Fast-forward 10 years, perhaps even as few as five or six, and the practice of medicine in general and cardiology in particular may look very different. Today’s physicians may well be standing precisely on the edge of a major shift in the medical paradigm.

The National Institutes of Health, along with the genome centers of many countries and numerous private enterprises, have been leading the way toward this paradigmatic shift for some time, and they may unveil the impetus for this change within only months. Soon, their endeavor—the Human Genome Project—will provide the scientific community (as well as the rest of the world) with a map of the entire collection of 100,000 or more human genes and three billion letters of deoxyribonucleic acid (DNA) encoding these genes (1). The availability of this map will in many ways change patients’ expectations of health care and physicians’ responsibilities, and society will find itself grappling with a whole new set of ethical, legal, and moral issues.

After the human genome is sequenced, the function of these genes and how they are regulated in health and disease will have to be ascertained. Dr. Robert Roberts, Chief of Cardiology and Director of the Bigher Foundation Center for Molecular Biology in the Cardiovascular System at Baylor College of Medicine, stated, “Hundreds, if not thousands, of genes that relate to cardiovascular disorders will be available by the year 2000. We as physicians must now prepare for the onslaught and all of its potential therapeutic and ethical implications. In addition to identification of genes and of mutations responsible for familial cardiovascular diseases, such as the lipid disorders, cardiomyopathies, and others, there will also be an abundance of genes that play a major role as risk factors for disorders, such as atherosclerosis and coronary thrombosis, other than the conventional, well-recognized lipid genetic influence.” (2).

Many genes associated with cardiac diseases have already been identified (3). Cardiac diseases with an identified genetic locus or gene include hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, long QT syndrome, familial heart block, Holt-Oram syndrome, DiGeorge syndrome, and Noonan syndrome (3). In areas other than cardiology, genetic screening can be used to predict, in many instances, who will have an increased risk of developing Huntington disease, cystic fibrosis, and Tay-Sachs disease. Shaywitz and Ausiello (4) predict that within the next five to 10 years, it will be possible to anticipate who might be most vulnerable to illnesses like diabetes, Alzheimer’s disease, and many types of cancer.

IMPLICATIONS OF MOLECULAR GENETICS: A NEW PARADIGM FOR MEDICINE

As Dr. Francis S. Collins, Director of the Human Genome Project, pointed out last year at the American College of Cardiology 48th Annual Scientific Session (ACC ’99) in New Orleans, every disease is in some way genetically related, and each person is in some way flawed (1). The fields of molecular genetics and genetic epidemiology are in many ways still in their infancy, but as they grow, they may provide a new taxonomy for the definition of disease (5). This new way of defining diseases—by their biochemical mechanisms instead of their pathogenesis—is going to dramatically alter the way physicians and researchers categorize patients, diagnose conditions, prescribe medications, choose treatments, and counsel patients about prevention and care.

Within the next decade, genetic testing may be used to inform a patient of a high risk for developing hypertension many years before a rise in blood pressure is detected. This “genetic prediagnosis” may lead to a specific therapy aimed at preventing hypertension in such a patient, and a pharmacological agent used to prevent hypertension arising from this patient’s individual molecular genetic make-up will most likely be available.

Look ahead a decade or less:

A 47-year-old man comes to see you, his cardiologist, because he has one sister and one brother who died in their twenties and thirties, respectively. He is diagnosed with familial hypertrophic cardiomyopathy with nonobstructive hypertrophy on echocardiography. He is asymptomatic. The family history indicates that he has two children, and upon learning that his condition is an inherited disease, he wants his children to be tested and evaluated. The father and son are tested, and both have the mutation Arg^{406}Gln in the beta-MHC gene. The average life span is 28 years, and death is primarily from premature sudden cardiac death. The father and son undergo genetic counseling and agree to have the triple helix therapy, which will prevent expression...
of the abnormal beta-MHC gene, while expression of the normal gene continues. The half-life of the human heart is about three weeks, and so it is expected that the heart will return to normal in ~15 weeks. He will return monthly for magnetic resonance imaging studies to assess his progress. Both have an indwelling defibrillator until restorative biology is complete.

Benefits for patients. As this scenario illustrates, the potential for changes in patient care is enormous. Although the Human Genome Project is not yet completed, already there are more than 24 genetic tests at physicians’ disposal. It may be only a matter of time before genetic tests are as common and easily administered as those in today’s arsenal, such as cholesterol screening (6). A 1998 survey by the American Medical Association (AMA) indicated that 59% of Americans believe they are at least somewhat likely to take advantage of genetic testing (7).

Perhaps the most exciting opportunity associated with genetic screening will be a renewed and strengthened outlook on preventive medicine. Molecular genetics will open up a whole new world of “risk factors.” As Dr. Collins suggested in his ACC ’99 convocation lecture (1), by the end of this decade, it may be possible to couple taking a history and doing a physical examination with predictive genetic screening. The results of this screening would enable each patient’s physician to identify whether that particular patient has genetic susceptibility to any of numerous conditions defined at the molecular level (1). Physicians may be able to move away from what have generally been “one-size-fits-all” prevention efforts (e.g., don’t smoke, exercise aerobically at least three times a week, follow a diet low in cholesterol and fats) and move toward counseling patients about their specific, genetically evidenced risks. Genetic testing for screening purposes is predicted to become straightforward and less expensive than it is at present, with the emergence of DNA microchip-array technology.

Clearly, the availability of these predictive tests will provide great benefits to patients. As Kinmonth et al. (8) point out, there are likely to be better tests for uncommon conditions, new tests for rare cases of common conditions, and new tests for common genetic contributions to common conditions. In addition to new efforts in prevention, these scientific advances will yield new means to risk-stratify patients and, therefore, better ways to predict the clinical course of disease and choose optimal treatments.

Additional targeted pharmaceutical choices will probably be one of the first results of the genetics revolution. Dr. John Bell has noted that many pharmaceutical companies have already introduced genotyping into clinical trials. New genetic information will not only lead to the discovery and development of new drugs based on a new understanding of disease mechanisms but it will also help physicians to avoid prescribing certain drugs to patients with genetic potential to experience severe side effects or even toxicity (5). As Dr. Philip Leder stated, “We will treat Patient A for breast cancer with this particular cocktail, for example, because we will have genetically determined that this form of therapy is appropriate for her.” (9).

New requirements of physicians. As the era of genetic medicine unfolds, physicians will be required to take on a wide variety of new responsibilities. For starters, physicians will need to understand the evolving new taxonomy of disease, which will be quite different from the one most mastered in medical school. This understanding will need to encompass the kinds of tests that are available, in whom each test is most applicable, how to interpret the results, and how to implement quality care on the basis of those results. The last aspect alone will mean staying abreast of what will no doubt be rapid advances and fluctuations in the whole new field of pharmacogenetics/pharmacogenomics. (Already, the genetics revolution has added new terms to our dictionary.)

Little time will pass before there will be a pressing need to integrate genetic risk assessment into medical practice. Primary care physicians are likely to feel this need—or demand, as Kinmonth et al. (8) have aptly suggested—first, but certainly patients will expect their cardiologists and other specialists to explain and, in many cases, administer tests for this type of risk assessment. In some cases, this may require knowing when to introduce the unique expertise of a genetic specialist, but the AMA survey revealed that two years ago, 72% of patients believed that their primary care physician would be able to interpret the results of genetic testing (7). This expectation is likely to grow, along with public awareness of screening potential. Unfortunately, in a recent study, physicians misinterpreted nearly one third of predictive test results for colon cancer, and fewer than 20% of patients received appropriate genetic counseling (10).

The results of this study suggest another crucial responsibility that will soon fall onto physicians’ shoulders. Physicians will need the ability to recommend tests to patients, to explain the possible advantages and the limitations of these tests, to interpret results in lay terms, and to assist patients in understanding the implications of the results for the patients themselves as well as their families. This will be a multifaceted and daunting undertaking, especially because, according to Dr. Collins, “Most practicing physicians have had not a single hour of instruction in this particular field and are ill prepared [to counsel patients about] the complexities of the molecular analysis of their DNA and the risks it may convey.” (1). Shaywitz and Ausiello (4) make the very important point that availability of individual genetic profiles “will demand a level of intimacy and trust between doctor and patient that is rarely seen today.” They go on to say, “After all, it’s one thing for patients to learn that they have a steep throat or a sprained ankle; it’s another for them to comprehend the implications of a progressively more complex genetic risk profile.” They also explain that this is not the kind of information that can be imparted in the usual 10-min office visit or a cursory telephone report. Informing patients of a genetic risk of disease will require enormous sensitivity and compassion.
At least one other responsibility will accompany the plunge into genetic medicine. There will be a pressing need to educate the public about genetic screening, and physicians and physician-investigators must be at the helm of most, if not all, awareness campaigns. If physicians do not take the lead in informing the public and the media, misperceptions about both the potential and the limitations of genetics-based screening, diagnosis, and treatment will prevail. Gill and Richards (11) have suggested that genetic researchers have a responsibility to draw attention to these facts and to foster “balanced media reporting.” Physicians must weigh in on these matters, too, and to do so, they will need to be literate in the field.

**Societal quandaries.** In 1998, a survey suggested that nearly seven in 10 Americans were somewhat or very concerned that genetic information might be used against them by either their employer or a health insurance provider (12). These concerns are not without merit, as medical progress of such magnitude certainly has the capacity to be exploited. Will confidentiality laws be adequate to keep genetically derived predictions in the hands of those who will use them for good? Will it be possible to avoid discrimination if employers and health insurance carriers have knowledge that will give them insight into how much care an employee or an enrollee might require? What about the possibility that higher insurance premiums will be levied on individuals merely on the basis of genetic risk? As Dr. Leder states, “When you’re able to define an individual’s genetic make-up in detail and make reliable predictions about his or her ultimate fate, that’s enormously powerful information.” (9). These are just some of the questions, controversies, and fears that society will have to tackle as adjuncts to such exciting medical progress.

And, of course, the issues related to cost-effectiveness that are already facing physicians and their patients in the current era of managed care will be further complicated by the availability of predictive tests. Even today, physicians’ orders for tests and procedures can be scrutinized. This scrutiny is liable to intensify as seemingly healthy people begin asking for and expecting screening tests that may turn out to be costly. Will payers defer to physicians’ judgment about whether to run these tests, seeing that the results may be costly. Will payers defer to physicians’ judgment about whether to run these tests, seeing that the results may be costly. Gill and Richards (11) have rightly predicted a need for rigorous assessment of both the economic and the psychosocial costs and benefits of genetic screenings.

**PREPARATION FOR THE ERA OF MEDICAL GENETICS**

Some would argue that the genetics revolution has already begun; others might contend that it is just around the corner, ready to launch when genetic sequencing is completed. Few would debate that the time remaining to prepare for this new era is waning. As evidenced by the numerous requirements and responsibilities likely to fall on physicians, there are steps to be taken now. Here are just a few:

1. At the very least, physicians should keep their minds open to the possibilities of molecular genetics. As Dr. Christine Seidman said during her Bishop Lecture at ACC 2000,

   “I would like to encourage you to embrace this—not to be afraid of it, not to be intimidated by differences in language and words we use from a basic science perspective. I want to show you how relevant molecular genetics is in terms of diagnosing these interesting conditions, and, ultimately, I want to convince you that this will improve the management of these disorders.” (13).

2. Perhaps most important is for each physician to become literate in genetics. According to Dr. Collins, the AMA considers this the greatest revolution in medicine since antibiotics (1). It will inevitably be the responsibility of physicians to educate their patients, if not the public, and doing so will require more than a rudimentary understanding of the research under way. Last year, Dr. Collins urged the ACC to take a significant role in educating its members in this field. The ACC will incorporate human molecular genetics into its educational curriculum so that its members will be prepared for the revolution in cardiovascular care expected in the post-genomic area, when routine genetic screening and new medical therapies at the level of genes and cells will emerge. A new working group, chaired by Dr. Roberts and supported by the Fund for the Future, will convene this summer to accomplish preliminary planning for a College-wide campaign to educate members about the implications for their medical practices resulting from the completion of the Human Genome Project. Titled “Preparing Cardiologists for the Genetics Revolution,” the group will propose a curriculum and a timeline as well as identify educational strategies and formats.

3. Finally, physicians may need to be the voice of reason and wisdom, as ethical, legal, and moral dilemmas related to genetic progress come to the fore. Dr. Susan Pauker (6) has urged physicians to “operationalize the Golden Rule: Treat the patient as you would wish to be treated when the Human Genome Project divulges genetic vulnerability information on all of us.” Physicians should play key roles in promulgating this idea as well as applying it.

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Reprint requests and correspondence: George A. Beller, MD, FACC, Cardiovascular Division, Department of Internal Medicine, Health System, University of Virginia, P.O. Box 800158, Charlottesville, Virginia 22908-0158.

REFERENCES

2. Roberts R. Syllabus. 31st Annual Cardiovascular Conference of the American College of Cardiology, Snowmass, Colorado.
12. Mitka M. Genetics research already touching your practice. American Medical News, April 6, 1998. (as cited in ref. 7.)