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Pharmacogenomics: DNA Gets Personal

NEW SNIP TESTS LIMIT DRUG FAILURES, SLASH COSTS, AND BOOST DRUG MARGINS. FORECAST: BUMPER PROFITS.

Irritable bowel syndrome won't kill you—just in severe cases trap you in your own home with unbearable cramps and diarrhea. So when the potent new wonder drug Lotronex came onto market a year ago, more than 300,000 Americans, including a patient of mine (call her Susan), flocked to it.

Most got good relief. Many were virtually cured. Yet, like all medications, Lotronex could cause side effects, for a few even worse than the disease. Nothing unusual about that. The contraceptive Norplant, for example, has been taken safely by millions of women, but it has also been linked to some two-dozen strokes. Imitrex has brought extraordinary relief to hundreds of thousands of Americans with severe migraines, but in a handful of cases, it may have caused fatal heart disturbances. And ten months after its FDA approval, about 70 people taking Lotronex developed a rare side effect called ischemic colitis. Some needed surgery. A few died.

When a disease is debilitating but not deadly, the FDA has a low tolerance for even rare fatal side effects. Patients sometimes disagree. When the FDA announced it was withdrawing the only drug that relieved her symptoms, a desperate Susan convinced a doctor to write an extra prescription for Lotronex, and drove to five different pharmacies hoarding all that was left on the shelves.

Susan's dilemma is becoming all too common. As medical practice increasingly favors pharmacotherapy over costly surgeries, the statistically inevitable result is a rising number of unforeseen side effects. But the law of averages provides little comfort to FDA critics riveted by individual human suffering, or for that matter to patients such as Susan who find effective treatments suddenly withdrawn because of dangers—not necessarily to her, but to the unknown patients who would be statistically certain to die if Lotronex were to stay on the market.

In a world of sophisticated markets catering to every conceivable individual taste and need, the drug industry often appears clumsy and old-fashioned. Conventional drug companies still assume that one drug should or can work the same in every human body. Regulators make the same assumption: side effects in even a miniscule fraction of patients can block new drugs. Conventional researchers devote little attention to figuring out the differences between patients who respond well to their products and those who don't. Doctors decide about dosages based on population averages rather than individual biology.

Molecular Diagnostics

All that is about to change, as biodigital medicine unlocks the therapeutic possibilities inherent in minute differences between my body's response and yours to drugs. Right now, Big Pharma is neglecting the key abundances of the era—genomic data and the computer power to process it. But very soon, thanks to emerging companies that do understand the power of this new paradigm, a patient like Susan will be able to spit a sample of mouthwash into a vial one day, and find out from her doctor the next that she can take Lotronex with no chance of deadly side effects.

Molecular diagnostics is the term used broadly by Wall Street to refer to the full spectrum of gene-based testing. As an investment vehicle, diagnostic tools have some advantages over new drugs: they

INSIDE:

are cheaper and easier to develop. About 90 percent of new drugs that make it into clinical trials fail. Bringing a new drug to market takes between five to 15 years at a cost of $400 million to $500 million. But less than half of new diagnostics in clinical development fail, and each new diagnostic test brought to market takes from 18 to 48 months at a cost of only $5 million to $20 million.

So why hasn't the smart money switched to diagnostics? On Wall Street, the conventional knock is that diagnostics don't earn as much as drugs. First-generation diagnostics looked for common markers like liver function enzymes or blood counts. They didn't uncover novel targets, like a gene, that could be patented. So scores of companies could easily create knock offs, whittling down each other's profit margins.

But molecular diagnostics are different. Driven by proprietary gene-based targets, new diagnostics yield broad patent protection and much higher margins, on the order of 70 to 85 percent three years or so into a product's life cycle. Conventional diagnostic tests represent a $32 billion market growing at 2 to 10 percent annually; the $1 billion molecular diagnostics market is growing at 30 to 50 percent and will capture the bulk of the existing market as more precise gene-based tests replace first-generation diagnostics.

Molecular diagnostics come in several types. Some help reclassify diseases based on their underlying genetic codes rather than surface appearances. Affymetrix's [AFFX] Lymphochip, for example, is a DNA chip that differentiates lymphoma tumors that look identical but require very different treatment protocols. A second type of molecular diagnostic uses DNA to predict a patient's susceptibility to certain diseases. Myriad Genetics [MYGN], for example, tests for BRCA1 and BRCA2, two genes linked to breast and ovarian cancer. DeCode Genetic [DCGN] is developing tests for genes linked to Parkinson's and schizophrenia.

This issue of the *Gilder Biotech Report* focuses on a paradigm-shifting medical revolution taking place at the intersection of the fields of pharmacology and genetics: *pharmacogenomics*, the science of using genetic data to predict how individual patients will respond to drugs. Conventional medicine assumes every human body responds more or less identically to the same chemical compound. In reality, how patients respond to drugs varies wildly; a few may face life-threatening side effects from a drug that helps millions. Many effective drugs are taken off the market because we cannot distinguish the endangered from the enabled. Pharmacogenomics will change that.

SNIP Tech

DNA is essentially an embedded computer code, bits and bytes of data ready to be read each time a patient has a problem. Every cell in your body is made of 23 chromosomes. Stretch out and iron these chromosomes flat, and they look like a long skinny ladder. Each rung in the ladder is composed of one of four possible biochemical combinations (like ones and zeros in binary computer code) called base pairs. Just as the sequence of ones and zeros defines a computer command, the sequence of 3.2 billion base pairs defines you and me. Like computer code, it takes thousands to millions of base pairs composed of nucleotides to make up each of the 40,000 genes in your body. When one of the rungs in the ladder is made up of the wrong kind of nucleotide, it's a mutation, a.k.a a *single nucleotide polymorphism*, better known as a *snip*.

The human genome contains an estimated 10 million snips, but only perhaps 300,000 or so are biologically relevant, containing the genetic variations that determine everything from the color of your hair to your propensity to develop ischemic colitis if you take Lotronex. Predicting drug toxicity is one blockbuster application of the new snip technology. One new snip test, developed by researchers at St. Jude Children's Research Hospital in Memphis, identifies patients who have mutations in the thiopurine S-methyltransferase gene, which is involved in metabolizing mercaptopurine drugs. Mercaptopurine drugs are lifesavers for victims of acute lymphoblastic leukemia, a deadly cancer afflicting some 2,400 American kids each year, according to the National Cancer Institute. But between 10 and 15 percent of children and teens have difficulty metabolizing the drug. Quick metabolizers don't gain any benefit from the standard dose, while slow metabolizers accumulate deadly levels of the drug. Before pharmacogenomics, there was nothing doctors could do but give the drug and wait and see who died from

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Fig. 1. Selected Metabolic Polymorphisms and Their Drug-Related Consequences.

Enzyme	Drug	Consequences of Genetic Polymorphism
CYP2C9	Warfarin	increased risk of bleeding
CYP2C19	Prilosec	decreased efficacy in peptic ulcers
Dihydropyridine Dehydrogenase	5-FU	severe toxicity from the drug
UGT1A1	Irinotecan	decreased metabolism of drug
Thiopurine Methyltransferase	6-MP	toxicity from drug in leukemia
ADBR2	Salbutamol	decreased efficacy in asthma
CETP	Pravastatin	efficacy in preventing heart disease
5HT2A	Clozapine	efficacy of drug in schizophrenia
5HTT	Fluvoxamine	efficacy of drug in depression
DD3R	Neuroleptics	development of tardive dyskinesia
PPAR	Insulin	variation in sensitivity to insulin
MiRP1	Clarithromycin	drug induced prolonged QT

leukemia or who died from mercaptopurine. Now, using a snip panel, doctors can identify the slow-metabolizers and give them a smaller, safer dose. The Mayo Foundation has given Variagenics Inc. [VGNX] an exclusive license to the markers for therapies and diagnostics.

And that is just one application. According to a 1998 study in the *Journal of the American Medical Association*, an estimated 2.2 million patients had adverse reactions to drugs: 106,000 Americans died. By some estimates, adverse drug reactions are the fourth leading cause of death. The frequent failure of drugs such as interferon-alpha for hepatitis C infection, many high blood pressure medications, and antidepressants is likely related to genetic variations in individual patient metabolism. As new snip tests uncover these and other genetic variations, drug companies that ignore snip technology do so at their own risk.

SmithKline Beecham recently settled a lawsuit that charged, among other things, that the company ignored warnings that a genetically identifiable class of recipients (as many as 30 percent) may develop an autoimmune disorder from LYMErix (its new Lyme vaccine). In December, a jury awarded $43 million to a woman who claimed the diabetes drug Rezulin wrecked her liver. Rezulin, a drug taken by nearly two million people before it was pulled from the market in March 2000, has been linked to 63 deaths from liver failure. Differences in liver metabolism are high on the list of variations pharmacogenomics is poised to uncover.

But if the first wave of the pharmacogenomics revolution is predicting adverse reactions like these, a second wave is ready to break right behind it: forecasting which drugs are most potent for which patients. Right now this is largely a painful, expensive, and sometimes deadly process of trial-and-error on the physicians' part. Drug failure is an even more common problem than adverse reactions. Even "good" drugs fail one-third or more of patients. Chemotherapies for some blood cancers work in fewer than 40 percent of patients. Even a blockbuster anti-cholesterol drug, like Lipitor, fails more than a third of patients in some studies.

How can pharmacogenomics help? Consider a new snip test discovered by the Johns Hopkins Oncology Center (now licensed to Virco Lab) that predicts which brain cancer patients won't respond to conventional chemotherapy. With aggressive brain cancers, a doctor usually gets only one shot at a cure; starting with the right combination of therapies means the difference between life and death. Preliminary data from another large university suggests that non-small-cell lung cancers with mutations in the beta-tubulin gene are less likely to respond to the standard chemotherapy, paclitaxel, than are similar tumors without this genetic mutation. Armed with this type of information, doctors can prescribe lifesaving drugs right from the start.

Drug response is a spectrum: some patients benefit a little, some a lot, and some not at all. Figuring out in advance such differences has enormous ramifications, dramatically increasing the productivity of drugs over alternate, more costly surgeries and hospitalizations. Thanks to pharmacogenomics, patients will get better faster, avoiding costly ineffective therapies and the even greater medical costs of allowing serious disease to progress unchallenged. And of course, the more we learn about why drugs are effective in some patients but not others, the more possibilities open up for new drug cures.

Testing Possibilities

As pharmacogenomics overthrows the old one-drug-cures-all assumption, one dramatic result will be the overthrow of our current cumbersome, costly, and increasingly ineffective drug-testing model. Right now, clinical trials require multiple tests with large patient populations in order to get statistically meaningful results. In phase I, researchers establish the maximum tolerated dose of a new drug on 25 to 50 healthy volunteers. In phase II, they test the efficacy, safety, and dosage range on several hundred sick people. And in phase III, they test for safety and efficacy on 5,000 to 10,000 patients.

This is an expensive way of doing business. A Tufts

Center for the Study of Drug Development study released last month found that the cost of developing a new drug now averages a whopping $802 million, of which clinical development accounted for about $466 million. Streamlined clinical trials made possible by pharmacogenomics could slash the costs of developing a new drug by more than 30 percent according to a report by the Boston Consulting Group.

Snip technology allows companies to restrict clinical trials to patients most likely to benefit from a new drug, making trials smaller, faster, and more efficient. Incyte [INCY], for example, is looking for pharmacogenomic markers for osteoarthritis, about half of all arthritis cases. Clinical trials for new osteoarthritis drugs are prohibitively expensive because the disease progresses so slowly, requiring drug researchers testing for efficacy to track very large numbers of patients over many years. Incyte seeks genetic markers for fast progressers, patients whose osteoarthritis gets noticeably worse in just one year. Testing new osteoarthritis drugs on these patients would yield clinically important results in a fraction of the time. Only the most promising drugs would move onto larger, expensive, time-consuming clinical trials including slow progressers. Quicker results allow companies to cut their losses on failed drugs (in clinical trials *most* drugs fail) much earlier.

In the new testing model enabled by pharmacogenomics, phase I will still be used to establish safety, but also to confirm the snip markers. Phase II will still be used to find the optimal dose, but also to confirm which groups respond well to the drug based on their snip panels. And phase III can then test only fast responders—people whose snip markers indicate they are responsive to the drug.

Fig. 2. Success Rates of Drug Candidates

Stage	% Success
Preclinical	1% - 8%
Phase I	8% - 25%
Phase II	25% - 50%
Phase III	50% - 95%
Registration	95%

Phase I will still involve some 25 to 50 volunteers. But phase II will be based on the number of patients needed to establish and validate the gene-based diagnostic profile—a number that is likely to vary from 400 to 2,000, depending on the network of genes involved. Phase II would identify the snip profiles later used to recruit people for the phase III study. Phase III is where the real savings are in time and money. Phase III could now test much smaller patient groups, recruiting only a screened group known to be responsive to the drug.

Pharmacogenomics will allow companies to slash the number of people required to conduct all three clinical trial phases by between one-fourth and one-half, saving about $130 million per successful drug. But that underestimates the savings to a company's development budget because most ineffective drugs will be weeded out earlier. Drugs developed biodigitally will be validated in silicon. Clinical trials in the future will mostly confirm previously established positive results. Most drugs that reach phase III will succeed, not fail.

Regulated Surveillance

Pharmacogenomics will also dramatically increase success rates by permitting otherwise risky or ineffective drugs to be approved for relatively narrow groups of patients likely to benefit. Every indication is while the FDA doesn't yet fully understand the pharmacogenomics, they endorse its potential application to clinical trials.

Since 1997, 14 drugs have been pulled from the market because of safety concerns—an embarrassing and unacceptable track record. Congress has told the FDA, in no uncertain terms, that it must implement a zero-tolerance policy to eliminate unsafe drugs. But under current methods detecting very rare adverse reactions will require very large and expensive test groups. Pharmacogenomics will replace the current one-time approval process (followed by embarrassing reversals) with a new, more efficient and effective regulatory process, which we call *regulated surveillance*. The FDA could require blood spots taken from hundreds of thousands of patients given newly approved drugs to be stored on filter papers in an approved location. As reports of rare side-effects surface, DNA from such patients could be extracted and compared with DNA from control patients, uncovering snip profiles that indicate patients susceptible to dangerous side effects. So when an effective new drug like Lotronex brings relief to hundreds of thousands, it won't have to be yanked off the market to protect 70 Americans genetically prone to a dangerous side effect.

Old, failed drugs will also get a new look as pharmacogenomics revives products that previously failed to win FDA approval because of rare side effects, or because the drug failed too many patients. Recovering the sunk costs in these failed products will be a huge boon to the sector. While many of these previously failed therapies will have little or no remaining patent term, they may be eligible for special FDA-administered market exclusivity of five to seven years.

Pharmacogenomics will alter the financial relationship between therapeutic and diagnostic products. In the past, drug development has been a high-cost, highly regulated, high-margin business, while diagnostic development has

been a relatively low-cost, minimally regulated, low-margin business. In the future, high-cost, proprietary diagnostic products will be developed and marketed in tandem with proprietary therapeutic drugs.

If claims to safety and efficacy of new therapeutic products depend on the results of diagnostic tests, coordinated marketing and regulatory approvals of the two products might even be legally required. In any case, as diagnostic tests are linked to therapeutics, the value of diagnostic tests—and the profit margins—increases dramatically. A HercepTest, the molecular diagnostic test that tells whether or not a woman would respond to the breast cancer drug Herceptin—is several magnitudes more valuable (and therefore commands a higher price) than the same test given prior to approval of Herceptin. Or consider the new diagnostic test for congestive heart failure developed by Biosite [BSTE]. Only patients with a B-type natriuretic protein (BNP) respond to Scios's drug Natrecor. The existence of a new drug for congestive heart failure, whose effectiveness depends on a specific diagnostic test, dramatically enhances the value of that test. It also enhances the value of the drug, reducing failure rates and adverse side effects dramatically. The now-sharp line between diagnostics and drugs begins to blur, as the two products become joined at the hip.

Here is how the two industries will link up in the near future: a drug company will come to a pharmacogenomics firm with a problem; data from a phase II study indicates that a compound was extremely effective in some patients, but the overall efficacy rate was very disappointing. No way will the FDA approve a drug that has significant side effects and fails 90 percent of patients. Should they proceed into a phase III trial? Or should they give up on this particular compound and bail out of expensive phase III trials altogether? The pharmacogenomics firm would analyze their phase II data, finding snips to identify the patients who responded to the drug. Suddenly the balance sheet between bailing out and proceeding is transformed. The drug company could take the drug into phase III studies for those for whom it will likely be effective, genetically selected patients, probably leading to a marketable drug for a smaller subclass of patients.

Taking the lead in switching to a pharmacogenomics paradigm among the big drug companies is GlaxoSmithKline [GSK]. In the next two to five years, Glaxo expects to ask for FDA approval of a pharmacogenomic test for the safety of its HIV-drug Ziagen. Around five percent of AIDS patients who take Ziagen (like other AIDS drugs) develop dangerous hypersensitivity reactions. If the FDA approves the test, then the right five percent of the population will know not to take Ziagen. Once such pharmacogenomic focusing enters the fray, companies that lag will be driven out of business by regulatory and litigation pressures. Who wants to play Russian roulette with dangerous side effects if a test can prevent it? Consumers will want it. Regulators will demand it. Juries in malpractice suits will ensure quick adoption.

But what impact will the diagnostic DNA revolution have on revenues? Pharmacogenomics is a disruptive technology, not a technology that sustains what organizations are used to doing. Although developing tests that predict side effects seems like common sense, it runs counter to almost every received notion of how drugs are developed and marketed.

Under the current model, big drug companies aim to produce a blockbuster prescribed to the entire patient population. Yet, genetic variations will cause even blockbusters to fail for 40 percent or more of patients. Beta-blockers, used to treat high blood pressure and heart disease fail for 15 to 35 percent of the patients for whom they are prescribed; tricyclic antidepressants such as imipramine fail for 20 to 50 percent of patients; and interferon for hepatitis C fails for 30 to 70 percent of patients. In other words, a typical blockbuster drug that generates revenues of $1 billion a year does so because it is distributed to 100 percent of the patient population—not because it works for 100 percent of patients. A pharmacogenomic drug would be given only to patients whose genotypes showed they would respond well.

So would a drug prescribed for just 60 percent of the patient population generate just 60 percent of the revenues? Hardly. Pharmacogenomics means drugs will work better with fewer side effects for the right patients. Such drugs will have a huge competitive advantage over alternatives and command premium prices. Development costs will be far lower and margins far higher, a combination pretty hard to beat on the bottom line.

Pharmacogenomics will extend patent life. As new diagnostic tests are developed that predict rare side effects, the patented tests become crucial to safe and effective use of the drug. Holding patents on diagnostic markers allows drug companies to extend the patents on the correspon-

Fig. 3. Total Drug Development Time from Synthesis to Approval in Years

	Pre-Clinical Phase	Clinical Phase	Approval Phase
1990s	6.0	6.7	1.5
1980s	5.9	5.5	2.8
1970s	5.1	4.4	2.1
1960s	3.2	2.5	2.4

Over the last four decades, the amount of time drugs spend in clinical trials has risen steadily. Pharmacogenomics can cut that time dramatically.

ding drugs as well. An entire industry is growing up for precisely this goal.

While pharmacogenomics will fragment the drug market, leading to more niche than blockbuster drugs, the overall drug market will become far larger. Big pharmaceutical companies will opt for strength in the big areas they do well—heart disease, neurology, and cancer. As new genetic tests continue to reclassify diseases into entirely different disorders, the snip maps for these newly defined diseases will lead to a series of tailored drugs ultimately allowing companies to replace their blockbuster revenues with profits from multiple high-margin drugs, developed at lower cost with far less vulnerability to generic competition.

Pharmacogenomics will save lives, ripping down any organizational barriers to its adoption. Consider one of the most common cancers, colorectal. This year, nearly 131, 000 Americans will be diagnosed with colorectal cancer and 56,000 will die. Currently, the world's most widely used chemotherapy is 5-FU, the standard first-line treatment for colorectal cancer. Yet as a single agent, 5-FU fails in about 80 percent of patients and causes severe neurotoxicity and even death in patients with specific alterations in a metabolizing enzyme called DPD. Variagenics, one of the leading discoverers of molecular markers that predict drug toxicity and response to treatment, is working to develop a test that can predict who will have a dangerous reaction to 5-FU, and who will benefit most. Getting treatment right the first time not only saves lives, it also saves money. It costs about $20,000 to treat a person with early forms of colorectal cancer (known as Dukes's stage A). By the time it reaches advanced stages (Dukes's stage D), it costs $40,000 per person or more.

There are a variety of ways to invest in the pharmacogenomic paradigm. The first is by investing in the diagnostic clinical laboratories that will benefit by performing the new diagnostic tests. Among the companies that will stand to benefit most by a surge in molecular tests are Quest Diagnostics [DGX], LabCorp [LH], Specialty Labs [SP], and IMPATH [IMPH]. Molecular diagnostics will allow these companies to expand their markets and capture higher margins from their business. For example, LabCorp's average price for tests was $26.34 in 2000, but the average testing price from the company's Center for Molecular Biology and Pathology (its molecular diagnostics division) was $113.08, a 330 percent differential.

A second way is to invest in the companies building the reagents, chips, and platforms to mine for snips and carry out gene-based tests in the clinical laboratory. The market for snip analysis was $250 million in 2001 and has been growing 38 percent annually on average since 1999. Companies selling platforms for snip discovery in the laboratory and detection in clinical samples include Nanogen [NGEN], Lynx Therapeutics [LYNX] (which isn't fully developed but promises parallel identification of millions of snips without prior knowledge of their sequences nor the selection of candidate genes), Caliper Technologies [CALP], Hyseq Inc. [HYSQ], Luminex Corp. [LMNX], Aclara Biosciences Inc. [ACLA], Cepheid [CPHD], Illumina [ILMN], Visible Genetics [VGIN], Promega, Third Wave [TWTI], and Pyrosequencing AB.

A third way is by investing in companies that are developing the clinically relevant collections of snips that will help doctors predict disease and drug response. The highest margins and biggest profits in the pharmacogenomics paradigm will likely flow to these gene discovery companies creating the intellectual property that make new diagnostics possible. Two of the leading pure plays in this market segment are Variagenics [VGNX] of Cambridge, Massachusetts, and Genaissance Pharmaceuticals [GNSC] of New Haven, Connecticut.

Each has developed sophisticated computational tools that streamline the process of snip discovery. Each is aggressively partnering with pharma to bring genomics into everyday clinical medicine. These companies will not only earn big profits by licensing the tests they develop, but also increase revenues through royalty agreements tied to future drug sales in return for the development of genetic diagnostic tests (not unlike Albany Molecular Research [AMRI] receiving royalty payments for Allegra because of its work on a molecular diagnostic for the allergy drug). As the lines between diagnostics and therapeutics continue to blur, new lines of revenues will develop for diagnostic providers that should result in higher sustained growth.

Genaissance Pharmaceuticals

Variagenics and Genaissance each look for *haplotypes* or groups of snips that work together to cause a particular drug response. The human genome is made up of millions of snips, but only thousands of haplotypes. Mining for haplotypes rather than individual snips thus reduces the search process by an order of magnitude.

Genaissance's innovation is to use proprietary software to find the stretches of DNA inside these haplotypes. Genaissance sequences small bits of the haplotype, and then uses a computer to reconstruct entire stretches of DNA, substituting in silico tools for one of the principal information bottlenecks, wet-lab DNA sequencing. Variagenics also uses this kind of haplotype inferral software, but after its computers have made these predictions, it still goes back to its experimental wet-lab haplotyping to confirm what the software has found. Variagenics would argue that wet-lab confirmation makes its process more accurate. Genaissance says relying on computers makes its process faster.

Genaissance recently finished recruiting people for a trial to look for genetic associations in patients' responses

to four major anti-cholesterol statin drugs. Earlier work by Genaissance, published in the *Proceedings of the National Academy of Sciences*, demonstrates that snips for the 2-adrenergic gene predict the severity of patients' asthma, as well as their response to the drug albuterol. In December, Genaissance signed a deal with AstraZeneca [AZN] in which its snip markers and informatics platform are going to be applied to one of AstraZeneca's drug discovery programs to locate predictive snips in conjunction with the development of a new drug.

Variagenics

Variagenics also uses clever in silico tools to overcome information bottlenecks, this time to speed uncovering of relevant associations from among the hundreds of thousands of snip possibilities. Linking snips to specific biological processes isn't always easy. It requires powerful computers crunching algorithms and access to genomic data on thousands of different people. Through a unique molecular modeling methodology, Variagenics searches for snips that are most likely to affect the structure of proteins, narrowing the search field considerably. Most drugs work by targeting proteins—cell receptors, enzymes, hormones, etc. As more protein structures are mapped over the next few years, and as proteomic tools get smarter, so does Variagenics's unique approach. As the human body's hidden molecular maps are converted into digital knowledge, the accuracy of Variagenics's approach accelerates at the speed of Moore's law.

Variagenics is aggressively expanding its clinical research programs, especially in cancer, where current drugs typically fail half or more of patients and have severe, deadly side effects. Genaissance by contrast seeks to penetrate mass markets—big-selling drugs targeting common conditions such as statins (to lower cholesterol) and hypertension drugs. Both approaches have long-term potential. But expect pharmacogenomics to break through first in clinical settings like oncology where getting the right drug the first time around may mean the difference between life and death. Variagenics is likely to hit first, breaking ground others will emulate.

Among companies positioned to capture revenue from each aspect of this paradigm are Sequenom [SQNM] and Orchid Biosciences [ORCH]. While the biggest margins will flow to the companies creating intellectual property, these two companies are engaged in this activity and more.

Orchid is involved in three pharmacogenomic areas. They manufacture consumable kits of chemicals for snip discovery and analysis. These are the razor blades companies need to operate their snip-discovery machines. Orchid's genetic diversity services include snip scoring for research and clinical applications. Finally, Orchid has a relatively modest business unit called Pharmaceutical Value Creation that signs up with drug companies to find snips for pharmacogenomic applications, an intellectual property business similar to Genaissance and Variagenics.

Orchid is also moving father down the revenue stream by providing its own lab services and investing heavily in identifying and patenting diagnostic snips to be used with drugs. Part of Orchid's strategy is to use its popular kits as a way to get its foot in the door: then, once inside, peddle their more lucrative, higher-margin snip services to clients.

Sequenom

Sequenom is more heavily invested in intellectual property creation, and at the same time is a one-stop shop for pharmacogenomics. The company offers: the industry's best genotyping equipment to mine for medically relevant snips; validated snip chips that can be used for research and clinical diagnostics; a subscription snip database for researchers looking for their own medically relevant markers; and proprietary snip collections that can be used by Sequenom to develop their own diagnostic tests. Sequenom also licenses gene targets that it uncovers to pharmaceutical partners for use in drug development and new diagnostic tests, putting it in the same space as Myriad [MYGN], DeCode [DCGN], and gene-to-drug companies like Curagen [CRGN] and Human Genome Sciences [HGSI]. Finally, Sequenom partners with pharmaceutical clients to develop snip collections that can be used to predict drug response to toxicity to new medicines, putting it in the same category as Variagenics and Genaissance.

Sequenom is the leader in using a process called mass spectrometry to mine for medically relevant snips and to validate these markers in diverse populations. Sequenom's MassARRAY technology eliminates many of the experiment-heavy processes associated with traditional snip discovery—no chemical labels and no separation steps are needed. Biomolecules can be detected directly and fed into Sequenom's software databases, providing a data quality more accurate than conventional technologies.

Sequenom's approach also allows snip genotyping of a large number of samples simultaneously, allowing it to scan many patients to mine for relevant snips. Their process is cheap and reproducible and offers a powerful strategy for industrializing the detection of medically useful genetic differences. The entire process maximizes in silico tools. For example, the company's software algorithms use artificial intelligence to determine whether a snip is medically relevant or not, just like Variagenics's systems do.

In May, Sequenom acquired one of the leading genomic information companies, Gemini Genomics, giving Sequenom one of the largest collections of DNA samples to

BIOTECH COMPANIES

Company	Technology Leadership	Reference Date	Reference Price	12/31/01 Price	52-Week Range	Market Cap
Vertex (VRTX)	Rational Drug Design	9/17/01	28.60	24.59	15.50 - 75.17	1.84B
Human Genome Sciences (HGSI)	Cellular Signaling	10/26/01	43.97	33.72	26.41 - 77.00	4.30B
Nanogen (NGEN)	BioChips	10/2/01	4.95	5.77	3.00 - 13.43	124.4M
Gilead Sciences (GILD)	Rational Drug Design	12/05/01	67.72	65.72	24.87 - 73.67	6.30B
Quorex (none*)	Rational Drug Design	12/05/01				
Sequenom (SQNM)	Pharmacogenomics	1/09/02	9.00		5.65 - 21.25	336.2M

* Pre-IPO startup companies.

NOTE: This list of Gilder Biotech companies is not a model portfolio. It is a list of technologies in the Gilder biotech paradigm and of companies that lead in their applications. Companies appear on this list only for their technology leadership, without consideration of their current share price or the appropriate timing of an investment decision. The presence of a company on the list is not a recommendation to buy shares at the current price. Reference Price is the company's closing share price on the Reference Date, the day the company was added to the table, typically the last trading day of the month prior to publication. The author and other Gilder Publishing, LLC staff may hold positions in some or all of the companies listed or discussed in the issue.

use for mining new medically relevant snips. Easy access to this kind of information gives Sequenom an important edge over its competitors. Sequenom is positioned to play in the same market as Variagenics and Genaissance, but the Gemini data trove gives it a vital and scarce gene-discovery asset Variagenics and Genaissance don't have: unique genetic information.

Drugs prescribed to 100 patients to achieve a response in 20 are becoming ever more difficult for health insurers—or patients—to swallow. Pharmacogenomics will replace expensive trial-and-error therapies with precision prescriptions based on certain knowledge of individual patient response. By increasing the efficacy of drugs and limiting their side effects, pharmacogenomics will reduce complications and improve the productivity of both drug therapy and drug development, while increasing profit margins and slashing development costs.

We are adding Sequenom to our list. It's a powerhouse shop for playing the full spectrum of pharmacogenomic investment opportunities from snip discovery to new diagnostic tests and new highly targeted drugs. It will profit from every step, as pharmacogenomics becomes the dominant diagnostic paradigm.

We will also be following Variagenics and Genaissance closely. Both are likely to be long-term winners. They are also trading at near all-time lows. Variagenics is trading below cash value, as Wall Street has largely missed the coming pharmacogenomic revolution.

Pharmacogenomics ushers in a new science of silicon medicine. This shift will take place gradually as older and currently marketed drugs are replaced by newer, more selective chemical entities with more accurate diagnostic tests. Sequenom will be at the forefront of that hugely profitable transition.

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