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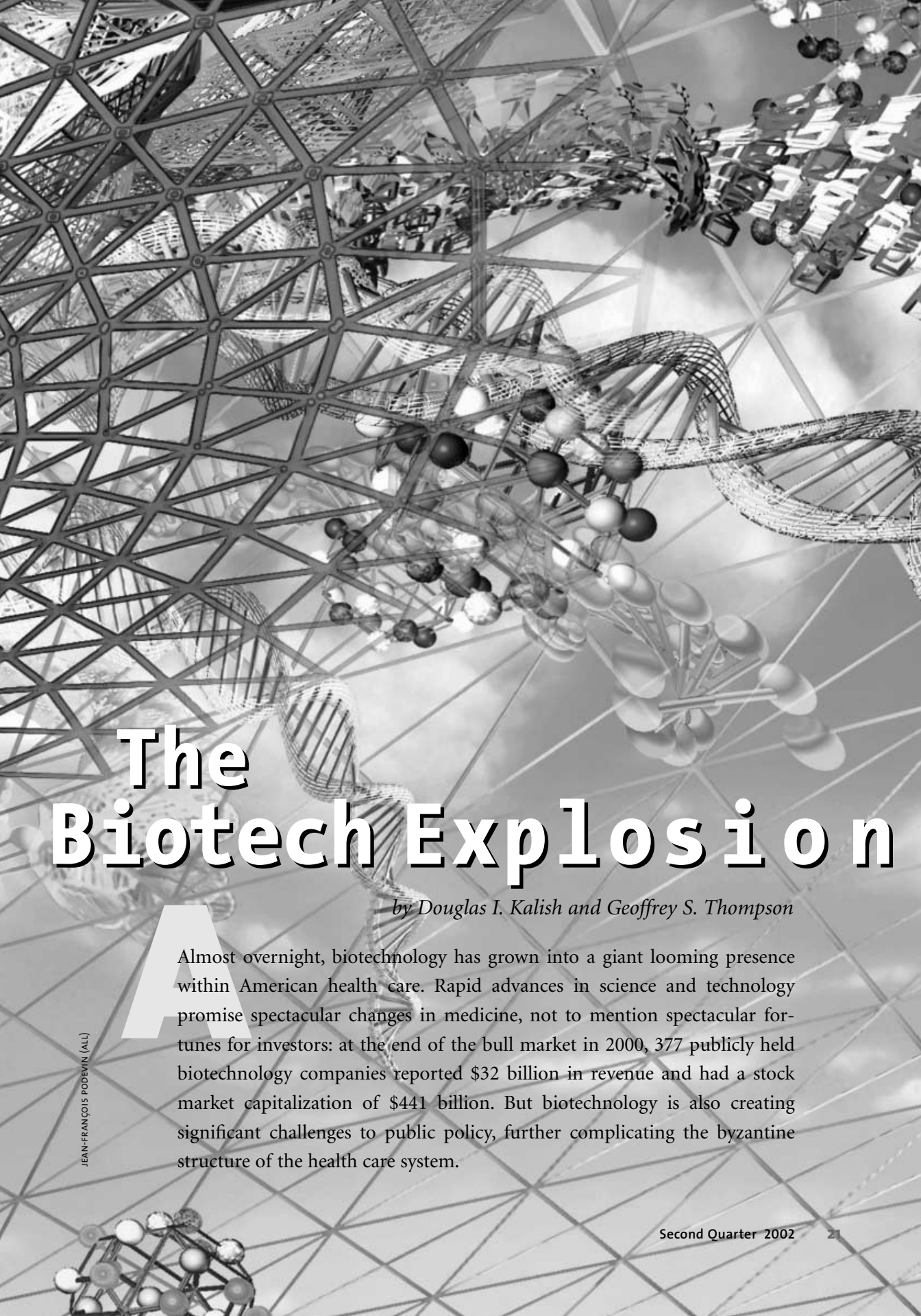

The Biotech Explosion

by Douglas I. Kalish and Geoffrey S. Thompson

Almost overnight, biotechnology has grown into a giant looming presence within American health care. Rapid advances in science and technology promise spectacular changes in medicine, not to mention spectacular fortunes for investors: at the end of the bull market in 2000, 377 publicly held biotechnology companies reported $32 billion in revenue and had a stock market capitalization of $441 billion. But biotechnology is also creating significant challenges to public policy, further complicating the byzantine structure of the health care system.

JEAN-FRANÇOIS PODEVIN (ALL)

Washington projects that by 2010 health expenditures will account for 16 percent of gross domestic product – an average of $8,700 per person each year – straining a system already burdened by conflicting incentives and inconsistent goals. Meanwhile, the coming of age of biotechnology – notably, gene-based diagnostics and therapies – will raise new and difficult payment and privacy issues, undermining the viability of existing business models as well as creating opportunities for flexible enterprises.

Predicting which technologies will make it out of the lab is exceptionally difficult. However, it is certain that advances in understanding the genetic basis of disease will significantly increase the number and efficacy of both diagnostic tools and therapies. And this flood of innovation will affect the cost and delivery of services. Here, we offer some predictions about how this medical-economic drama will play out.

BIOTECH WILL SHARPLY INCREASE THE EFFICACY OF DIAGNOSTICS

An estimated $30 billion to $45 billion is spent annually on diagnostic laboratory services, and the gene-based testing component is growing at an annual rate of 25 percent. What's more, diagnostics are often the tail that wags the dog: though testing represents just 2 to 4 percent of total health expenditures, the results influence perhaps 70 percent of treatment decisions.

While drug therapies based on genetic information hog the headlines, molecular diagnostics that identify disease from an individual's genetic profile are a necessary precursor – and one subject to less regulatory oversight since they are generally noninvasive. If biotech delivers on the promise of treating genetically based diseases, it will also deliver the means to identify individuals who carry defective DNA.

Gene-based testing will propel the diagnostics industry as diagnostics and therapy converge. Many drug therapies today are effective for only a subset of the population. For example, Genentech has developed a drug, Herceptin, specifically for women with breast cancer who overproduce a gene product called HER-2.

Treatment with Herceptin provides no benefit for women whose breast cancer is attributable to other causes and in fact can generate dangerous side effects. At the end of last year, the Food and Drug Administration recommended the use of a gene-detection test that identifies women with the HER-2 gene, targeting a therapy to a genetic profile for the first time. Many other genetic diagnostic tests are in the works.

At-home (and at-the-mall) testing and diagnosis will lead the charge. The success of home-testing kits for HIV and hepatitis C, in no small part fueled by patients' ability to retrieve lab results directly (and anonymously) over the Internet, has emboldened diagnostic laboratories to reach for broader markets.

Aging baby boomers are more educated and affluent than previous generations – and unlikely to take no for an answer when it relates to a medical intervention that promises a longer existence and better quality of life. Already, for-profit providers are offering expensive diagnostic services like full-torso MRI scans to health-conscious consumers with deep pockets.

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PHARMACIES WILL EXPAND DIRECT CONSUMER RELATIONSHIPS

Though the number of pharmacies has remained stable since 1992, prescriptions have grown 150 percent and revenues are up 270 percent. In addition to the traditional role of verifying prescriptions, checking drug interactions and ensuring proper dosage, pharmacists are being asked to administer insurance benefits – and in some cases to help patients manage their diseases.

Pharmacists have the opportunity to move up the value chain, offering more skilled services for more money. And drug makers are accelerating this process through aggressive direct-to-consumer marketing. Since 1997, when the government relaxed restrictions on drug advertising, billions of dollars have been spent to help Americans "discover" their untreated ailments and the latest drugs to tame them. Advertisements on the evening national news are dominated by invitations to ask a doctor about medications for high cholesterol, osteoporosis and acid reflux. With the drug companies' complicity, pharmacists can become the human face of direct-to-consumer marketing.

HEALTH CARE WILL SHIFT FROM LABOR-INTENSIVE (PROVIDERS) TO CAPITAL-INTENSIVE (DRUGS)

From 1997 through 2000, the number of prescriptions for the elderly grew 7.1 percent, while this segment's total drug spending increased 18.5 percent; for the nonelderly the number of prescriptions grew 4.7 percent with total outlays increasing by 15.6 percent. High growth rates in drug outlays will undoubtedly continue, if only because of the rapid aging of the population.

New medical products and technologies are driving America's rapid increase in health

care spending, in which capital-intensive medical products are being systematically substituted for labor-intensive services. This shift has generated serious questions about the cost efficiency of these new medical technologies – specifically, whether there are incentives in place to ensure that only cost-effective technologies are adopted and used.

NEW DRUG DEVELOPMENT INCREASES THE LOAD ON REGULATORS, BUT LITTLE WILL BE DONE ABOUT IT

Since a new therapy cannot be sold without Food and Drug Administration approval, the speed, efficiency and expertise of the FDA has long been subject to critical scrutiny. Enabled by the 1992 Prescription Drug User Fee Act and 1997 FDA Modernization Act, the FDA has instituted a faster, more efficient drug review process. Average approval times decreased from 30.3 months in 1991 to 12.6 months in 1999. However, in 2000 the trend reversed, and the approval process increased to 17.6 months. This has generated concern among manufacturers, since recent biotechnology discoveries are expected to increase the number of drugs that need approval.

A user-fee system in which pharmaceutical companies seeking drug approval pay for the process has enabled the FDA to add 600 reviewers. However, if even a small fraction of the 30,000 to 50,000 genes in the human genome yield candidates for therapeutics or diagnostic tests requiring approval, the system will be overwhelmed.

The approval sequence is just one link in the drug discovery and development chain under FDA control. Getting the average drug from laboratory to patient now requires 14 years and costs in excess of $500 million. While defenders of the current system argue that this deliberate process is the price of sustaining the FDA's fine safety record, the high cost of drug development and regulatory approval is generally seen as a major limitation to innovation.

The rigidity and high cost of regulation discriminate against smaller companies and drive the industry's focus toward "blockbuster drugs." While the adverse consequences of stifling innovation and perpetuating monopolies are widely acknowledged, the FDA development and approval process remains arcane and obscure to most. For this reason, radical reform of the FDA is unlikely to be supported by society at large, particularly if such reform is seen as benefiting large pharmaceutical companies.

DRUG DEVELOPMENT IS A BOON FOR ACADEMIC MEDICAL CENTERS AND CLINICAL RESEARCH ORGANIZATIONS

In addition to increasing the burden on regulators, the projected increase in new therapeutics will tax drug developers' capacity to test drugs. Most clinical research is performed in academic medical centers, the minority of hospital complexes that are affiliated with medical schools and dedicated to clinical research. Such centers have been financially strained because they are typically high-cost health-care providers in an environment of declining reimbursement by insurers. Academic medical centers say the cost-cutting tactics used by managed care organizations inhibit clinical trials and slow innovation. This inhibition can be direct, through restrictions on patients' participation in clinical trials, or indirect, through refusal to reimburse providers for unproven therapies.

Academic medical centers will continue to face strong competitive pressure as managed care steers patients to lower-cost community providers. However, with the huge potential for new therapies generated by biotechnolo-

gy, academic medical centers will be well positioned to replace their money-losing operations in primary care with clinical trial services. Research by Richard Retting of the RAND Corporation suggests that the ability of academic medical centers to conduct clinical trials – and thus drive competitive pressures – turns on their ability to identify patients for trials and to maintain sophisticated patient tracking systems. Recognizing this, a new industry of clinical research organizations has emerged to enroll patients and manage clinical trials. As specialists in the design and implementation of drug tests, clinical research organizations can leverage their investments in information technology over dozens of drug trials and tens of thousands of patients.

OVER-THE-COUNTER AND LIFESTYLE THERAPEUTICS WILL PROLIFERATE

The demand for over-the-counter therapies will grow considerably as the population ages. More than eight out of every 10 Americans take an over-the-counter pain reliever in any six-month period, and one-third take pain relievers more than eight times a month. Drug makers are adjusting their marketing strategies accordingly, shifting prescription drugs with waning patent lives into the consumer market. The major pharmaceutical companies may find that close alliances with – or even outright acquisition of – retail pharmacy networks or distributors will give them more control over the over-the-counter value chain.

By the same token, demand for "lifestyle" drugs on the part of age-anxious baby boomers is growing. Antibaldness drugs generated $180 million in sales in 1998, the antiwrinkle drug Botox earned $90 million in sales in 1997, and Viagra's sales approached $800 million in its first year. One industry analyst projected that with more than $20 billion now being invested in developing drugs for lifestyle conditions, annual sales of lifestyle drugs will soon reach $11 billion. Since most lifestyle drugs aren't covered by insurance, a large portion of the discretionary health care dollar will be directed toward them.

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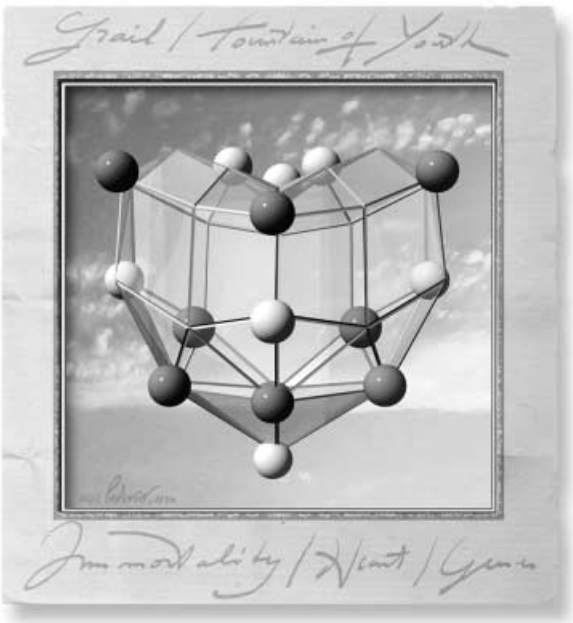
TREATING DISEASES' CAUSES INSTEAD OF SYMPTOMS WILL SHARPLY INCREASE LONGEVITY

Over the last century, the causes of mortality and morbidity have shifted from infectious to

chronic disease, which now cause 7 deaths in 10. Even deaths attributed to infection are often the indirect result of an underlying chronic condition – for example, chronically bedridden patients are susceptible to respiratory failure.



This shift is both the cause and effect of increased life expectancy, which has risen by about 12 years since 1940. Currently, 34 million adults are aged 65 years or older. That number is expected to jump to 70 million – one in every five Americans – by 2030.

Biotechnology promises to treat the underlying disease, not just the symptoms. For example, cystic fibrosis is a devastating disease caused by a genetic defect that affects the operation of ion pumps in cells, resulting in gastric and respiratory symptoms. Today, therapy for cystic fibrosis treats only the symptoms. Sufferers usually succumb to the cumulative effects of the disease and its therapies in their early 20s.

Genetic therapies under development will deliver normal copies of the defective gene to the appropriate cells, enabling them to make working versions of the ion pumps and effectively curing the disease. The promise of gene replacement therapy is far from being realized. But it holds out the prospect of true cures for chronic diseases, including cancer and heart disease. The eventual result will be a decrease in genetically related chronic illness and a concomitant increase in life expectancy.

DRUG COMPANIES ARE SHIFTING TO DISEASE MANAGEMENT

The growing complexity and information collection requirements of more personalized diagnostics and therapies will encourage wholesalers and pharmaceutical manufacturers to diversify their business models. These companies are moving toward one-stop shopping for individualized disease information, patient support and management, and health products and supplies.

For example, Pfizer hosts a Web site (www.pfizerforliving.com) providing interactive health tools and health care information on topics including diet and exercise, allergies, high cholesterol, diabetes, high blood pressure and osteoporosis. The site offers software tools for calculating target body weight and heart rate, a nutrition analyzer and a personalized medication log. Biogen recently signed a deal with Salu to create a clinical information Web site to reach neurologists and their patients with multiple sclerosis, providing them with a variety of information. Roche Diagnostics offers stand-alone diabetes management software for physicians. Not only do disease management programs "lock in" patients over the long term, they also offer the opportunity of additional revenue from associated products and services.

GENETIC INFORMATION ALLOWS GREATER DISCRIMINATION BETWEEN THE HEALTHY AND SICK

Third-party payers traditionally minimize risk by pooling the health care expenses of groups. Genetic testing and tailored therapies disrupt the insurance pooling paradigm because they provide much more reliable information on the likelihood of disease and cure at the individual level.

Such information should benefit payers in two ways. First, knowing a patient's genetic profile will allow the payer to determine the most clinically effective and the most cost effective courses of treatment. Where a therapeutic benefit generates net savings for the payer – say, by substituting for hospital stays – this therapy is likely to become part of the benefit package. However, where the savings are uncertain or take many years to materialize, benefits are less likely to be included even if the clinical advantages are unambiguous. Preventative therapies are even less likely to be covered because typical rates of employee turnover means that little of the future savings will accrue to employers or payers.

Second, genetic testing will allow private managed care organizations to charge higher premiums to those more likely to develop a disease or to avoid insuring those persons altogether. Managed care organizations will gain the practical ability to price coverage on an individual basis because they will be able to predict accurately who is a "bad" risk. Uncovering an individual's genetic propensity to illness poses a real threat to those who depend on the averaging of costs over the group. In the absence of strong legislation or social pressure to buttress "community" premium rating, individuals' insurance premiums will reflect their genetic profiles.

The enthusiasm for genetic testing as a means for discovering the biological causes of disease and for advancing individualized therapies has been tempered with ethical and practical concerns over privacy. A 1998 study by the National Center for Genome Resources reported that 85 percent of adults believed employers should not have access to a patient's genetic information and 63 percent indicated they would not undergo genetic testing if they knew that insurers or employers could gain access to the results. To address similar concerns, Britain recently enacted a five-year moratorium on the use of genetic information by insurance companies.

The promise of gene replacement therapy holds out the prospect of true cures for chronic diseases, including cancer and heart disease.

The response in the United States has been more measured. In 1996 Congress passed the Health Insurance Portability and Accountability Act, which introduced new standards on the use and transmission of patient-specific health information. The goal was to prevent abuse of such information and to increase public confidence that health data would be used prudently. The act prohibits insurance companies from using genetic information to deny or limit insurance coverage for individuals enrolled in a group plan, prohibits charging a higher premium to one member of a group and prohibits considering patients' genetic information as a pre-existing condition without a supporting diagnosis.

However, the National Human Genome Research Institute points out that many gaps remain. Following are things the Health Insurance Portability and Accountability Act does not do:

- Prohibit the use of genetic information as a basis for raising health insurance premiums.
- Limit the collection of genetic information by insurers and prohibit insurers from requiring an individual to take a genetic test.
- Limit the disclosure of genetic information by insurers.
- Apply to individual health insurers except if covered by the portability provision.

The act's approach is to rely on personal consent, where the individual rather than the government determines access to genetic information. Individuals can give consent to genetic testing when it offers a legitimate health benefit, but can prohibit the use of that information for any other purpose. Patients can opt-in to therapy and opt-out of discrimination at the same time.

But critics note that most requests for genetic testing come at moments when patients find it nearly impossible to say no – say, when applying for health coverage. The debate over genetic testing is in its infancy, but any American solution will probably include some mixture of government oversight and individual control.

While the concern about genetic privacy is growing, opposition remains largely unorganized and dispersed compared with the focused clout of the organizations that support the increased availability of genetic information. The collection and use of personal genetic information will be slow at the start as the ethical and logistical safeguards are reinforced. But powerful industry interests will stop legislation that jeopardizes its availability. The resulting potential for misuse of information will dissuade some people from pursuing gene testing and therapy until it begins to produce clear personal benefits. Ultimately, privacy concerns are likely to be traded away to the clinical advantages of genetic profiling.

BIOTECHNOLOGY MAY CUT DRUG DEVELOPMENT COSTS, BUT WON'T LOWER PRICES

In 1999, *Fortune* ranked the pharmaceutical industry as the most profitable in America, with a net profit margin of 18.6 percent, compared with the Fortune 500 median of 5 percent. The industry has long defended its profitability as the driving force behind the risky and expensive process of developing and commercializing new therapies.

Research-based pharmaceutical companies spent some $30 billion – 18 percent of revenue – on research and development in 2001, compared with an average of 4 percent across all industries. These outlays reflect the quintupling in recent decades of the total costs of discovering and developing new drugs. Fewer than 2 percent of pharmaceuticals in development actually become commercial medicines, and the payoffs from those that do make it are a long time in coming.

Biotechnology will undoubtedly increase the number of new drugs, but may not reduce their average price. At first, new information on genes and biology will do little to reduce the number of "failed" research and development activities, perpetuating companies' rationale for high prices. Eventually, biotechnology promises to increase the productivity of drug discovery and development efforts, and to lower required economic returns, by reducing the risks inherent in research and development. To date, though, no company has suggested that biotech tools have decreased the cost of drug development.

Without legislated price controls or a drastic increase in the negotiating power of payers or consumers, premium prices on new pharmaceuticals will presumably reflect their value to consumers.

Moreover, prices are not based on cost (even if they are justified that way), but on what the traffic will bear. Without legislated price controls or a drastic increase in the negotiating power of payers or consumers, premium prices on new pharmaceuticals (and medical engineering miracles such as artificial organs) will presumably reflect their value to consumers.

Even if biotechnology results in highly efficient drug discovery and patient targeting, the specificity of new therapies may work against profitability. Advances in molecular diagnostics will allow for the specific targeting of pharmaceuticals, which will increase their clinical efficacy. However, molecular diagnostics will reduce the overall demand for individual drugs by shrinking the pool of patients for whom the chemical will be prescribed. Instead of marketing, say, a new anticholesterol drug to tens of millions, it might be sold only to a few hundred thousand who would show clinical benefits because they inherited a gene producing a faulty enzyme.

Even as pharmaceutical companies attempt to lower the costs of drug development and testing, they will be aggressively pursuing strategies to protect and extend their product portfolios. Typically, development and clinical testing absorbs a significant portion of the time in which the producer maintains a patent monopoly. Patents are awarded for a total of 20 years. But because of the time required for development and clinical testing, the average effective patent life of a new drug is considerably shorter.

Every month of a monopoly on a blockbuster drug can be worth hundreds of millions of dollars. Since drug patents are granted for specific uses, producers are actively looking for new uses of their existing drugs. Under current law, drug companies can get three years of additional exclusive marketing when they demonstrate that a drug can treat another disease. A manufacturer agreeing to test the product on children gains an additional six months of exclusivity.

One anticipated benefit from the human genome project is a more complete understanding of the interactions of gene products. One drug, perhaps in combination with other therapies, could be used to treat a variety of diseases. Expect the pharmaceutical companies to use biotechnology at both ends of the manufacturing process: to decrease cost and increase the number of candidate drugs, and to find novel uses that extend their monopolies over drugs in production.

THE GOVERNMENT WILL MAINTAIN PRESSURE TO LOWER DRUG PRICES IN SOME MARKETS

Another factor complicating the drug price equation is the impact of government insurance. For Americans over 65 and for certain disabled persons, Medicare pays for drugs received as a part of a hospital service. Medicaid, which is partially financed by the federal government but administered by individual states, pays for health care services and products for the indigent. Many states choose to cover prescription drugs for those eligible for Medicaid. In 1999, 39 million persons were enrolled in Medicare and another 32 million were enrolled in Medicaid.

In countries with universal government health insurance, governments have been able to leverage their huge spending volume and status as monopoly buyers, exacting discounts from pharmaceutical manufacturers or simply legislating price ceilings. The ability to price their products at a premium in the United States has helped the pharmaceutical companies remain very profitable. However, cost pressures on government insurance programs could effectively eliminate the United States as a high-profit sanctuary.

In the absence of federal action, a number of states are already moving to control spending on pharmaceuticals. Soaring Medicaid drug costs and heightened media attention to pharmaceutical prices gave many state and localities the political will to enact purchasing legislation aimed at lowering outlays for drugs. Florida, with the third largest Medicaid program (behind New York and California), faces a $650 million deficit in its Medicaid budget. It recently imposed an extremely restrictive "formulary" – a list of drugs approved for reimbursement. To make the list, manufacturers had to promise price cuts of 6 percent on top of the previously mandated 19 percent discount. Several other states, including Louisiana, Maine and Michigan, are proposing similar restrictions.

If managed care organizations support price controls or other sorts of government intervention, they run the risk of creating a monster.

The pharmaceutical industry has challenged the legality of these cost-containment measures, claiming that states do not have the authority to restrict patient access to prescription drugs. Most controls have been limited to lowering prices for those eligible for Medicaid and the uninsured. However, baby boomers, who use a growing proportion of drugs produced, will probably support legislators who pursue price controls.

Proposals to extend prescription drug coverage to Medicare, the largest single payer for health services, could have huge ramifications on demand, prices and profits. Drug manufacturers' biggest concern is the de facto price controls that Medicare would place on existing and new therapies, if it were to extend coverage to out-of-hospital use. Another serious concern for the drug companies is that benefit coverage, payment and delivery decisions could become politicized and (further) bureaucratized. Getting a new therapy approved for sale is already a decade-long process costing millions of dollars. Getting a new therapy approved for government reim-

bursement could add years to the process. For these reasons, pharmaceutical companies will oppose any Medicare drug coverage and get their allies, like the managed-care lobby, to follow suit. They will be greatly helped by the looming insolvency of Medicare.

Managed care organizations provide health coverage to millions and have a strong financial interest in lowering pharmaceutical expenditures. Their cost-control strategies and benefit coverage decisions can have a significant impact on the type, price and quantity of therapies provided. Managed care organizations have thus far been relatively unsuccessful in reining in the soaring pharmaceutical costs – indeed, the managed-care and pharmaceutical industries have often joined forces to limit government regulation. However, the coalition seems to be breaking down under the tension created by rising pharmaceutical costs.

If managed care organizations support price controls or other sorts of government intervention, they run the risk of creating a monster. As for-profit companies whose return is dependent on setting their own premiums, they have a vested interest in keeping the health care market free of price regulation. Managed care organizations face a difficult balancing act, supporting government initiatives that serve their direct interests while maintaining the political coalition favoring minimal government interference. Hence, they will quietly support certain legislation aimed at curbing pharmaceutical spending – but very quietly, indeed.

MANAGED CARE ORGANIZATIONS WILL BE THE "BAD GUYS" IN THE DRUG-PRICE BATTLE

Prescription drugs are popular and expensive, and payers are in the unwelcome position of deciding which ones will be covered. Managed care organizations will increase their efforts to slow their expanding outlays for drugs by streamlining coverage, stepping up efforts to extract discounts from manufacturers and service providers, and adopting more sophisticated arguments for nonpayment. A combination of direct-to-consumer advertising and the historically strained relationships with physicians will force managed care organizations to wear the black hat. Lobbying efforts, legal actions and heated negotiations will be more common as managed care organizations fight against the high prices of new pharmaceutical products.

CONCLUSIONS

Thirty years ago, the information technology market was transformed by technologies that enabled a complete computer to be built on a single silicon chip. Today's microprocessor and software technologies are dominated by a few companies; all of the first-generation minicomputer manufacturers – and most of the mainframe manufacturers – have disappeared. The potential for realignment in the health care industry is no less significant.

The interactions between drug manufacturers and payers, payers and providers, and providers and patients will evolve as biotechnology and information technology reduce the information asymmetry on which the relationships are currently based. The flexibility and adaptability of health care business models will be challenged by the rapid pace of biotechnological change. Firm predictions about the future health care landscape are difficult because they depend on science as yet undiscovered and will be tempered by the political process and social demands. But health care professionals who don't understand that biotechnology will be the dominant force in the health care industry risk becoming dinosaurs. M