



The Question of Compliance

The full potential of personalized medicine cannot be realized if patients don't follow their treatment regimens. The authors address this issue, using diabetes as an example, and discuss new clinical monitoring and feedback systems that could complement the industry's drug development efforts.

betes must take insulin every day just to stay alive. We find Type 1 diabetes developing most often in children and young adults; however, the disease can appear at any age. The symptoms of Type 1 diabetes usually develop rather quickly, although the destruction of the beta cells could have begun many years earlier. Scientists believe a combination of genetic and environmental factors cause the body's immune system to wage this war against the pancreas. Viruses also might be involved.

Type 2 diabetes is far more common, representing greater than 90% of diabetes cases in the United States (1). It tends to develop in adults over age 40, and is most common in people over age 55. The patient with Type 2 diabetes typically is overweight, and because of the increasing prevalence of obesity among children and adolescents in the United States, this type of the disease is becoming more common among young people. Symptoms develop gradually, with an onset that is much less sudden than with Type 1. Some people exhibit no symptoms but still are susceptible to diabetes complications.

Type 2 diabetes differs from Type 1 in that early in the course of the disease the pancreas usually is producing sufficient insulin but the body can't seem to use it effectively. Researchers have yet to determine the precise molecular reasons for this insulin resistance. Eventually, insulin production decreases, resulting in the development of overt diabetes; that is, persistent elevation of blood glucose levels.

Despite the fact that diabetes always is categorized as Type 1, Type 2 or "gestational" (a problem faced by about 4% of all pregnant women in the United States (2) and that usually disappears after the child's birth), genomics research suggests that there probably are many types — or at least sub-types — affecting patients in minutely different ways.

To get an idea of just how serious the diabetes epidemic is, consider that dia-

As we've discussed in earlier columns, the promise of personalized medicine held out by greater understanding of the genetics of disease is perhaps the greatest impetus for research in this area. To understand the genome is to understand the drugs to which patients will respond and that they can take safely. This could bring a future where there isn't just the disease but a "family" of that disease about which we know more — and about which we can do more — than ever before.

But while we very well could develop better treatments for a variety of diseases thanks to genomics, proteomics and other "omics" drugs that could be personalized for the individual patient's disease characteristics, one important issue remains: we still have to get people to take their drugs and follow their disease management programs. This column will discuss some emerging approaches to combining drug technology with behavioral science to ensure compliance with clinical guidelines and, thus, realize the fullest potential for patients.

The Diabetes Epidemic

Let's use diabetes as an example. Today we talk of Type 1 and Type 2 diabetes. Type 1 diabetes is an autoimmune disease, where the body's immune system attacks and destroys the insulin-producing beta cells in the pancreas, which then produces little or no insulin. A person with Type 1 dia-

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betes is the fifth-leading cause of death by disease in the United States (3). Additionally, because people with diabetes are at higher risk for heart and blood vessel disease, kidney failure, strokes, blindness, amputation, nerve damage and a host of other chronic conditions, the disease makes a significant contribution to higher rates of overall morbidity.

Furthermore, the prevalence of the disease is higher among certain ethnic and racial minorities, and the U.S. population is becoming increasingly diverse both racially and ethnically. This, argues the American Diabetes Association (ADA, Alexandria, Virginia, USA), "portends a substantial increase in the size of the population with diabetes. If diabetes prevalence rates remained constant over time, controlling for age, sex, race and ethnicity, then based on U.S. Census Bureau (Washington, DC, USA) population projections, the number of people diagnosed with diabetes could increase to 14.5 million by 2010, and to 17.4 million by 2020" (4).

Worldwide, "the scale of the problem that diabetes poses to world health is still widely underrecognized," according to the World Health Organization (WHO, Geneva, Switzerland). "At least 177 million people worldwide suffer from diabetes [in 2000]; this figure is likely to more than double by 2030" (5).

To round out this rather dour picture, mull over some economic figures for the United States. According to ADA, "direct medical expenditures alone [in 2002] totaled \$91.8 billion and comprised \$23.2 billion for diabetes care, \$24.6 billion for

chronic complications attributable to diabetes and \$44.1 billion for excess prevalence of general medical conditions. Inpatient days (43.9%), nursing home care (15.1%) and office visits (10.9%) constituted the major expenditure groups by service settings" (4).

Quite obviously, the cost of diabetes care is enormous. The complications mentioned earlier drive these high costs. On top of this, a huge percentage of diabetes patients don't ever receive the care recommended by the WHO, Centers for Disease Control (CDC, Atlanta, Georgia, USA) and ADA. And a good half of diabetics do not carry out their recommended self-care.

Combining Technologies

All too often, research focuses on the technical side of a question, to what seems like the total exclusion of the personal side. Personalized medicine is a case in point. Many researchers look at creating individualized drugs, but who is thinking about making sure the drugs are taken properly?

We think there's a very promising opportunity to combine drug technology and behavioral science to ensure compliance with diabetes clinical guidelines and, thus, realize the fullest potential for patients and society. After all, the greater the compliance, the greater the benefits from customized drug treatment.

The Program on the Pharmaceutical Industry (POPI) at the Massachusetts Institute of Technology (Cambridge, Massachusetts, USA) recently sponsored a workshop on diabetes that brought together leading researchers in the field. Our co-sponsor was the Joslin Diabetes Center in Boston (Massachusetts, USA). At the workshop, we all learned about research into the behavioral end of the diabetes question, and we began to think about the possibilities for combining self-care and the future therapies promised by personalized medicine.

InterMed Advisors Inc., (Boston, Massachusetts, USA) showed attendees its solution to the problem of how to capture the information necessary for clinicians to monitor effectively diabetes patients who are involved in self-care programs, and how to get feedback to patients every day to help them comply

with their prescribed treatment plans. As InterMed put it, the solution aims to simplify the transmission of more frequent self-monitoring data, provides the most useful data to clinicians and encourages patients to take care of themselves in a dynamic, informative and engaging way.

This kind of closed-loop feedback system could go a long way in the future of personalized drugs because it could be a key component of whatever formula is needed to solve the compliance problem. Such a system also could facilitate data-gathering in clinical trials and detect true time-to-effect in an outpatient setting more accurately than with currently accepted approaches.

In the system, patient self-monitoring of data is transmitted automatically via the use of a wireless radio frequency receiver connected to standard telephone lines. Each day, the system analyzes the data at the level of the individual patient, using time-series analysis and other advanced mathematical techniques. Communications technology delivers customized feedback from physicians and nurses to patients in their homes, through their televisions.

The system looks promising, and InterMed might be right when it claims it would decrease disease complications, emergency room visits, hospital days and total costs of care. That's good news, given the billions of dollars at stake.

Getting the Person in Personalized Medicine to Comply

It looks to us as if this combination of technologies — the drug development technologies being researched by scientists working on genomics and the computer technologies being utilized by companies such as InterMed — affords a good start toward solving the problem of compliance. We can imagine how it might be beneficial in the hypothetical future of personalized medicine.

For diabetes, we can posit that clinicians will be able to identify the specific pattern of diabetes (what might be called the diabetes "sub-type") based upon an individual's unique pattern of glucose and response to treatment. One patient will have her "type" of diabetes

Computer systems can simplify the transmission of more frequent self-monitoring data and encourage patients to take care of themselves in an informative and engaging way.

that is relatively easy to control, while another will have his “type” that is very difficult to control — with marked fluctuations of blood glucose over the day — both within the broad context of, say, Type 2 diabetes as we define it today. For the latter patient, intervention assumes a greater criticality. More diligence is needed. But maybe our patient is no more willing to comply with his treatment plan than seems to be the case typically for patients. The existence of a closed-loop feedback system could be a major prompt for positive action. And the benefits are not limited to individuals with diabetes.

Let’s consider atrial fibrillation, which is the most common form of cardiac arrhythmia. It affects about two million people in the United States each year, and it can be quite serious. Though a few years ago most healthcare providers thought it was merely a “nuisance” arrhythmia with few consequences, recent research has uncovered complications directly related to atrial fibrillation that are quite devastating, including congestive heart failure, stroke and cardiomyopathy.

We don’t know the definitive cause of atrial fibrillation, but researchers do know that during atrial fibrillation there is a high risk of blood clot formation, which can lead to stroke. Anticoagulation with warfarin has been shown to be effective in reducing the risk of blood clot, and the prescribed dosage of anticoagulants is tied to the results of various laboratory tests.

Just as with diabetes, the future of personalized medicine likely will reveal widely variant individualized risk pro-

files. Some patients will be “controlled” relatively easily with the kinds of anticoagulants available today, while others might not fare as well on standardized treatment regimens. Increasing our knowledge of the disease’s genetic foundations also could tell us details that are unknown today about the difficulty of compliance.

Combining the technologies, we think, is a way to propel the promise of personalized medicine significantly forward. Yet, whether these advances involve a closed-feedback loop system or some other technology that has not been developed yet, we are convinced that this question needs to be answered: What good is personalized medicine if people don’t take their personalized drugs?

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