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The Coming Biochip Boom: Gene Chips Go Clinical

Which biochip platforms will pour into doctors' offices and clinical labs as gene chips become the key to diagnosing disease? Companies with winning technologies will share a slice of a $20 billion pie.

Sarah jumped from her swing set and landed flat, shattering a leg bone where most kids would have sprained an ankle. Why? An X-ray revealed the problem: Where there should have been hard bone, there was soft tumor. Sarah had cancer.

But what kind? Sarah needed a precise diagnosis, and pronto. If her cancer was aggressive, the best hope was immediate treatment with the powerful but toxic drug Adriamycin. If Sarah's tumor was the slow-growing kind, we had time to try out weaker, but safer medicines.

A biopsy was inconclusive. Like many pediatric bone tumors, Sarah's was a type doctors call small, round, blue-cell tumors. They may look alike, but in the human body they behave very differently. How to treat Sarah? Adriamycin can cause serious heart damage, so it's not a drug doctors like to give an eight-year-old. Of all the small, round blue-cell tumors, only one kind, Ewing sarcoma, spreads aggressively enough to require this potentially deadly medicine.

Five years ago, Sarah's doctors hoped the less toxic medicine would be enough. She died, just six months after falling from her swing.

Today, rapid advances in biotechnology are giving doctors new answers and patients like Sarah new hope. Where once physicians were forced to rely on tumors' visual appearance, amplified by X-rays or microscopes, new technology allows doctors to go straight to the genetic codes that instruct tumors how to grow, finding the invisible molecular signals that differentiate cancers, as well as a host of other deadly diseases.

The key to this vast new life-saving, cost-slashing diagnostic power is a tiny glass chip, peppered with DNA strips, alternately known as the microarray, the biochip, or the gene chip. Today, 60 percent of gene chips are sold for research purposes, where they are speeding up drug design and helping researchers mine genomic databases (more on this market in future Reports). But thanks to recent improvement in biochip platforms along with a tsunami of new genomic knowledge, gene chips are about to burst out of the confines of the research lab and into the hands of doctors and hospitals, transformed from research aides into amazing diagnostic tools.

In the not-too-distant future, a single gene chip will be able to screen for hundreds of diseases from heart disease to diabetes, sometimes years before patients develop symptoms. Even as we speak, gene

INSIDE:

chips are about to help doctors diagnose particular life-threatening illnesses faster, exchanging expensive, time-consuming ordeals like biopsies and sigmoidoscopies for simple blood, saliva, stool or urine tests. Gene chips will uncover dangerous antibiotic-resistant strains of infections instantly, or differentiate between cancers of patients like Sarah that may look alike but require very different treatments. Gene chips are even creating whole new diagnoses, reclassifying diseases based on their underlying molecular signals rather than misleading surface symptoms.

The coming biochip boom will be fueled by a new generation of diagnostic biochips

Gene chips are also the key to *pharmacogenomics*, the emerging science of tailoring treatments to a patient's individual DNA profile. (I recently met with Orchid Biosciences (ORCH), the industry leader in this technology, and a real class act: more about them in future issues). DeCode, which uses its huge Icelandic genomic database to mine for disease markers, recently collaborated with biochip maker Affymetrix (AFFX) to develop DNA-based tests to predict how individual patients will respond to treatments for depression, asthma, hypertension, breast cancer, migraine, and high cholesterol, among other diseases. Last month, Agilent (A) and Incyte (INCY) expanded a similar licensing agreement to enable Agilent to use Incyte's gene patent portfolio and its Life-Seq gene database to design custom gene chips. (There is also a lot of promising intellectual property, a subject we'll explore in the future).

But in this issue, we're focusing not on genomic databases, but on the companies that make biochips. While gene chips used in research fuel a great many amazing biotech innovations, for gene-chip companies themselves, the coming biochip boom will be fueled by a new generation of diagnostic biochips designed for clinical, not research, use.

Micro Lab on a Chip

Gene chips were born at the intersection of microelectronics and molecular biology, the brainchild of recent advances in microfabrication, microfluidics, microelectromechanical systems (MEMS), and genomics. Like most great ideas, biochips are simple in concept: thin wafers of glass or plastic etched not with tiny transistors, like ordinary microchips, but with strips of DNA. All biochip platforms, whether designed for clinical or research use, exploit the natural tendency of double-stranded DNA molecules (once separated) to rejoin their complementary partner, a process called hybridization.

Separate the twisting pairs of a single DNA fragment and you create an amazingly elegant system for genetic analysis, including diagnostics. Here's the basic idea: Isolate one-half of a DNA pair from a patient's sample. Wash it over a chip embedded with potential mates—DNA strands associated with particular diseases (known to the trade as DNA probes). Watch and wait to see which DNA strands re-entwine. These DNA hits allow researchers to identify promising new drugs. They help mine genomic databases for new disease markers. And they are also the key to fast, accurate diagnoses.

The first step is to saturate the gene chip with the sample of a patient's DNA or RNA (mRNA, to be exact). Gene chips have built-in "laboratories" that exploit microfluidics—a fancy way of saying they use minute quantities of chemicals mixed and channeled in microscopic wells to multiply a few copies of DNA into millions (a process called amplification). The point is to make sure the DNA sample fully saturates all the DNA probes embedded on the chip. Next, the amplified double-strands of DNA are split up, then washed over the chip.

In hours, a remarkable feat of pattern matching occurs. Strips of DNA bind naturally to their complementary probes on the silicon surface. But how to read the submicroscopic DNA hits quickly and accurately? Different biochip platforms have come up with different answers. But the first idea was brilliantly simple: Use fluorescent dye to tag the patient's DNA samples a different color than the DNA probes embedded on the chips. DNA hits take on a unique coloration caused by the merger of the two dyes. Imagine the patient sample is dyed yellow and the DNA probes are dyed blue. DNA hits would glow vibrant green, easily detected and catalogued by a computer.

This summer, scientists at the National Cancer Institute used such a biochip system to distinguish dif-

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ferent types of blue-cell tumors, the same tumor Sarah had, which once stumped even the best-trained pathologists, peering through powerful microscopes. More than a simple clinical breakthrough, this biochip system has led to a dramatic discovery: the criteria doctors are currently using to classify cancers are wrong. This discovery will yield untold future medical advances.

David Botstein's Stanford University lab recently used gene-chips to analyze 65 primary breast cancers. The results are transforming not just treatment but the very definition of the disease. Breast tumors with few or no estrogen receptors used to be considered more curable. But using gene-chip analysis, Botstein's lab showed breast tumors are more accurately classified into four subtypes. Most surprisingly, estrogen-receptor negative breast tumors appear to consist of at least two biologically distinct subtypes that may require totally different treatment protocols. And last year, Stanford University medical researchers used a "lymphochip" developed by Affymetrix to show that a lymphoma, previously identified as a single type of cancer, was in fact two genetically different diseases.

Gene chips are beginning to tell us that tumors in the same organ that look the same under the microscope develop and respond in entirely different ways. Today everyone with, say, pancreatic cancer, gets similar treatment, but 90 percent fail to benefit. (Many cancer cures have at least a 50 percent failure rate). Why does the same treatment save some patients' lives and speed others to an early grave? Gene chips will tell us why, because they discriminate between cancers based on the molecular signals that instruct tumors how to grow. What we once thought of as one disease, pancreatic cancer, will become many pancreatic cancers.

And not just cancer. "We're going to learn it's not just MS," or multiple sclerosis, said Kathleen Giacomini, a University of California at San Francisco researcher who is identifying genes that affect drug absorption and transport. "It's going to be MS a, b, c and d. We can develop new drugs for each of these types"

Scientists originally developed biochips for research purposes, so to understand the technology story, that's where we start: with Affymetrix, the industry pioneer.

High-Density Pioneers

Making gene chips a research reality required two key innovations. The first was chips made of non–porous solid supports, mostly silicon and glass. A big improvement over nitrocellulose screens, Affymetrix's silicon and glass supports made possible high-density chips, jam-packed with thousands of DNA probes. For researchers, the higher the density, the better: The more DNA probes on a chip, the most potential drug interactions you can test for, in a process called comparative gene expression analysis.

Affymetrix's second big innovation was high–density synthesis of oligonucleotides (aka DNA probes). Affymetrix founder Steve Fodor adapted the same photolithographic techniques used in semiconductor manufacturing to produce gene chips with as many as 400,000 distinct oligonucleotides, each in its own 20 m^2 region—smaller than the width of a human hair. In two years, Fodor boasts he'll be able to burn a chip with the entire human genome on it. I believe him.

Biochip companies whose tech platform comes to dominate doctors' offices and hospital labs will see explosive growth

The worldwide market for gene chips, arrayers, scanners and microfluidics was more than $400 million in 2000. Even by the most conservative projections, the industry will break $1 billion worldwide by 2005, growing an average of about 25 percent per year during the next five years. The market for gene chips alone, divided into high-density chips (greater than 5,000 spots per array), and low-density and customizable chips, is expected to reach about $550 million by 2005 with an annual growth rate of about 20 percent.

Today's undisputed market leader, Affymetrix, has a 60 percent share of the current biochip market. Affymetrix's GeneChip is heavily used in genomic research labs, selling more than 100,000 units annually, at anywhere from $45 to $2,000 each. Current products include an HIV chip that detects drug-resistant HIV strains, a p53 chip for detecting mutations that predispose people to cancer, and a cytochrome P450 chip for identifying which people's livers will have difficulty metabolizing common drugs.

But for a gene-chip play, Affymetrix's biochip technology platform has limitations. In the research end of the gene chip market, Affymetrix will likely remain the industry giant. Many patients' lives will be saved as a result of products Affymetrix's high-density biochip made possible. But from an investment standpoint, this is the wrong end of the industry in which to be. The really big profits lie elsewhere.

As always, the big winners in the biochip market will be companies whose products suit the clinical, with its larger market and higher margins, rather than the research market. Biochip companies whose technology platform comes to dominate doctors' offices and hospital labs will see explosive growth.

For the clinical market, Affymetrix's techno-forte, density, just isn't important. Does a patient have a particular

disease? To find the answer, doctors using gene chips will need to look only among a small, defined universe of DNA disease markers—rarely more than 100. For diagnostic purposes, speed and accuracy are far more important than density. One hundred probes per chip, or less, will usually do.

Low-Density Platforms

Think the way a doctor thinks, about say, sepsis (or infection of the blood), a condition which affects approximately 350,000 Americans each year. To treat sepsis efficiently in these days of antibiotic resistance, it is not enough for docs to know *that* a patient has a bacterial infection; we need to find exactly *what* bug bit him. Right now, doctors wait days or weeks for blood cultures to grow visible under a microscope. Cultures are not only slow, they are notoriously imprecise. Sometimes doctors are forced into shotgun treatments. Worse, sometimes we treat for the wrong infection. Sometimes, patients die.

One man I knew died of an overwhelming infection in his knee. It wasn't entirely his doc's fault. The patient had a history of gout, a disease which causes painful joint swelling easily confused with infection. Just another gout attack, the doctor figured, and missed the deadly bacteria lurking within.

Diagnostic gene-chip technologies are about to transform that arduous hit-or-miss process. Each year, for example, thousands of newborn babies with temperatures higher than 100.4 degrees are hospitalized to "rule out neonatal sepsis." Most feverish babies have colds, and would be better off at home with Mom and Dad. But because newborns are fragile and the stakes are so high; babies are given three days of intravenous antibiotics while doctors wait for blood cultures.

More than half the time, the cultures come back negative. Three unnecessary days in the hospital worrying about a newborn baby is an expensive ordeal for families caused entirely by slow and crude diagnostic technology. But the tests are also notoriously inaccurate. Babies mistakenly discharged sometimes return with dangerous infections. Under certain conditions, as many as 60 percent of culture results may be false negatives. Even in the best cases, where babies just have colds, the entire ordeal costs $10,000 to $16,000, according to one recent study in the *Journal of Infectious Diseases*. DNA chips pre-programmed with probes for all the likely sepsis-causing bacteria, by contrast, will soon pinpoint sepsis instantly and accurately.

Or consider a doctor trying to figure out which strain of a sexually-transmitted disease his patient has. Right now, doctors essentially pause to culture the bacteria and then see if antibiotics slam them, a method both crude and time-consuming. Or they use polymerase chain reaction (PCR) testing to fish for nucleic acids associated with drug-resistant strains. But PCR is expensive and slow. With PCR, you take a urethral or cervical swab to look for nucleic acids (DNA) from each one of say ten possible bugs. But you'll need to run a separate PCR reaction for each one of the 10 possibilities, and each test can take as long as 6 to 8 hours and cost $25 to $200 each. PCR works fine when you're looking for one virus, such as Hepatitis C or HIV, but when you're looking for dozens of possibilities, it's expensive, slow, and impractical. As drug resistance climbs, so will the demand for the precision and speed that only diagnostic gene chips offer.

Costs are dropping dramatically. The capital cost for both an arrayer and scanner is now less than $60,000, compared with $250,000 a little more than a year ago. This is still expensive compared with diagnostic platforms typical in doctors' offices, but about the same for machines such as the PCR that are routinely used in clinical labs. Eight years ago, only elite academic centers had pricey PCR machines. As costs came down, private Quest labs around the corner bought one. Look for a similar cost implosion and rapid expansion in diagnostic biochip systems.

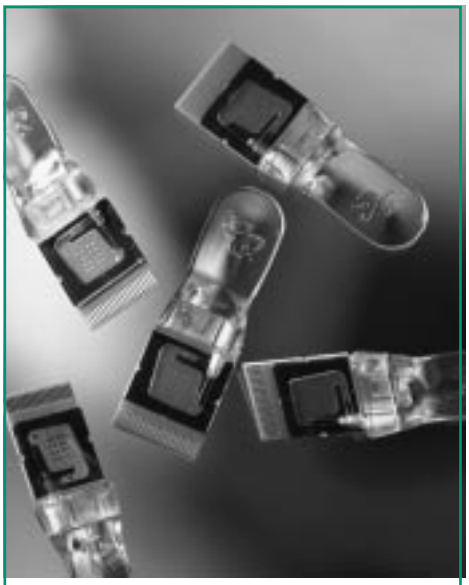
At the current pace of technological development, I expect DNA chips to be inside the doctor's office in ten years or every hospital lab in two to four. Which companies are likely to benefit most from the coming diagnostic biochip boom?

Standardized Platform

Biochip companies recognize the big prize is a flexible, standardized biochip platform, which easily allows third parties to create new hardware and probe chips (much as Microsoft's operating system has been buoyed by the scores of vendors willing to write applications for it). Doctors and lab directors won't want to buy a whole new scanning and analysis system every time a new disease marker is identified, especially given the expected avalanche of such new markers from both academic researchers and IP companies, such as diaDexus, Diversa (DVSA), Gene Logic (GLGC), Celera (CRA), and Incyte. For the clinical market, the best chip platform is not only the fastest and most accurate, but the one that attracts the widest and best collection of diagnostic DNA probes.

Affymetrix, like other chip companies, knows that is where the big money lies. To bring down costs and encourage manufacturers to adopt the Affymetrix model, the company is aggressively partnering with other manufacturers and chip providers to create a common technology platform. But the Affymetrix GeneChip isn't as well suited as some competing systems for the emerging clinical gene-chip market.

For one thing, Affymetrix's chip platform is slower. Affymetrix GeneChips use a passive technique called hybridization to allow separated DNA strands to bind spontaneously with complementary strands embedded in chips. That takes time. Researchers using GeneChips often leave them overnight, just to make sure all the DNA probes have time to bind. For researchers, that is a small price to pay in exchange for the ability to test thousands more possibilities. But if you are a doctor trying to figure out how to treat a newborn with a fever, speed and accuracy are the premium.



The Motorola eSensor DNA Detection biochips contain up to 36 different DNA or RNA probes for genetic and microbial testing.

ESensor: Bioelectronic Circuits

Motorola's (MOT) BioChip Systems Unit believes it has the answer. Its eSensor DNA Detection System uses low-density chips to test up to 36 DNA or RNA targets simultaneously. Its lab-on-a-chip hybridization process is active, not passive, functioning somewhat like a microprocessor. And then there's the input-output interface. Affymetrix's GeneChips use fluorescence to detect DNA hits. But reading DNA hits this way requires expensive scanning equipment, costing $50,000 to $100,000. Motorola's eSensor DNA Detection System takes a different approach to registering hits, reading bioelectricity on a chip just like cells on a memory array.

Motorola obtained the core of this technology when it acquired Pasadena-based Clinical Micro Sensors for $280 million. The system uses organic molecules to form electronic circuits—a process known as bioelectronics—to detect DNA matches. The company deposits up to 36 DNA probes on a printed circuit board, called a biochip, which measures roughly one square inch. Rather than using fluorescence to identify hits, Motorola's system generates current from an organic iron compound bound to a nucleic acid probe. When a target (genetic mutation, unique bacterial or viral sequence) is present, it will bind the complementary probe on the circuit board. The binding of the complementary strand from a sample completes the circuit: when a small voltage is applied by the reader the biochip electrodes with bound target have a complete circuit and generate current. Signal processing technology then identifies and quantifies each DNA match. The biochip can be spotted with any combination of multiple DNA or RNA fragments, thus making it useful for a broad range of genomic diagnoses such as cystic fibrosis, where researchers have identified 26 different genotypes, each affecting what type of treatment patients receive.

While the device contains far fewer probes per chip than the Affymetrix chips, it is cheaper both to manufacture and read, making it well suited to the mass medical market. An entire system capable of simultaneously scanning 48 eSensor DNA Detection System chips cost around 1/10th of what other biochip readers cost while a smaller model capable of processing 12 chips at a time cost well under $10,000. The chips themselves are cheap: anywhere from $20 to $40 each. Why are they so inexpensive? The printed circuit boards used as the basis for the chip are basically the same as ones used in consumer electronic applications, so the quality is high and the cost is low. The readers and the chips don't use fluorescence, a more elaborate process that requires expensive scanning equipment.

If you haven't heard much about the eSensor DNA Detection System, it's because so far, Motorola has been keeping fairly quiet about its biochip products. Two reasons. First, Wall Street's dim view of the unproven biotech sector. Second, the company believes investors want Motorola focused on its troubled cell phone business, where marketing missteps and shrinking profit margins have squandered its once-dominant market position. As a gene-chip play, Motorola's main drawback is that biochips represent only a small part of its operations and generates a tiny sliver of its $40 billion in revenues. But the staggering $500 million Motorola has already spent on biochip R&D is a strong indication of industry faith in the technology's ultimate promise.

In a NanoChip Second

So where else can investors similarly convinced of gene chips' ultimate promise turn? Another company with a biochip platform well-suited to clinical tasks: the San Diego-based Nanogen, Inc. (NGEN). Like Motorola's eSensor DNA Detection System, Nanogen's NanoChip technology also makes use of bioelectricity, but this time also to customize the chip. The NanoChip is fast—about 1,000 times faster than Affymetrix's GeneChip, generating results in just a few minutes compared with hours or days for the latter's passive hybridization process. Like the

eSensor DNA Detection System, Nanogen has ingeniously designed a way to use DNA's natural electrical properties to bring DNA probe and test site together, quickly and efficiently.

How do they do it? DNA naturally has a negative electrical charge. To move the DNA sample directly to a particular test site probe, the NanoChip gives a charge to the DNA probes on the chip, a process called electronic addressing. The negatively charged patient DNA samples leap to the positively charged DNA probe sites, where they are concentrated and bound by a chemical process. Wash off the biochip and another solution of distinct DNA probes may be added, activating different test sites. Site by site, row by row, users can assemble or address a custom array of DNA probes on the microchip in a user-defined order. The process is entirely automated.

Nanogen extends the power of biochips through the use of electronics. Most biological molecules are charged and can be moved and concentrated electronically on the chip's surface.

NanoChips are also highly accurate, more accurate than Affymetrix systems in studies I've reviewed. Affymetrix's passive hybridization system increases the possibility that, in rare instances, a patient's DNA sample will not fully saturate the chip, creating a false negative. Affymetrix's GeneChips also allow some samples of DNA to bind to probes that aren't really complementary, giving false positives. In published studies, Nanogen's active hybridization results in a remarkable 100 percent accuracy rate. Faster diagnosis with 100 percent accuracy—for clinical applications, that is a techno-edge hard to beat.

The base price of Nanogen's blank chip is $500, although a fully-loaded chip costs more. Nanogen's biochip platform allows the company to pursue two different strategies for the clinical market: it can offer both pre-loaded chips, containing all the probes relevant to a particular clinical question (such as a single NanoChip for neonatal sepsis, for example). But Nanogen also markets a blank chip that's capable of being customized with the specific probes of the lab or doctor's choice. (One downside of the latter approach: it may be harder to persuade the Food and Drug Administration the system is easily standardized by laboratory technicians and isn't prone to contamination).

An even more basic design advantage: Nanogen's chip platform looks at DNA while most rival systems are based on RNA analysis. (Motorola's chip can look at DNA or RNA). Analyzing DNA directly instead of examining RNA copies has natural advantages that will likely propel Nanogen's NanoChip further ahead of rivals like Affymetrix. With one prominent exception (the HER2/NEU gene, which indicates a susceptibility to certain forms of aggressive breast cancer), there are no existing examples of using RNA as a diagnostic tool. RNA analysis provides a relatively static picture of any particular collection of genes, and researchers agree this can miss mutations responsible for many diseases. Going straight to the DNA code provides a more reliable way to search for genetic mutations.

The value-added in gene chips is both coming up with the most intellectual property (DNA probes) as well as the best chip platform to analyze them. Nanogen sees itself playing in both fields. For example, the company currently holds rights to a chip that identifies whether patients suffer from hemochomatosis, an inborn error of iron metabolism that can lead to liver failure, diabetes, and even death. Nanogen is getting ready to roll out five specific molecular-based tests designed for medium-sized diagnostic testing centers like Quest, with many more in the pipeline. Among the most exciting new probes in development? Nanogen's CEO Randy White told me about a protein excreted in urine that has 1,000 different isoforms. Preliminary studies show different patterns are reliably associated with different forms of cancer. In the future, doctors may skip the knife and accurately diagnose many cancers using just a simple urine test.

The entire Nanogen platform, including chip loader and chip reader (array processor and scanner)

Nanogen is aggressively marketing its system for research and diagnostic applications, seeking a large base of installed machines, even as it develops the next generations of chip systems. Nanogen has adopted a reagent-rental strategy, selling its machines for a loss but earning a premium on the sale of reagents used to run the tests. This September, the company released a round of data demonstrating the effectiveness of its first clinical diagnostic, a test for the genetic mutations that decrease the level of Factor V Leiden, increasing the risk of heart attack, strokes, and certain pulmonary emboli blood clots. Nanogen is pursuing FDA approval for the test.

Beats Biological Warfare

Nanogen also has a number of collaborations worth knowing about. The NanoChip is ideally suited for military applications, especially battlefield tests for biological warfare, towards which new defense dollars are likely to flow big-time. Nanogen recently entered into an agreement with the U.S. Army Medical Research Institute of Infectious Disease (the lead medical lab for the U.S. Army Biological Defense Research Program) to develop a biochip system for rapid identification of infectious disease agents. The company received an initial payment of $1.1 million for a system portable enough for battlefield deployment, expected to be ready in as little as two years. In 1998, Nanogen received a five-year contract for up to $7.6 million from the Space and Naval Warfare Systems Center in San Diego for the Defense Research Projects Agency, also for the creation of a miniaturized laboratory for biological warfare defense.

In December 1997, Nanogen entered into an exclusive R&D collaboration with Aventis for research and immunodiagnostic tools. Last July, that agreement was updated to include the formation of a new joint venture, Nanogen Recognomics GmbH, based in Frankfurt (60 percent owned by Nanogen), for the joint development of new diagnostic tests. In 1997, Nanogen also entered into collaboration with Becton Dickson to develop commercial tests for infectious diseases, retaining distribution rights to the infectious disease market. Nanogen also has collaboration with Hitachi for the manufacture of the platform, but retains rights to the entire platform and the chips sold outside Japan. This year Nanogen will place about 80 NanoChip systems in academic hospitals and research labs, and the company expects to place an additional 160 next year.

Nanogen's ultimate goal is to develop the FDA-approved clinical diagnostics market, which represents a $20 billion slice of the life sciences industry. How big is the potential market?

Take the market for sepsis. There are 1 million serious bacterial infections diagnosed each year, 350,000 cases of sepsis, and about 300,000 cases where infections spread to organs. At a test price point of $400, the potential market revenue for this case pool of patients alone is well more than $400 million. Similarly the national incidence of neonatal sepsis is more than one in 1,000 live births for full-term infants (and tenfold higher for premature infants). Mortality can be as high as 25 percent. Compared to 3 days of hospitalization, a NanoChip system is cheap. Expect a product with this great a techno-edge to rapidly spread among cost-conscious hospitals and insurers.

Nanogen's current revenues are about $20 million. In a time of rapid technological development, market cap is hard to estimate. But here is a conservative estimate: DNA diagnostics (including PCRs) currently account for about $500 million of that $20 billion market. The current market for microbiology tests (blood cultures, etc.) is about $1.3 billion alone growing at 5 percent a year. If Nanogen captures one-fifth of that combined market, that would bring it more than $1 billion in sales.

How will diagnostic gene chips penetrate the clinical market? They'll follow the natural evolution of other clinical tests. "I remember a point in time in the late 1970s when a thyroid test T4 was only run in 15 or 20 labs in the United States. Now that test is run in every hospital," White told me. He should know, having built American Medical Laboratories into one of the largest clinical reference labs in the country. First, a diagnostic test will be adopted by the large, regional medical centers, just like the early days of PCR testing for HIV. Then it will become adopted by every hospital, and finally every Quest diagnostic lab around the corner.

Biochip technology is advancing so rapidly, it's going to quickly leave behind companies like Affymetrix, now an industry giant, but whose platforms don't easily provide innovative solutions to common medical problems. While there will remain a place for Affymetrix's biochips in research niche, the biggest margins are always found in the clinical application of key medical technology.

Platforms by Motorola and Nanogen meet all the specifications that doctors will need to bring genomics into their daily medical practice. That's why we're adding Nanogen's name to our list, and will be keeping a close watch on Motorola.

The molecular revolution in medicine is just beginning. But not long from now, gene chips will touch the lives of every American. When it starts to happen, it will happen quickly, for a few pioneering companies that believe in it, and millions of patients who are its beneficiaries.

Dr. Scott Gottlieb
October 1, 2001

MEMO FROM DR. SCOTT GOTTLIEB

Is Now a Good Time to Invest?

For many biotech investors, staying optimistic feels hard. Major biotech indexes are down about 30 percent this year alone, and the sell-off has prompted pundits to call the industry a lot of names: exuberant, risky, over-inflated, a bursting bubble and, since early last year, a bear. One thing it's not called is a bargain. Let me be the first.

Biotech has fallen dramatically in the months running up to September 11, and now some of the best biotech stocks are dirt-cheap. After the attacks on New York and Washington, biotech stocks sold off across the board, as investors cycled money into perceived safer havens, such as pharmaceuticals. But September 11th does little to change even the short-term outlook in biotech, and increased government defense spending may even boost companies, as America seek new ways to fight bioterrorism on the battlefield and here at home.

So this initial pullback won't last long. Back in my Wall Street days, we used to say that the rest of the market climbed on a wall of fear, biotech rose on pure enthusiasm. High-profile product approvals, positive results from clinical trials, and lucrative deals between biotech and big pharma lift all boats.

The fall calendar is usually chock full of market-moving biotech conferences announcing market-driving results of clinical trials. Most of these were pushed back as a result of concerns over airline travel. Most of these events are being rescheduled for the winter, so you can expect the same bounce, only this year; a little later.

But rest assured. Biotech, once driven by pure enthusiasm, is now being driven inexorably by new technological innovations. Expect high-profile announcements from successful clinical trials or drug approvals (such as recent FDA approvals of IDEC Pharmaceutical's (IDPH) cancer drug Zevalin for non-Hodgkin's lymphoma, and Amgen's (AMGN) long-acting drug for anemia, Aranesp), to grab investors' attention.

The biggest news of recent weeks is the $2 billion deal between Bristol-Myers Squibb (BMY) and biotechnology company ImClone (IMCL). Bristol-Myers will spend $1 billion to acquire 20 percent of ImClone's common shares through a tender offer that values the company's shareholders at a 40 percent premium to its previous close. The drug giant will also pay $1 billion to ImClone in three separate milestone payments tied to the development and approval of the company's cancer drug, known as IMC-C225. ImClone works with so-called signal transduction, a fancy name for manipulating messaging between cells. We'll be taking up signal transduction in the November *Gilder Biotech Report*.

Of course, a rebound requires discrimination. When the market returns, valuations will briefly rise across the board, but in the longer run, the big winners will be not just any biotech company, but companies whose technology platforms confer crucial advantages that will lead them to outperform their rivals.

The first wave of biotech companies such as Amgen and Genentech (DNA) and Chiron (CHIR) were market winners because they had unusually low risk profiles. They sold individual products like recombinant insulin, where the non-recombinant form was already on the market. They didn't face a drug-discovery risk as much as a manufacturing risk, enabling them to raise large sums of money from Wall Street. The money was used to pay for single-product bets, and, by and large, those bets paid off.

Wall Street assumed the same thing would happen in round two, becoming focused on particular novel drugs. But for investors this is a poor paradigm: the more exotic and specialized the research and development programs became, the less investors knew with any degree of certainty about its true value. That's one reason genomics companies plummeted after the initial excitement over decoding of the human genome. In the absence of any consensus about valuation, the safest bet is the lowest one.

To profit from the coming bioboom, investors now need to understand not just a company's product but the underlying technology. Superior platforms will convey huge competitive advantages on certain companies, leaving others (including some of today's market leaders) far behind. The big profits are now not in developing any one particular product, but in a technology-driven process of streamlining and rationalizing product development that will guarantee some companies a full pipeline of future medical innovations, and leave conventional companies holding an empty test tube. Our goal is to find the companies with these core technological advantages.

When the dust from the downturn settles, the next round of medical miracles, and the companies that profit from them, will be the fruit of this ongoing radical transformation of medicine from an art to an information science. Stay tuned.

- SG