine tamoxifen's clinical outcomes is not ironclad. "We have one clinical trial that says it is the case," Flockhart said. There have been many clinical trials of tamoxifen, but none collected DNA data.

Dr. Richard Weinshilboum, a pharmacogenetics researcher at the Mayo Clinic, said that more and more studies are collecting and storing participants' DNA, and there is increasing interest in looking for genetic variations that may determine whether a person responds to a particular drug. "It has frustrated me to see the pace," he said. "Sometimes, from my perspective, it has been a glacial pace. But I think we have to be patient. Those of us who do the research are sometimes the least patient in trying to get the research out." But, he added, "We want to be sure it's right."