nyone working in or near any aspect of healthcare has undoubtedly heard the term personalized medicine. Its most common definition is “the right drug for the right person in the right amount.” That phrase refers to the day when all healthcare decisions will be based on each person’s genetic profile. Once science identifies which gene causes which disease — and who has a predisposition to what condition — medicines and treatments can become individualized, based on the illnesses people currently have or might one day develop. That sounds promising, doesn’t it? Certainly this only begins to describe the opportunities presented by pharmacogenomics, the study of how our genetic code relates to drug response.

Those companies able to figure out early in the process who will benefit from a specific drug stand to earn enormous profit. Problems with side effects could become trivial if each medication is proven to help or perhaps even cure certain patients. Patient recruitment for clinical research would then target people for their particular genetic profiles. Healthcare costs could be brought under control by eliminating expensive but unnecessary testing. In theory, each person’s genetic profile would perfectly predict a lifetime of health issues, and physicians could prescribe preventive medication before symptoms appear.

It all sounds utopian. Although tremendous opportunities lie ahead with personalized medicine — already there are some impressive success stories — this field is still in its infancy. As Sir David Weatherall of the UK’s Royal Society says, “Personalized medicines show promise, but they have undoubtedly been overhyped” (4). We certainly believe it will eventually come about. The complexities involved in shifting a worldwide healthcare delivery system from its current model to something genetics-based are substantial. But significant signs show that we are heading down the personalized medicine path:

• The pharmacogenomics business is attracting significant venture capital dollars. Venture capitalists are often first to identify and support what ultimately becomes a successful product or trend.
• In 2005, the US Food and Drug Administration (FDA) published a procedural pharmacogenomics guidance (5). The agency states in its introduction that “the guidance is intended to facilitate scientific progress in the field of pharmacogenomics and to facilitate the use of pharmacogenomic data in drug development.” That move certainly reflects a growing number of FDA submissions related to genomic markers.
• A Genetic Information Nondiscrimination Act, which would prohibit discrimination on the basis of
are therefore expensive because they are chronic conditions. Clinical studies tend to target drugs that can help researchers and development engines “blockbuster” business model. So their research and development engines tend to target drugs that can help the greatest number of people with a chronic condition. Clinical studies are therefore expensive because they require large numbers of patients so drug sponsors can determine statistically significant responses.

Seventy-nine percent of investigational new drugs fail in clinical development because blockbusters are effective in only 40–60% of the patient population (6). To move away from searching for the next blockbuster and toward more “personalized” medicine requires a dramatic paradigm shift in which identifying the cause of variability in response will become the focus of clinical research. Clinical research hypotheses might shift from looking for the biggest number of people that share a very similar response to a compound to looking for a subset of patients who have the best response to a compound regardless of that subset’s size. But in an industry that spends on average more than $800 million to develop each commercialized product (only 30% of which are actually profitable) (7), there’s certainly a financial incentive to consider a different business model.

A New Model: Two hallmarks of pharmacogenomics have historically discouraged big pharma from entering the field: high start-up costs and narrower markets. To take advantage of what biotechnology offers, such companies will either have to reengineer their infrastructures or acquire smaller organizations with demonstrated success. And instead of formulating drugs with peak annual global sales of a billion dollars annually, they will have to accept significantly smaller markets. Annual sales between $350 million and $500 million might be considered a more realistic definition of success in the world of personalized medicine (6).

Such smaller market opportunities have fueled at least part of biotechnology’s success. Recognizing that the blockbuster business model inherently limited research into diseases affecting smaller populations, the US Congress passed the Orphan Drug Act in 1983. That act guarantees developers of orphan products seven years of market exclusivity following approval of their products by the FDA, which provided a strong incentive to smaller biotechs.

Another incentive is the US government restriction on generic versions of biotechnology drugs even after the seven years. Because of their typically smaller size, biotech companies became the natural place to develop drugs for rare diseases with smaller market potential (2). Of course, developing the only drug available for treating a rare and deadly disease allows such a company to set a high price on it because there is no competition. Consider that spending on biotechnology drugs and other more expensive medicines is growing twice as fast as that for traditional prescription drugs — and it is expected to continue growing by 20–50% annually (8).

**Some Industry Data**

In the second quarter of 2005, venture capital firms invested $1.6 billion in biotechnology and medical device start-ups, which represented 27% of all venture financing in the period (1). Growth in the biotech sector rose 17% in 2004 — compared with just 9% in the pharmaceutical industry (2).

Nearly two-thirds (62%) of Americans surveyed support genetic testing for improved medications (3).

Almost half (48%) of Americans surveyed say they would be willing to contribute a DNA sample to a national databank to be used exclusively for health-related research (3).

The current model for healthcare delivery in many western countries relies on physicians with narrow specialty areas of treatment. The medical education system is structured to create specialists. But pharmacogenomics cuts across categories. In the future, once personalized medicine becomes standard, a primary care provider with an understanding of genetics might provide all aspects of healthcare. But right now, most clinical practitioners have only a rudimentary understanding of the subject. And without substantial additional physician training, it will be difficult to demonstrate the value of incorporating personalized medicine into the current clinical system.

**Ethics and Information:** Some questions about the warehousing of genetic information are still unanswered. Who will safeguard the confidentiality of information from employers and insurers? What new kinds of informed consent will be required? What protections will guard against racial or ethnic profiling? How will we ensure that the benefits of personalized medicine reach everyone rather than just the affluent or educated? What genetic tests should insurance companies cover? How do we keep insurers from using the resulting genetic information to deny coverage to individuals who are at risk for developing certain diseases?

**The Legal Side:** Intellectual property is also an issue of import. Right now, companies with successful pharmacogenomic discoveries depend on patent protection for single genes and individual markers. But what happens when scientists begin to discover how individual genes and markers behave differently in combination? Companies will no doubt want to protect their research investments for at least as long as patents protect them now. But any system that seeks to protect extremely narrow pockets of intellectual property could wind up slowing the progress of related genetic treatments. Common in other industries, the practice of patent pooling (in which one company licenses its patent to another) may be adapted to drug
discovery. That’s just one small example of what personalized medicine could require in laws and regulations. Those will certainly become more complex as lawmakers begin to accommodate new definitions and address new concerns. They will need to revise safety precautions to protect smaller patient populations with particular genetic profiles. Global clinical studies will have to adhere to guidelines from multiple governing agencies — even though more targeted studies might mean just a few patients in any given country.

**And in Doctors’ Offices . . .**

Personalized medicine will force clinicians to rely more heavily on technology. With the exception of imaging, medicine has been slow to integrate technological advances; in fact, technology has been underused in healthcare. Just think about the number of physicians still relying on handwritten medical records, despite the fact that those are more time consuming and error prone. If each person’s genetic profile one day resides in some centralized database, clinicians will need to become much more adept at accessing and reporting electronic information.

So what do all the very substantial challenges add up to? In a highly decentralized and market-driven industry, it equals nothing short of a revolution. Personalized medicine will affect every player in the healthcare field: patients, pharmaceutical companies, insurers, clinicians, scientists, regulators, and legislators. Each will have to reexamine, and in many cases redesign, how he or she experiences or provides services.

There will be less autonomy because solutions to such complex challenges can grow only out of cooperative efforts by people with decidedly different interests.

**Clinical Trials, For Example**

Personalized medicine is being driven incrementally by small diagnostic successes. As detailed in the “Case Study” box, AstraZeneca’s Iressa product (gefitinib) is one example. Originally developed for treatment of all non–small-cell lung cancers, it’s now believed to help only those patients with a particular genetic profile. Another example is Genentech’s Herceptin drug, which targets the HER2 protein found on cells in 25% of breast cancer patients. A third success is the BiDil product from Nitromed, Inc., the first medication approved in the United States to treat heart disease in African-American patients. In the next decade, we can expect to hear about more stories like those.

In the future we are likely to see more retrospective analysis of previous clinical research. Compounds previously tested and approved may be revisited as statisticians try to find genetic links among patients who have responded best to treatment. The same studies may be looked at anew to discern genetic patterns among those reporting side effects and screen out future patients likely to suffer such toxicities.

**In the Short Term: Clinical studies involving pharmacogenomic substances will need special patient recruitment activities. The need to collect genetic information could affect patient motivation. Locating sufficient patients with particular genetic profiles may be difficult. Additional screenings and more expense may be required. Companies may turn increasingly toward advocacy groups to locate patients. Once they are recruited, smaller patient populations place additional importance on retention activities. Clinical study design may shift to requiring two patient strata: one with the target genotype, the other heterogeneous. With narrowing studies, sponsors may even have trouble identifying an adequate number of principal investigators with needed disease expertise. All these additional levels of complexity could make pharmacogenomic clinical trials more expensive in the short-term.**

**A Case Study in Personalized Medicine?**

The history of the Iressa (gefitinib) drug may one day be looked upon as the pioneering model that pharmaceutical companies pursue in their efforts to carve out a slice of the pharmacogenomics pie.

After data from clinical research showed that AstraZeneca’s product caused significant shrinkage in tumors in about 10% of patients, the FDA approved the drug in May 2003 for treating patients with non–small-cell lung cancer who had failed two or more courses of chemotherapy. The drug was believed likely to increase patients’ overall survival times (9).

Because this product had been approved under the accelerated approval program, AstraZeneca was required to continue clinical studies. Those additional studies indicated that it did not in fact prolong survival when compared with patients taking placebos. In fact, some serious consequences appeared among nonresponders, including an incidence of interstitial lung disease.

In 2004, AstraZeneca withdrew its application to market the drug in Europe, and the FDA issued a statement that patients taking it should consult with their physicians as soon as possible for considering alternative therapies. In June 2005, AstraZeneca made a labeling change to the product, indicating that it was to be prescribed only in patients who had previously taken it and seemed to be benefiting. No new patients were to be given the drug. Meanwhile, clinical data continued to be reviewed.

Of particular interest was information showing that a small subset of patients (~10%) actually benefited significantly from this treatment. Further study identified genetic mutations in eight of nine responders, whereas no mutations were identified in the seven nonresponders.

Enter biotechnology. In September 2005, Genzyme Corporation announced that it would market a test to detect those mutations in an effort to predict which patients might respond best to AstraZeneca’s treatment (10). If that test, in combination with the drug, is eventually shown to prolong the lives of some cancer patients, it could spur other pharmaceutical companies to reevaluate their own clinical research data to get more “mileage” out of already approved drugs. Maybe even some products abandoned as “duds” could return to development.
to patient expectations. Media reporting of specific scientific breakthroughs is likely to raise expectations long before they can be met. As more pharmacogenomics success stories are reported, patients may begin to expect (even demand) more precise genetic testing and prescribing of their medications. Once a drug is known to work in a specific subset of breast cancer patients, for example, it won’t take long for patients with other kinds of cancer to ask for similar precision in the treatment of their own diseases. Patients could begin asking why tests are available for some conditions but not others. And they will want to know who is behind the decision-making. Imagine what could happen to public expectations once the media reports on the first pharmacogenomics breakthrough involving treatment of a widespread condition such as diabetes, heart disease, or high cholesterol.

Down the Road: The long-term implications of personalized medicine are still decades away. But we can project some of the changes likely to occur.

There’s a potential for tremendous savings in clinical research. By stratifying patients at the start of clinical trials, screening should become much more targeted and efficient. Because fewer patients will be needed for each study, the drug development cycle could be reduced by years. In fact, one estimate suggests development times will come down from 10–12 years for traditional clinical trials to three to five years for pharmacogenomics-based trials (11).

Pharmaceutical companies may no longer need to spend millions of dollars on marketing campaigns for newly marketed drugs. If a genetic profile proves the drug’s efficacy, a new medication has a ready-made market “audience.” And when drug discoveries are targeted to narrower markets, competition should substantially lessen.

The blockbuster model that pharmaceutical companies have relied on for decades will recede. Smaller life science companies, previously relegated to second-tier status, will account for a larger share of industry commerce. Big pharma will likely acquire such smaller enterprises, or small to midsize biotech companies may begin to compete with big pharma in certain specialty areas.

Currently, most of the economic push for personalized medicine is still coming from venture capitalists. So it’s possible that personalized medicine will evolve slowly, one success story at a time.

Another possibility is a sudden and radical paradigm shift, a watershed moment. If pharmacogenomics achieved a breakthrough in a high-profile, life-threatening illness (like cancer, Alzheimer’s, or amyotrophic lateral sclerosis), the resulting media coverage might create a public groundswell of support for personalized medicine. If a biotech company discovered a single gene that causes a variety of cancers, a range of psychiatric disorders, or all autoimmune conditions, that too could immediately alter the game. In either case, patients would begin calling physicians to demand testing and treatment. Patient advocacy groups would lobby legislators to enact guidelines to ensure that all diseases get attention. Medical associations would immediately draft guidelines, and clinicians would start seeking out genetics expertise. A tidal wave of support could materialize virtually overnight, providing just the economic driver that the pharmacogenomics cause needs.

A Patient Recruiter’s Viewpoint

Sure, all this talk about science and the future is exciting. But what about right now? Can the healthcare community personalize patient care in a way that makes a difference today? I think so.

We need only to look to our own industry to get a clue. The good news is that the clinical research community is on the right track. Patients report that the care they receive in a clinical study feels better to them. It’s more thorough; more personal (1). There’s time to ask questions and get answers. The overall perception is that they feel heard, well cared for, and educated about their health.

That stands in striking contrast to what people experience in managed care and national health systems, where physicians are forced to justify and rationalize every decision and are always pressed for time. With that time crunch and emphasis on evidence-based medicine, the human connection gets lost. And with it, sometimes a certain intangible ingredient that makes all the difference to the big picture — accurate diagnosis and patients’ overall health and well-being — gets lost, too. That intangible is the “art” of personalized medicine.

A trend in “boutique medicine” that emerged in the late 1990s seemed to recognize that deficit. The promise was for a return to old-fashioned medicine — for a price. The truth is, high-end practices that charge an annual fee for unlimited physician access are great for some people but simply too expensive for most. And as patient rosters increased with this niche-market boom, some of those doctors found themselves too busy to provide the level of care they and their patients had envisioned.

It’s time to start a new trend. The clinical research community has an opportunity to learn from and build on its own good track record of patient satisfaction. Leading by example, it can practice the art of personalized medicine: a combination of listening and sensing. It’s about asking the right questions and really listening to their answers. Applying the art leads physicians to follow paths that they believe relevant because of how a patient describes his or her feelings, rather than following only the science of symptoms.

Clearly, we’re going against the grain here. Healthcare systems seem to be moving further away from any idea of individualized care. But we know that a system is only as good as its results — and that healthcare is ultimately human care. In the patient recruitment industry, we say it another way: “It always comes back to the patient.”

— Bonnie A. Brescia

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A Mystery Revealed By the Past:
It isn’t actually all that difficult to predict how personalized medicine would affect patient recruitment for clinical studies. Just look for lessons from the past. Each time the clinical trial industry has expanded, the complexities surrounding patient recruitment have increased. Remember when female patients were first randomized into studies. Currently, the pressure is on to recruit more minorities in clinical research. Each change forces companies to reevaluate their recruitment strategies and tactics. As personalized medicine unfolds, we’ll be doing it again.

Fortunately, some basic patient recruitment tenets will never change:

• Patients must come first. Successful recruitment will remain centered on patients and their awareness, understanding, and willingness to participate in research.

• Informed consent documentation is needed to maintain a balance between full and comprehensive disclosure and the ability of lay patients to understand what they are reading.

• Patient willingness to enroll in studies will continue to depend on how their needs and concerns are addressed, even if those concerns are new (e.g., warehousing of genetic information and notification of health findings).

• Patients will always respond well to more information about their condition, about healthcare options, and about the risks and benefits of a given study.

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FOR FURTHER READING

Bonnie A. Brescia is founding principal at BBK Healthcare, Inc., 320 Needham Street, Newton, MA 02464; 1-617-630-4477, fax 1-617-630-5090; bbrrescia@bbkhealthcare.com, www.bbkhealthcare.com. The consultancy has over 23 years of experience in clinical trials focusing on patient recruitment issues.

This article is adapted from Section Four, Chapter Five of the upcoming book, Reinventing Patient Recruitment: Revolutionary Ideas for Clinical Trial Success. A comprehensive, best-practice primer on patient recruitment for clinical trials, it is due to be published in late 2006 by Gower Publishing (www.gowerpub.com).