GILDER
BIOTECH
REPORT

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Medicine Meets Microchip: The Biodigital Revolution

Speeding cure, slashing costs, the long-hyped biotech revolution is finally here and the business of medicine will never be the same.

Late one evening, David walked into the emergency room, hiccuping. "I want Thorazine," he told me. Being a doctor, David knew what most people do not: Thorazine is not just an excellent anti-psychotic, it also stops hiccups cold by blocking the nerve impulses that trigger them.

But why did David have the hiccups? Doctors are trained to fear the worst. Was something irritating his phrenic nerve, the long thin connection between the brain and the lungs that carries the signals instructing the body how to breathe?

Five years ago, David had had malignant melanoma, aka skin cancer, and was now allegedly cured. But malignant melanoma is a particularly aggressive cancer, rapidly invading distant organs. The hiccups could mean nothing. Or a tumor could have traveled to his chest, where it was now sitting on his phrenic nerve triggering continuous hiccups, a common way for chest cancer to present.

Suspicions heightened, I ordered a chest X-ray.

The radiologist stared at me incredulously. "You're worried a doctor might have a tumor in his chest and all you ordered was an X-ray? If it was me, I'd want a CAT scan."

A CAT scan would pick up even tiny tumors, but at $700 a pop, they are rarely used for routine cancer screening. Even with a past history of cancer, managed care often declines. But as a doctor, David was afforded professional courtesy. I ordered the test. The hospital quietly agreed to pay.

David was slowly lowered into the tube-like scanner, still hiccuping. Then, together, we waited for the radiologist to interpret the results. . .

Breaking Medical Boundaries

This is the art of medicine as it has been practiced with increasing skill—and at increasing cost—for the last century or so, a material medicine dominated by bumps, bruises, or other symptoms felt by the patient, or ferreted out by the physician with eyes ever-magnified by increasingly sophisticated scanning technology: the X-ray, the microscope, the CAT scan. But however powerful the machine, the underlying model remained the same: to find the illness, you look for the symptom. To diagnose the cancer, you have to see the tumor.

In conventional medicine, diagnosis remains an art, mostly the art of neglecting more remote dangers in favor of likelier ones. You save more patients that way. Would you test for a disease if the odds are a

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hundred to one against it? Probably. Now what about a thousand to one? Maybe. What about a ten thousand- or a million-to-one chance? If the test is expensive or has risks, the answer is almost certainly: no. And of course for most common symptoms there is not just one remote lethal possibility, but dozens. Dizziness, for example, could be nothing but a head cold, or low thyroid. Or a brain tumor. Bad news if you are that one patient with a deadly disease that might have been treated if it were less costly or invasive to diagnose.

Now medicine is being hurled up the learning curve...

All that is about to change. Medicine is breaking through the boundaries of the visible, material world, and neither the practice nor the business of medicine and medical research will be the same. In the near future, new diagnostic tools will rely not on spying crude symptom formation but detecting the underlying molecular processes that trigger disease weeks, months, or years before the patient feels a twinge. Cheap as spitting into a paper cup, new gene-based tests will diagnose tumors and other diseases with greater accuracy than the most sophisticated body scanner, at a fraction of the cost. As diagnosis moves beyond the visible sphere, the extensive testing now reserved as a tribal courtesy for fellow docs will help save the lives of all patients.

Not only diagnosis, but medical treatment, business models, drug discovery, and delivery will be revolutionized. As medicine meets the microchip, new drugs will no longer be scattershot one-size-fits-all affairs, but carefully targeted to a patient's unique DNA profile. In a breathtaking paradigm shift, medicine moves from the species level—the ingrained assumption that drugs and diseases work the same in all human beings—to the individual level, unlocking new healing possibilities in minute differences between my body and yours.

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The same digital tools will radically streamline the discovery of new drugs, at least for those drug companies that understand the new paradigm and move quickly to grasp its opportunities. Biodigital medicine will finally deliver on the failed promise of HMOs—better, cheaper medical care through prevention—fueled not by penny-pinching, care-denying bureaucratic rules, but by miracles of market innovation.

Ten Seconds to Take-Off

Ten years ago, five years ago, two years ago, the biotech revolution was still more science fiction than fact. It is Moore's law, the doubling of computer power from an already impressive base, that is transforming the once-far-fetched promise of the human genome into a medical, entrepreneurial and commercial reality.

Why? To crack the digital DNA code requires more than mere mapping its sequences. It requires understanding how each twist and turn in our genetic strands interacts with molecular processes to produce health or illness. We stand at a unique moment in history; medicine is being hurled up the learning curve, as the awesome geometric advances in analytic power ruled by the Moore's and Metcalfe's laws unite with the accelerating information about the human genome. The next avalanche 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.

Who will the winners and losers of this tectonic shift in medicine and medical research be? What matters most for future company value is not current products, but process. Companies that understand and capitalize on this new fusion of medicine and IT will have a powerful edge over companies wedded to the old ways. In the race for new leaders of the emerging, vastly expanded, more efficient, and revolutionized medical industry, slow and steady will lose every time. When paradigms shift, not just new leaders but new industries emerge. Drug companies that proceed with business as usual, are in for a rude shock.

From Symptom to Cure

The history of medical progress has been the history of moving from surface to cause, from symptoms to underlying processes. Hippocrates and his fellow physicians probably killed as many patients as they saved with "cures" that ranged from leeches to arsenic. Then, with the Renaissance came anatomy; anatomy begat physiology and medicine for the first time moved towards science. In the 19th Century, germ theory marked the next great leap from surface symptom to underlying process. A whole class of deadly diseases—typhus, whooping cough, measles, malaria—could be cured or prevented, because for the first time we understood their cause.

Understanding the body's internal disease process took longer. Early in the twentieth century, biologists gained some understanding into what genes actually do: they make proteins. Proteins consist of strings of different amino acids. Scientists in labs can construct an almost infinite variety, but nature it turns out, makes just 20 kinds. All the millions of different proteins on Earth are compounded from that basic amino acid set, just as all 415,000 words in the *Oxford English Dictionary* are compounded from 26 letters.

The task of genes is to make sure that amino acids line up in the right order to produce the right protein. In biology the right protein is everything. Cell membranes consist of proteins and fats. Fingernails, hair, and muscles are proteins. Proteins function as hormones, antibodies, or enzymes. Proteins, in short, run the show. They form the structure, they direct the metabolism, they carry messages, and they form defensive forces.

In 1953, with the discovery of deoxyribonucleic acid or DNA, the tools needed to investigate how proteins cause and cure disease were finally at hand. But research was characterized by a doomed reductionism: for years the big picture of how different genes interacted with different proteins to produce different symptoms was ignored, largely because scientists lacked the processing power to generate and analyze the huge volumes of information necessary. The merger of medicine and microchip is in one sense only natural. DNA can be thought of as a three-billion-year-old Fortran code easily transduced into bits of data, captured on databases, and analyzed with sophisticated software. But until recently, the body's digital code was just too complex to crack.

The true potential of emerging genetic knowledge remained locked in complexity, awaiting the development of a sufficiently advanced information technology. The key is abundant processing power to generate and manage huge data sets linking gene sequences to body functions and dysfunctions. In the simplest cases, such as sickle-cell anemia, diseases can be linked to a single gene. But most important diseases are determined by multiple gene markers at many different locations. To find the culprits requires large sample sets and powerful software algorithms that can hunt down genetic patterns among millions of data points, tracking associations with disease.

George Weinstock, co-director of the human genome center at Baylor College of Medicine, calls this new computer-assisted ability to crack the DNA code at least as big as the microscope. "Before the microscope they never realized the structure of cells and the presence of disease-causing microbes in water," Weinstock says. "The gene sequence will likewise have an impact over a number of centuries."

From Art to Information Science

Our growing mastery of genetics has finally met up with an information technology sufficiently advanced to exploit it for commercial, medical purposes. The winners will be not only companies that create new miracle cures, but an emerging medical IT industry to service them—invent drug algorithms, streamline computational chemistry software, and assemble more effective genomic databases. The $687 million market for genomic tools used for drug discovery will more than double to $1.4 billion by 2005. The genomic software used to analyze this information, a $500 million market last year, will more than triple in five years.

Conventional test-tube companies are grappling to adjust to *in silico* technique. But many smaller, nimbler biotechnology companies are already masters. BioCryst Pharmaceuticals Inc (BCRX), Tripos (TRPS), 3-Dimensional Pharmaceuticals Inc (DDDP), Gilead (GILD), Vertex (VRTX), and Agouron Pharmaceuticals, a subsidiary of Pfizer (PFE), are just a few of the publicly traded companies following the technology. Several big drug companies including Abbot Laboratories, (ABT), GlaxoSmithKline (GSK), Merck (MRK), and Roche (RHHBY), also have launched small biodigital drug design programs, though usually far from core operations. There are also a host of privately held companies exploiting in silico techniques, among them: Astex Technology, De Novo Pharmaceuticals, Locus Discovery, and Structural Bioinformatics.

The problem isn't information overload, it is infrastructure underdevelopment

The ultimate goal is to integrate digital tools into one seamless platform that can take drugs through discovery to design to testing, one seamless digital system for biodiscovery that minimizes slow and costly wet-lab experiments.

The concept isn't brand new. In fact, under the name structure-based or rational drug design, biodigital techniques were first applied two decades ago by Bristol-Myers Squibb (BMY) to design the popular blood-pressure medication Capoten. But back then, computers were too slow to learn combinatorial chemistry very well. The molecules they designed didn't act like drugs, so big drug companies flipped back to beakers. They never returned, despite recent leaps in processing power that have made biodigital research immensely superior.

Today, conventional drug companies complain about a "target rich but lead poor post-genomic era" with millions of new gene sites at which to aim drugs, but no idea what these DNA sequences actually do. In reality, the problem isn't information overload, it is infrastructure underdevelopment. Swamped with new targets, conventional pharma-

ceutical companies haven't re-tooled to take advantage of the new information technology that allows digital experiments. So, in the words of Physiome Sciences CEO Jeremy Levin, PhD, they pan for drugs from the genome instead of, like new paradigm companies, diving straight for the motherlode.

"Big pharma has some outdated ideas about what's very important," John Thomson, a researcher at Vertex, told me. "Why wander from what's worked in the past? Well you wander from what's worked in the past because if you don't, you'll be overtaken by the new guys one day."

The transformation of medicine, medical research, and drug discovery into a digital science will revolutionize the science and business of medicine, slashing costs, increasing efficiency and generating new medical miracles. New biodigital tools and software advances bring drug discovery out of the physical sphere of the test tube and onto an electronic platform where the scientists can harness the speed of Metcalfe's and Moore's laws, replacing the slow, expensive, and essentially random wet-lab world of beakers with one animated by digital intelligence.

Today's roughly $300 billion per year drug industry is entirely based on drugs targeting no more than 500 different proteins. All the drugs discovered by man in all of human history are in this small class. Yet in just the next three years, thanks to biodigital medical advances, the number will suddenly leap twentyfold, to upwards of 10,000 new protein targets ripe for drug development.

Which companies will turn the human genome into hugely profitable new drugs? Past performance or present product pipeline are no guarantee of future returns. Instead, it is companies that shift most quickly to fully exploit the technologies that will be rewarded with a stream of new miracle medical products developed at a fraction of current costs.

Vertex: The End of Random Drug Design

I recently visited one of the new guys, Vertex Pharmaceuticals (VRTX), poised to tap the motherlode of miracle cures unleashed by biodigital medicine.

How do conventional pharmaceutical companies find new drug leads? Blind luck, mostly. Most drugs work by binding to proteins and altering their function in some small way. So the first step en route to new miracle cures is finding a molecule that binds to a protein. In the old wet-lab model, that means mixing millions of different chemicals and hoping one of them sticks.

Pharmaceutical companies sink billions into IT upgrades that make this antiquated model work a little better, with automated systems that help PhDs synthesize and survey thousands of chemical compounds a week, hoping to stumble upon a few hits. Still many of these sticky compounds fail the minute they leave the test tube. Another day, another drug dollar—or billion—wasted on leads that don't pan out.

Vertex has a different model. Companies like Vertex that specialize in "rational drug design" deploy information technology intelligently to design drug-like qualities right into the molecules from the very start.

Stroll down the hallways of their research facility. Sitting atop every lab station is a computer workstation where biologist and chemist tap into shared information about everything from the digital structures of candidate compounds, to exhaustive algorithms that predict whether a new drug is likely to be excreted through the liver or the kidney. Scientists shuttle between their test tubes and their computers, huddling regularly over computerized models like architects examining blueprints to a new skyscraper—scrutinizing every twist and layer to construct the perfect molecule.

Instead of mixing compounds in test tubes at random, Vertex starts the drug search process by teaching its computers what the molecular structure of an effective drug ought to look like, and what molecular structures it ought to avoid. What do drugs that end up being poorly metabolized or unable to cross the blood brain barrier look like? Or those that end up damaging the liver? For example, certain molecular structures, promising in the test-tube, bind to sites in the liver's p-450 system, where enzymes break them down, leading to poor absorption in the body. Another drug bites the dust.

Vertex's computers intelligently construct medicines atom by atom, fitting drugs like finely cut jewels onto settings made of protein. Their system expands on the single-structure approach by maintaining a massively parallel drug design platform based on genomics, structural biology, and in silico structure-based drug design. They don't rely on one technology, old or new. Instead they employ a battery of different biodigital tools to create one seamless operation that can feed back data from both wet labs and biodigital tools into the drug development process.

Vertex has multiple core competencies, outshining its rivals especially in computational tools and, with its recent acquisition of Aurora (ABSC), cellular assays. For example, Vertex has some of the industry's best structure-based design software, and proprietary systems for actively sharing data across multiple research platforms. So information from a big, wet-lab screen of a potential drug can be fed back into the silico system to teach the software how to modify the drug to make it more potent. The system plugs each tool into one seamless wheel, turned by a new scientific culture merging chemistry and computing.

One of those new tools is a machine called nuclear magnetic resonance (NMR). Much like the traditional magnetic resonance imaging machine (MRI) radiologists use, this tool evaluates in real time how tightly the tiny chemicals

Vertex Clinical Milestones for 2001-2002

- Initiation of Phase II trial for VX-497 with pegylated interferon for hepatitis C
- Results from Phase II trial for VX-740 in the treatment of rheumatoid arthritis
- Results from Phase II trial for VX-745 in the treatment of rheumatoid arthritis
- Results from Phase II trial for Timcodar in the treatment of peripheral neuropathy
- Completion of Phase I trials for VX-148, the second generationIMPDH inhibitor
- Initiation of Phase II trials for VX-148 in the treatment of autoimmune diseases
- Completion of Phase III trials and filing for approval of VX-175 in the treatment of HIV
- Naming of more than 5 new preclinical candidates to the product pipeline
- Expansion of chemogenomic approach to drug discovery to another gene family

that Vertex's researchers come up with are binding to their protein targets. One of Vertex's NMR methods is a fragment-based approach known as "shapes"—a word that stands for nothing. It's a joke on the tortured acronyms that are often used to describe these methods.

NMR is especially good for detecting weak interactions, particularly between small molecules and macromolecules like proteins. Why are weak interactions valuable? Conventional drug companies are seduced by potency. But most big potent molecules end up useless because they are poorly absorbed in human stomachs. Weak binders are usually smaller and therefore better absorbed, but they're much more difficult to detect with traditional wet lab techniques. Vertex's computers are trained not only to find them, but to modify them to improve their drug-like characteristics.

Success requires more than the right machines. New research groups must be assembled in radically new laboratory environments. Conventional chemists trained in wet-lab techniques do not find it easy to become computational chemists, designing drugs on computers using weird stick-and-ball models projected on screens in three dimensions.

The first step in the development of Vertex's AIDS drug Agenerase, for example, was to use a process called x-ray crystallography to get a three-dimensional picture of a key enzyme (called a protease) that the HIV virus uses to reproduce. In this process, scientists crystallize the virus particle and then aim radiation at it. Computers capture the radiation as it bounces off the crystal, and reconstruct the diffracted signals into a three-dimensional picture of the enzyme.

On computer screens, the protease looks like a mass of sticks and balls. Vertex's computers home in on about 10 different regions on the enzyme on which different drugs could be hooked. Computers screen different drugs against this site, digitally docking them with the protease to see what fits. One early version of the drug Agenerase seemed to fit its pocket well, but part of the molecule hung out of the edge, meaning the drug was easily dislodged. So Vertex scientists snipped off three carbon atoms, which gave it a smaller profile and thus a snugger fit. Sales of Agenerase alone are expected to top $90 million this year.

And that is just the beginning. Vertex now trades as a technology platform company, but its future wealth will be generated from the abundant flow of new products generated by its in-silico drug discovery engine. The company already has eight products in clinical development. Over the next year, Vertex will introduce at least five new drug candidates into pre-clinical testing.

And the competitive advantage of companies like Vertex will only increase. In the wet lab, a single new drug costs about $300 to $500 million and 10 to 15 years to design, test, and manufacture. In-silico technologies can cut drug development costs by half and shave five to ten years off the development cycle. Conventional companies when they discover one drug, must go back to pan the human genome at random for the next one. But with each new drug, Vertex expands its rapidly accelerating knowledge base, fueling the next round of intelligently designed drugs.

Conventional drug companies try to target proteins without really understanding their function. By restricting its search to structures that are already known to be pharmaceutically relevant, Vertex fishes in a smaller but more densely populated pond—giving itself a vastly better chance of reeling in something good with each cast.

Vertex Pipeline and Products

Infectious Disease	Agenerase® VX-175 VX-497	HIV HIV HCV	Market Phase III Phase II	GSK/Kissei GSK
Cancer	Incel™ VX-853	MDR MDR	Phase II Phase I/II	
Inflammatory and Autoimmune Disease	VX-148 VX-944 VX-745 VX-850 & VX-702 pralnacasan (VX-740) VX-765	Autoimmune, antiviral Autoimmune, antiviral Rheum, arthritis (RA) Inflammation, cardio RA, OA, cardio Inflammation, cardio	Phase I Preclinical Phase II Preclinical Phase II Preclinical	Kissei Kissei Aventis
Neurological Disease	timcodar	Diabetic neuropathy	Phase II	Schering AG

Gene Chips: Tools of the Transformation

As Esther Dyson famously observed, scientific advances oft await the development of appropriate tools. So biodigital medicine is the child of yet another chip revolution in the making. Only these chips don't crunch data like their forbearers, the integrated circuit. They read genes, scanning a person's DNA for naturally occurring markers that could indicate proclivities for diseases such as cancer.

When David was first diagnosed with melanoma six years ago, the sickest patients had few attractive options: surgery, followed by radiation to shrink big tumors, and chemotherapy for cancer that had already spread.

Then last summer, in one of the first practical fruits of the human genome project, researchers working at the National Human Genome Research Institute and the National Institutes of Health discovered a genetic "signature" that showed how malignant melanoma invades distant parts of the body. The result? A new test that predicts whether or not a patient's skin cancer will metastasize.

Out of the millions of possible gene sequences, how did they locate the ones triggering malignant melanoma? Gene chips—a silicon chip with thousands of genes embedded on its surface—were able to digitize information about a half million genes from 40 different tumor samples, searching for hidden patterns that might reveal how melanoma is triggered by surreptitious changes in DNA.

Exploiting the human genome requires such data processing on a massive scale. To find these individual genetic differences, known as polymorphisms, scientists scan databases, looking at a lot of strands of DNA to find genetic markers strung along chromosomes like mileposts along a highway. Called single nucleotide polymorphisms or "snips," these are the sites that vary most commonly between different people, accounting for about 80 percent of known mutations. The human genome contains an estimated 10 million of them and about 300,000 are thought to contain the genetic variations that determine everything from hair color to heart disease. Snips are particularly easy to study because they can be quickly read with newly developed gene chip technology.

Nineteen melanoma tumors were found to be very similar, differing from other tumors in the expression of roughly 500 genes. When these 19 were lined up against patient histories, their tumors tended to be the least aggressive of the bunch, explaining why some patients' melanoma spreads to distant locations, while others' remain largely indolent. The next step is to look for genetic tags that can be detected in a simple blood or saliva test. Today, doctors are just beginning the exciting task of turning the knowledge they are acquiring into this kind of practical use.

Alternatively called biochips, DNA microarrays, gene chips are also starting to be used to lock down early diagnosis. The chips take minutes, or at most hours, to search out disease-causing mutations from the full length of a patient's DNA. They go right to the target, scouring DNA for regions that predict cancer, allowing doctors to detect microscopic changes long before illness is obvious. Soon doctors will detect early lung cancer from say, saliva, using chips to scan for genetic changes in lung cells naturally sloughed off into the viscous fluid. Biochip companies such as Affymetrix (AFFX) and Illumina (ILMN) say an affordable desktop system could be deployed in clinics and physician offices as early as 2004. The market for gene chips, estimated at more than $397 million in 2000, will likely quadruple to over $1.5 billion in just five years.

"We're going to burn a set of chips with the whole humane genome," said Stephen P.A. Fodor, president and chief executive of Affymetrix. Fodor headed a group of Stanford engineers that pioneered the field of biochips, with a 1991 paper in *Science* describing how photolithography, the standard process by which semiconductors companies etch circuits in silicon, could also be used to synthesize biological materials on a chip.

In a random drug-design universe, scientists target a mere manageable handful of genes they only guess are likely candidates, wasting years exploring narrow bands of irrelevant DNA. Gene chips quickly scan the entire strand of DNA and let cancer cells tell us what the important genes are.

The chips look like ordinary microprocessors, but instead of tiny transistors embedded on their surfaces, the thin wafers of glass or plastic are peppered with strips of DNA. These tiny strands snag and flag telltale information as it is washed across the chips. Some chips use electricity to force genetic material to bind to their surfaces, but mostly they exploit the unique properties of the double-stranded DNA, which quickly reunites with its partner once the molecule is separated into two complementary strands.

With a single drop of blood, gene chips can screen patients' DNA for thousands of disease-causing genes in a single pass. After the sample is washed across the chip, the DNA is allowed to passively bind to matching probes on the chip, a process called hybridization. Doctors use computers to read chips for genes bound to their surfaces, indicating they were active in the original sample. As researchers collect more information about the genetic fingerprints of various diseases, they're able to craft customized chips that diagnose patients with previously unheard-of accuracy. In the near future, doctors will be able to scan a single drop of a patient's blood for all the DNA strands that predict, say, a heart attack, colon cancer, or diabetes.

Beyond One-Drug-Fits-All

Gone are the days of one-size-fits-all diagnostics, the medical equivalent of producing cars in any color the customer wants so long as it's black. Instead these tools will allow sophisticated genetic analysis to be performed at the individual level, making possible early prediction or moni-

toring of disease, increasing diagnostic precision, and powering the development of customized therapy.

This highly individualized knowledge is the second great paradigm shift in medicine: from species to individual. Medicine has been based on the largely unexamined assumption that disease process and treatment is species-specific. Vets treat animals. Doctors treat humans, all of whom have the same basic biological processes. What cures disease in one human being will cure all other human beings. But in reality, human bodies differ, and so do individual responses to drugs and other treatments.

For example, researchers recently discovered that one likely reason African-Americans die more often from heart attacks is that ACE Inhibitors, one of the drugs given to heart attack patients, is much less effective in people of African than European ancestry. Biodigital medicine gives us the tools to collect and analyze such ethnic, family, and individual genetic variations. "Medicine never really focused on our differences," explains Huntington Willard, president-elect of the American Society of Human Genetics. "Our hearts are all different and the differences have implications for function and performance. Sequence knowledge will change doctors' perspective to providing care for the individual."

"By learning about what makes each patient's tumor grow, what makes it spread or not spread, hopefully you could tailor therapies to the individual patient rather than use a one-size-fits-all kind of approach," said Dr. Paul Meltzer, a senior investigator at the National Humane Genome Research Institute. Researchers at the Cambridge-based Millennium Pharmaceuticals (MLNM), developed a test called Melastatin which detects a protein that accurately predicts whether a melanoma will recur. The next step is to come up with a drug that turns on the proteins that turn on Melastatin, blocking skin cancer from metastasizing. It's not that the patient with the Melastatin gene would lose it. The gene would still be there, but the drug blocks the body from turning on the disease process.

Another key biodigital strategy focuses on using receptors on the surface of the cancer cells as targets for monoclonal antibodies.

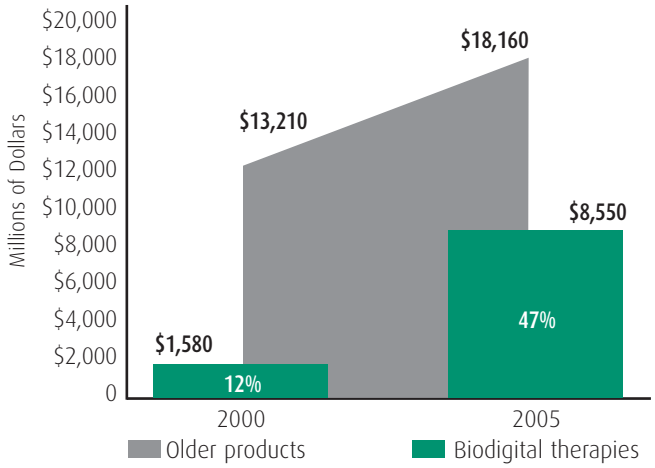
Monoclonal antibodies are one of the first genetically engineered products. In 1975 two future-Nobel-Prize-winning scientists, Georges Kohler and Cisar Milstein, stimulated an immune reaction in mice, cloned the antibody-rich immune cells, and then harvested the antibodies. Such refined antibodies are called monoclonal because, unlike the antibody cocktails our bodies create, they all react in a uniform way to a particular antigen. Recently, these antibodies have been "humanized" to get rid of all the mouse parts that used to cause nasty reactions in people who took them.

Monoclonal antibodies can be designed to disable cell signals that, for example, tell a particular system how to go awry or carry the messages that instruct cancer cells how to grow. Alternatively, antibodies can be used as transport vehicles to home in on cancer cells and deliver toxic payloads. Like tiny divining rods, these drugs hunt down only diseased cells, avoiding the shotgun approach of past chemotherapies.

In many ways, monoclonal antibodies represent the low hanging fruit of genomics. They are relatively easy to make once you identify the protein expressed on the surface of the specific cells you want to destroy, whether it is malignant cancer cells or inflammatory molecules that trigger arthritis and asthma. Once latched onto, say, a cancer cell, monoclonal antibodies can be engineered to flag it for destruction by a person's own immune system, or they can destroy the cell outright by blocking its growth or punching holes into its membrane. Seattle Genetics (SGEN), for example, is developing an antibody that targets melanoma with a toxic drug called melphalan. By zeroing in on the cancer's microenvironment, the drug's toxicity to normal tissue is dramatically reduced

There are six therapeutic monoclonal antibodies currently approved and marketed for several different diseases in the United States. Today they generate more than $2.8 billion of combined annual revenue. And tomorrow? More than 15 percent of the hundreds of drugs in clinical trials in the United States are antibodies.

Worldwide Market for Cancer Therapy Products



Markets Succeed Where HMOs Fail

I was bringing coffee back to my Wall Street desk in 1995, when U.S. Healthcare Chairman Leonard Abramson hit us with a quixotic request: "We need to buy a software company, a big one," he said. He had a lot of extra cash on his books, and a hunch that medicine would become a data-driven enterprise. Vintage Abramson: He was on to something, he just didn't know what.

Too early and wrong industry. The HMO giant was never able to use data streams for anything better than

trimming costs and denying eligibility. Medicine has indeed become an information science, but it is innovative biotech companies—and patients—who are the big beneficiaries, not insurance drones.

Biodigital medicine is on the verge of making good the failed promises of HMOs: using preventive medicine both to reduce costs and save lives. The central idea of HMOs was that costs on the back end caring for sick patients could be cut through aggressive screening and prevention at the front door. The HMOs business model assumed that relatively inexpensive drugs coupled with regular check-ups could avoid costly health problems like cancer.

HMOs ultimately failed because their bureaucratic top-down cost containment strategy was based on a medical fiction: they never had the diagnostic tools and treatments they needed. Estrogen didn't prevent heart disease. Mass osteoporosis screening cost more than pinning a few fractured hips. Even paying for a few runaway cases of breast cancer turned out to be cheaper than giving every healthy woman an annual mammogram. Mother Nature turned out to be a tough adversary for the actuaries.

Even HMOs no longer believe their business model. With the average person changing healthcare plans every three years, bean counters have no incentive to, say, ferret out pre-malignant polyps when the lesions won't turn into colon cancer for another decade. By that time, patients are another insurer's problem or covered under Medicare.

"For the HMOs, cash in the bank today, earning interest, is better than some unforeseen expense in the future, so it paid to delay treatment a few years," says healthcare economist J.D. Kleinke. Ironically, HMOs have abandoned their prevention-is-cheaper business model just as the new biodigital medicine is making it possible. Diagnosis and treatment is moving from the visible sphere—a lump on the breast, a hacking cough—down into the biochemical microcosm of DNA. In the process, medical care is being transformed from a symptom-based art into an objective science, saving lives at reduced cost.

Take colon cancer, for example, which strikes 134,000 Americans every year. Colon cancer kills because it is hard to diagnose. Patients discover it only after a tumor grows large enough to block bowel function and migrate to other parts of the body. Conventional testing for blood in bowel movements is a relatively inexpensive but not especially reliable way to diagnose early-stage colon cancer. The next level is to physically examine the colon for suspicious-looking polyps. Not everybody gets a full colonoscopy (or wants one either!).

How much of your colon will your doctor decide to look at? Just the first few feet around the rectum, where most tumors are found? Or all ten feet where polyps sometimes do grow? A rectal blood test costs roughly a buck. A flex sig, or partial colonoscopy costs about $200, while a look up and down your whole colon takes about an hour and costs up to $600. Diagnosis based on visible symptoms of illness is expensive, invasive, and time-consuming. You just can't test everybody.

But suppose we could spot colon cancer from a simple stool test? Dr. Jin Jen from the National Institutes of Health developed a method of purifying DNA from stool and then compared paired stool and tumor DNA samples from 50 patients with colorectal cancer, looking specifically for three gene mutations commonly found in the cancer. Using these three genetic markers, they were able to correctly identify colon cancer in almost all the patients who had it.

For a buck-a-patient, mass routine screening for colon cancer and a host of other deadly diseases is suddenly feasible. As we go beneath the level of visible symptoms to the biological processes that eventually produce them, vast new possibilities in testing and treatment emerge that make the practice of medicine *both* cheaper and more effective.

The Biotech Bonanza

In between hiccups, David heaved a deep sigh of relief. The CAT scan was negative for cancer. It was gastroesophageal reflux disease—heartburn—after all. He left the emergency room with a prescription for Prilosec and hiccups that subsided for good in a few days.

But what if David had had cancer? In the biodigital age, he won't haggle with his insurance company to pay for a scan. He will give a blood sample, tested against a gene chip, to see if he has a relapse. If so, doctors will be able to take proteins produced by his personal cancer to design custom-made drugs—tailored to his tumor and his DNA profile—that will rapidly knock it out.

Traditional human efforts are being empowered with digital tools that annotate life with silicon technology and displace enormous material efforts with an exercise in artificial intelligence. Moving from wet lab to computer, from random to rational drug design, from species biology to the individual's unique DNA profile, companies adopting the insilico paradigm are unlocking the long-hyped promise of the genomic medicine, making drugs and diagnosis and drug development faster, cheaper, better.

In the future, a supercomputer sitting in an air-conditioned room at companies such as Vertex will work day and night; crunching billions of bits of information to design the kind of drugs that will make sure David's cancer is cured the first time around. Multiplying at the speed of Moore's law, it will never need to rest or ask for higher pension payments, and it will be the ultimate beneficiary of an abundance of genomic information and the deciding factor for success in an age of digitally driven research.

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