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Deconstructing Diagnostics

The future belongs to those who mine for markers, but outsized profits will still flow to those who run the tests.

I've seen a lot of women recently diagnosed with breast cancer who were forced to make very difficult decisions with imprecise information. Should they have breast-sparing surgery, opt for chemotherapy, radiation, or all three? Or should they have a total mastectomy? These questions aren't easily answered by doctors or their patients.

That's because doctors still use inexact criteria to guide these medical decisions, such as how big tumors are, how they look under their microscopes, and how far the tumors have spread. Before now the technology didn't allow for anything more sophisticated, and cancer, after all, is life-threatening. So, many patients choose the more aggressive strategies even though in some cases we know they don't have to. The problem is that it's impossible to tell who will respond to conservative management and who will not. And above all else, the goal is to preserve life. Doctors, and patients, played it safe.

That's about to change. Cancer researchers are increasingly confident they can identify molecular fingerprints in tumors that will predict whether a given cancer is likely to spread quickly or respond to conservative treatment. These molecular tumor signatures are already being used to guide the management of some pediatric tumors, and they will soon be useful in the entire spectrum of diseases—especially cancer. The signatures will help doctors predict which patients are most likely to respond to radiation or chemotherapy, allowing oncologists to personalize treatments to a much greater degree and avoid the shotgun, one-size-fits-all treatments that dominate today's practice.

Take one study published this past month in the *New England Journal of Medicine*. A group of researchers demonstrated that a fingerprint derived from the activity of just 70 genes found in breast cancer tumors can predict whether early-stage breast cancer is likely to metastasize or spread aggressively. Doctors can use such a simple battery of gene markers to predict with confidence which patients should get breast-sparing surgery, which patients are most likely to respond to chemotherapy or radiation, and which should probably opt for more aggressive measures. No more guesswork. No more shotgun approaches to therapy.

The market for clinical diagnostic tests has been growing rapidly, driven by the wider use of the two-dozen available molecular

Dr. Scott Gottlieb

Impath is an attractive partner for drug developers as well as a unique platform for developing new molecular tests.

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tests for things such as sexually transmitted diseases, AIDS, and hepatitis C. New genomics and proteomics technologies, combined with advances in bioinformatics and computational power, are challenging fundamental concepts of early disease detection and diagnosis. But as we've discussed before on these pages, these available tests are just a primitive first wave of what will be a paradigm leap in the way doctors diagnose and treat illness. They are still mostly aimed at the task of cracking a diagnosis. The next wave of tests will offer opportunities for identification of new kinds of prognostic tests, especially for cancer. They may even serve as possible screening tools to determine who is likely to develop certain diseases even while they're still healthy.

Genetic Fingerprints

These techniques are known collectively as gene-expression analysis. The technique involves the study of tens of thousands of genes in cancerous tissue from a variety of patients to unearth the genetic markers that have predictive value.

Because most cancers are thought to result from genetic damage to cells, researchers figured a close look at variations in gene activity across tumors might help them identify aggressive cancers at an early stage. They were right. Discovering these genetic markers is made possible by gene chips, which are used to show which genes in a tumor cell are unusually active or unusually quiescent. Gene chips are layered with pieces of DNA from thousands of known human genes. The chips are washed with samples of DNA drawn from a tumor. When a piece of DNA is active in a tumor, a reaction takes place on the surface of the gene chip, and a signal—usually an electrical impulse or a fluorescent tag—is generated to alert an operator. These signals can then be easily read using standard lab equipment.

Take the genetic fingerprint recently generated for breast cancer, where doctors compared microarray data from tumor samples that had been stored from 295 women and matched the results against these patients' medical records. Using the 70-gene fingerprint previously plucked from tens of thousands of tumor-gene signals by sophisticated pattern-matching software, scientists found that patients classified by the fingerprint technique as having a good prognosis had an 85 percent chance of living 10 years without metastasis, versus only a 51 percent chance for the poor prognosis group.

Cancer, and particularly breast cancer, isn't the only place where gene chips and molecular fingerprints are being used to gauge cancer prognosis and revolutionize diagnosis. At Dana-Farber, a group of doctors recently reported a 128-gene fingerprint that appears to predict whether a variety of tumors known as adenocarcinomas (typically implicated in stomach and colon cancer) will metastasize. Meanwhile, last summer, researchers at the National Cancer Institute used microarrays to generate four signatures of 17 genes that could predict survival after chemotherapy in patients with large B-cell lymphoma, a type of blood cancer. Keep in mind that all of these are just first-generation tests. And already they are able to act as powerful tools to aid in diagnosis and to predict which patients might need more aggressive treatments. Next-generation tests could make such determinations with near certainty.

Diagnostics: genes vs. proteins

Two paradigms emerge in clinical diagnostic testing: the first looks at proteins; the second looks at genes. As we've said before, genes tell doctors what is going to happen; proteins tell us what is already happening in the body. Remember, proteins are the products of genes—they are basically the tools that genes use to carry out their instruction sets. Normally, to produce a protein like insulin, our body first scans for the gene that contains the code for manufacturing insulin and then copies it out from the DNA into an intermediate set of instructions, called messenger RNA (*mRNA*). The process of copying the gene is called *transcription*.

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Another set of molecules, ribosomes, uses the mRNA as templates to manufacture proteins. Proteins are the "business end" of genes, the final products that carry out all the DNA instructions.

How do diagnostics based on detecting genes differ from those that detect proteins? To make the distinction, we'll first consider protein diagnostics. One example: an ongoing National Cancer Institute study looking at a new drug called imatinib mesylate.

This drug works by blocking a protein receptor called tyrosine kinase. Tyrosine kinase works as a microscopic on/off switch inside complicated signaling cascades, sending subtle instructions to turn on or shut down other regulatory nodes. Tyrosine kinase inhibitors jam the signal. Why would a doctor want to jam that signal? In order to turn off the molecular signals that instructs a patient's cancer cells to proliferate.

Imatinib mesylate is being tested for its potential to block ovarian tumors. But researchers are also testing a different possibility: whether four weeks into treatment the activation of a protein marker in the tyrosine kinase pathway correlates with standard measures of drug efficacy, such as reduction in tumor size on an X-ray.

Thus the result of these clinical trials may not only be a new drug, but also a new diagnostic tool. A simple blood test may replace the X-ray or surgical biopsy as a way to gauge the spread or retreat of hard-to-detect ovarian cancer. In this case, the protein is measured as a way to detect how well a patient is responding to the drug. Like most protein diagnostics, the test is measuring a dynamic marker.

That's the difference. By comparison, a gene-based diagnostic usually measures a fixed indicator and answers a binary question—is a certain cancer present, yes or no? And rather than being used to measure an ongoing response (a dynamic process), they are more inclined to be used as markers of prognosis (a static process). Each type of clinical diagnostic will profoundly change the way doctors practice medicine. These two technologies—protein diagnostics and gene diagnostics—are complementary, not competitive, and there are ample markets for both. For this issue, we'll focus again on gene-based diagnostics.

Nearly all cells in the human body carry exactly the same set of genes, and many of these genes, so-called "housekeeping genes," are turned on in most cells. But skin cells are different than muscle cells because a unique set of skin genes are turned on in skin cells, and a unique set of muscle genes are turned on in muscle cells. Genes give cells their unique characteristics, but the genes have to be turned on, or expressed, for the unique characteristics to appear. By identifying the pattern of gene expression for muscle cells, skin cells, or any other type of cells, including cancers, scientists can create a genetic fingerprint of that cell type. Genetic fingerprints can uniquely differentiate one cell type from other cell types.

Gene chips and fingerprints

As we've mentioned, to create these fingerprints, scientists use a device called a gene-expression microarray, or, more commonly, a gene chip. The chip is simply a glass slide on which thousands of known gene samples have been printed in tiny spots. Cells to be tested are then manipulated in such a way that genes expressed in the cell will match up with the known gene samples, like two pieces of Velcro attaching to each other. Cellular genes are treated in such a way that they literally light up the gene dots on the chip. The luminescent pattern is then measured with a special type of microscope and the results fed into a computer for analysis.

Gene chips are the innovation that makes the discovery of these diagnostics possible. The chips are valuable because they let scientists screen thousands of genes to find which ones are useful. Sometimes they end up with only a few dozen. Sometimes it's just a handful.

When it's just a dozen or so genes that doctors are interested in testing, those kinds of tests don't require sophisticated gene chips in the laboratory or at the bedside—they can be integrated into fairly ordinary clinical diagnostic equipment. For example, in the case of pediatric tumors, while the research team started with more than 6,000 genes, the artificial neural network analysis narrowed that number down to a mere 93 unique genes needed to differentiate four tumor types. And of those, 41 were new genes that might provide important insights into the biology of the cancers and offer possible targets for new treatments.

The complete picture

The place where genetic diagnostics is poised to have the most far-reaching impact is in the diagnosis and treatment of cancer. Cancer-based molecular diagnostics are allowing us to more accurately stage cancers and target treatments to patients who are likely to have maximum benefit. Peering in microscopes to look at pieces of cancerous tumors or looking at X-rays provides a crude, inexact picture of a cancer's propensity to spread or to respond to treatments. The genetic fingerprints of

a tumor, however, provide the complete picture.

Such is the case with the breast cancer test that doctors unveiled in the *New England Journal of Medicine* that will allow them to prescribe optimal treatments to particular patients based on how aggressive their tumors are. Perhaps most importantly, molecular diagnostics are also revealing that tumors we previously classified as a single type of cancer are really distinct diseases. So, breast cancer isn't a single disease. By looking at molecular signatures, we're finding that it's really a collection of many similar diseases—maybe a dozen or more—each similar enough to appear the same to the doctor or the pathologist who peers under a microscope, but different enough to require unique approaches to treatment.

Or take news last June, when scientists at the National Human Genome Research Institute and Lund University in Sweden developed a method of genetic fingerprinting that can tell the difference between several closely related types of childhood cancer: neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma (Burkitt's lymphoma), and Ewing's sarcoma. As a group, these cancers are referred to as the small, round blue cell tumors of childhood because of the way they look under the microscope.

The method that the scientists used combined, for the first time, the cutting- edge technology of gene chips with a form of artificial intelligence called an artificial neural network (the FBI already uses the same artificial neural networks to analyze fingerprints at a crime scene). The neural networks automatically analyze the large amounts of data produced by the gene chip to make a highly accurate diagnosis.

Using standard medical technology, the four types of childhood tumors used in the study are difficult to tell apart because they look alike under the microscope; their similar appearance can lead to misdiagnosis and improper treatment. Molecular fingerprinting, on the other hand, was used to find the patterns of gene activity that could tell the cancers apart and help doctors to prescribe appropriate treatments.

An accurate diagnosis can be critical for the child's survival. While these tumors are physically similar, the treatments are quite different. When a patient gets the right therapy, up to 90 percent of the children with Burkitt's lymphoma recover; about half will survive Ewing's sarcoma and rhabdomyosarcoma, and up to 40 percent will recover from neuroblastoma. Without accurate diagnosis and proper treatment, few children survive.

Business paradigms

The marketplace of companies poised to benefit from the revolution in molecular diagnostics basically breaks down into three broad categories: the clinical laboratories that process these tests; the platforms and chemistries on which the tests are conducted; and the companies developing the genetic markers that make a new diagnostic possible. In this report we aim to provide an overview of each of these business paradigms and pick out a few companies in each category that we believe have the most promise. First, we'll discuss the clinical labs.

The biggest margins will accrue to the companies that own the proprietary platform that sets the standard for molecular testing and the companies that own the markers that make up the tests. But in the near-term over the next five years, as companies begin to launch these technologies and achieve critical penetration, the outsized profits that flow from the exponential growth in molecular diagnostics will accrue to the companies that do the testing. That's the surest way to profit from these trends.

The U.S. clinical laboratory market is now valued at about $30-$35 billion in revenues per year, accounting for about 3 percent to 4 percent of total health care spending. Breaking down the market, hospitals currently account for about 56 percent of the market; independent labs like Quest and LabCorp account for about 34 percent; and physicians' labs account for less than 10 percent of the market. Clearly, Quest and LabCorp are the biggest, free-standing players, accounting for a combined $6.6 billion in revenue, or more than 50 percent of the total independent laboratory market.

In addition to processing ordinary blood tests, labs like Quest and LabCorp perform what's referred to in industry lexicon as "esoteric tests," the kinds of molecular diagnostics that require sophisticated equipment and personnel to perform them. Most hospitals and smaller independent laboratories do not have the capability to perform many of these esoteric tests, and as a result, they must typically be referred out to the larger laboratories and academic hospitals. This esoteric testing segment is what represents the lion's share of the growth in clinical diagnostics.

Revenue growth for these companies is predicted to be on order of 5 percent to 6 percent this year, driven by favorable demographic trends, faster patient discharge rates from hospitals (which means more tests are performed on an outpatient basis, outside of the tentacles of the hospital-based lab), and increased use of diagnostic

tests. The most significant driver, however, remains the increasing use of sophisticated molecular diagnostics, which command huge premiums over standard tests.

LabCorp and Quest are continuing to dominate this market, but consolidation is expected to remain a key driver for growth of the big established players, as well as innovation by niche players. Thus smaller clinical lab companies, especially those focusing on high-margin businesses such as molecular diagnostics, could provide the most profitable way to play the trend in diagnostics.

Impath stands out

Of the publicly traded lab companies that fit these criteria, we think one stands out: **Impath** (IMPH). With more than $190 million in revenues, Impath is big enough to make itself a tempting acquisition candidate for one of the bigger players in this market such as Quest and LabCorp. With cutting-edge technology, an active research program centered on cancer diagnostics, and a focus on molecular tests, Impath is also positioned to capture a growing share of the high-margin diagnostics business, fueling internal growth as well as increasing its value in a potential merger.

Impath specializes in providing diagnostic, prognostic, and treatment information to doctors who treat cancer patients. In performing its analyses, Impath has amassed a sizable database of patient profiles which it has leveraged to assist oncology drug developers.

In many ways, Impath is a pure-play on the cancer market. Although considered a clinical lab, Impath provides more specialized information than most of its peers. Through its Physicians Services division, Impath diagnoses tumors of unknown primary origins and provides the biological and genetic characteristics of already diagnosed tumors. It has become expert in developing and incorporating new technology. Among the free-standing clinical diagnostic companies, Impath is probably the furthest ahead in incorporating molecular diagnostics based on gene printing. Aside from Impath, most of this work is still confined to labs inside academic medical centers.

Impath's database now contains more than 900,000 cancer cases, and its cancer registry contains samples and outcomes on more than 2 million patients. As a result, Impath is an attractive partner for drug developers as well as a unique platform for developing new molecular tests. The company leverages its critical mass of information through its Predictive Oncology division, which has signed deals with six large biotechnology and pharmaceutical companies.

Impath's focus

Lymphoma and Leukemia represent Impath's fastest-growing product segments. In 2001 it represented about 35 percent of total case volume. Breast cancer is another core focus. Last year Impath provided patient-specific prognostic information on more than 30 percent of all breast cancer cases in the United States. Breast tumor samples at Impath may be tested for eight or more particular proteins or genes. Cancers that have the estrogen receptor, for example, generally have a better prognosis and respond better to the drug tamoxifen.

Due to its focus on high-margin and niche diagnostics and prognostic testing, its specialty cancer services don't have any capitated business. It's strictly fee-for-service. That's good for pricing. And as a result, Impath is able to capture higher profits on its tests. There are also some barriers to entry into this space which Impath has overcome: technology is one and another is amassing the critical amount of information that gives it greater intelligence in difficult diagnoses and an edge on new entrants. As a result, Impath is one tough competitor.

So what's the rub? Impath has hit a number of bumps over the past year, notably problems with billing and significant debt relative to its cash position ($70 million in debt against just $3.6 million in cash). On the latter point, Impath's new CEO has committed to using the bulk of the company's free cash flow to pay down debt. In the past, free cash had been used to build out Impath's cancer tissue depository.

The company is still committed to completing this ambitious project, dubbed GeneBank, but at a slower pace as it diverts cash to retire debt, which in our opinion represents a smart, disciplined approach in the current environment. It should help the company's stock. Impath has also been hurt by an industrywide slowdown in R&D spending—there are fewer people collaborating with Impath or paying for access to its bank of cancer information, and the situation is unlikely to change in the near future.

Clearly there are near-term problems at Impath, most of which have to do with unfavorable market conditions and some rocky execution. The company has new management that seems to be righting the ship. And the underlying technology remains the best in the industry. So the company's low stock price provides a tempting opportunity to get this technology at a bargain valuation.

On the platform side of the molecular diagnostics

business, we've talked in the past about **Nanogen** (NGEN) and identified its hardware as one of the leading pieces of equipment for carrying out tests on multiple gene markers. For this issue, we'll focus not on the nuts and bolts of diagnostic tests, but the liquid that makes them run. All of these tests turn on the chemistry that allows the reactions to take place between a genetic probe (the clinical test) and a sample (the cancerous tissue). For many purposes, **Roche** (RHHBF) has owned the space for molecular tests through its system known as *polymerase chain reaction* or PCR. But like all large companies, it has treated its purchasers with arrogance and has been exceedingly slow to innovate—preferring instead to milk profits out of its existing patents. As a result, we believe they are well positioned to be displaced.

Third Wave's Invasion

One company we recently visited in New York is building a better mousetrap: **Third Wave Technologies** (TWTT). Much of the sequence and gene expression detection done inside hospital and commercial laboratories today is through PCR, a technique first conceived of more than a decade ago by **Roche** (RHHBF.PK). PCR works well, especially when you're only looking at a single gene or just a few genes. But when have tests involving panels of a dozen or more genes—as many of the newer diagnostics will—PCR is slow, cumbersome, and imprecise.

Third Wave, we believe, has a better solution, its Invader technology. And as the small minnow, it seems to be penetrating successfully what was a previously closed market for these types of platforms—on performance alone. The Invader uses a patented enzyme known as Clevase, which recognizes and cuts only the specific sequence that you're trying to detect, emitting a fluorescent tag when the reaction takes place that be read easily using standard laboratory equipment.

With Invader, the enzyme amplifies the signal rather than the target sample, as is the case with PCR. A single target generates a signal linearly, allowing quantification of target concentrations. When the Invader reaction is complete, the enzyme can produce millions of fluorescent signals—one for every target—depending on how much of the gene targets were present in the original sample.

This kind of reporting allows doctors to develop a reading on how much of the original target was present in the sample, something that could be medically useful for things such as infectious disease detection or even cancer. Since the system doesn't rely on duplication of the sample through PCR, there's also less risk of contamination, meaning that Invader can be used in less sophisticated labs and operated by less experienced personnel. Invader doesn't need to be confined to the esoteric labs: it can move downstream. For example, Third Wave has already been able to sell the technology into some ordinary cancer labs. This will dramatically increase the company's potential market. Invader can also be used on nearly all the major instrumentation systems in place today.

There is one drawback to Third Wave's system, however. So far, Invader is less sensitive at detecting some targets that are expressed in very low quantities. It's a problem the company says it is correcting. But right now it only matters in a few diseases like HIV and hepatitis C. Yet Invader is far more specific than PCR by all of the company's internal as well as independent benchmarks. That's important—perhaps even more important than sensitivity. PCR is prone to false positives. Invader is more inclined to give a right answer every time. If there is a trade-off that needs to be made between sensitivity and specificity, Invader makes the right choice.

David vs. Goliath

Eliminating PCR is the reason we like Invader. It's about time a new system came along that had enough of the old platform's familiarity to be accepted easily by technicians, but eliminated enough of its drawbacks to provide a distinct advantage. Invader is cheaper, faster, and eliminates the need to customize the process for each strand of DNA to be detected. The customization required with PCR isn't a problem when you 're trying to detect only a few unique strands of DNA. But modern tests, including the new, widely used genetic test for cystic fibrosis, require doctors to look at dozens of different DNA targets simultaneously. With PCR, the search for each target needs to be individualized: it's too slow. With Invader, it can all be done in one easy process: it's fast and easy.

An increasing proportion of Third Wave's revenue comes from diagnostic test sales, which we believe bodes well for their earnings growth. The company is right to focus on this market, allowing it to ride the wave of broader trends. Third Wave is focusing on cancer diagnostics and is actively signing up academic and corporate partners interested in devising molecular tests that would be proprietary to its platform. Third Wave's sales

of diagnostic tests are expected to double next year, representing new growth as well as more sales to the company's existing accounts.

Truth be told, Third Wave has stumbled over the last year, missing its earnings targets amidst an industrywide meltdown, and its stock price has suffered. That's a familiar event in this sector, which has had its knocks. But the worst may be behind. Keep in mind that Third Wave also has all the competitive issues inherent in being a small company competing against an entrenched giant. But management has laid out a fairly conservative path to profitability. Its technology continues to gain a foothold and is currently in use by about a third of the sophisticated labs eligible to perform molecular testing. In fact Third Wave recently got its foot in the door at one of the largest—**Quest Diagnostics** (DGX). The company has cut its cash burn and is on track to break even in 2003. We spoke independently to a few technicians who were enthusiastic about Third Wave's new platform.

Leaders of the pack

So what about the companies working on uncovering the markers that will comprise the next generation of molecular diagnostics? Who is tops in this space? The answer is that this market remains highly fragmented, and you're likely to see clinical tests come from a disparate set of players. Every biotechnology and pharmaceutical company has a niche of expertise, and all are equally well positioned to stumble upon a killer diagnostic. That said, there are some common ingredients that guide us to a few companies we believe are likely to lead the pack. First, we will give a brief background to this marketplace.

Investors remain skeptical of biomarker-oriented companies. As a recent article in the industry publication *In Vivo* lays bare, investors are cognizant of past failures in the field and the challenges and expense of obtaining solid, nonbiased data to verify the efficacy of a new diagnostic test. They are particularly hard-nosed because it's difficult to think of successful stories in this area. As a result, the stocks of companies that work on diagnostic markers have been under pressure. But we believe an inflection point has been breached in the technology's evolution. As a result, past performance does not predict future success.

For companies working in this space developing the clinical markers that will make breakthrough diagnostics generally requires a few key ingredients. First, they need access to reams of patient-related gene data. Then they must have the ability to correlate this data with a library of actual tissue samples comprised of tumors taken out of these patients. Finally they need to have use of powerful microarrays and gene-sequencing equipment that can rapidly tease out the molecular fingerprints that will predict the incidence and prognosis of cancer.

The fruits of this discovery process are likely to fall to companies with established gene-based drug discovery companies or genomics companies with clinical infrastructure such as **Humane Genome Sciences** (HGSI) and **Millennium Pharmaceuticals** (MLNM). Among those companies, we believe one stands out easily—Millennium, which we profiled in the last issue of the *Gilder Biotech Report*. We'll skip another lengthy discussion here. Some other companies toiling in this space are **Celera Diagnostics**, a division of **Celera** (CRA) and **Genzyme Genetics** (GZMO). But remember—there's no single company poised to dominate the search for new molecular tests over the next five years. We believe banking on a steady stream of discoveries from any one player would be a poor way to profit from this new technology. Consider it an added bonus from a company like Millennium that is already firmly entrenched in drug discovery.

Yet there's no question what will differentiate clinical labs like Impath and platforms like Invader—and drive adoption—the ability to sign exclusive deals with partners that have new diagnostics or to develop them in-house, providing a reason why doctors and hospitals need to do business with them. Proprietary tests mean leverage. Rest assured, everyone is after this elusive goal.

Determining how bad a person's cancer may become is only one use for genetic analysis. As the *New York Times*'s biotech reporter Andrew Pollack recently noted, genetic signatures will also make traditional screening, like mammograms, more useful, allowing doctors to profile small tumors—the sort of early cancers that used to give doctors the most trouble deciding on treatment.

We believe that developments in genomics will lead to explosive growth in advanced testing, especially for cancer. The fundamental understanding of cancer is being modified as a result of developments in molecular technologies that will enable scientists to characterize malignancies based on the genetic makeup of the tumor. For now, we believe the safest and surest way to benefit from the trends in molecular diagnostics is through Impath.

Impath's future

True, the highest margins will eventually flow to the companies that come up with the intellectual property that's put on these tests—the companies discovering the individual gene markers. But that's years away. The past year has shown that other companies will profit handsomely in the interim as these trends take hold. Companies like Third Wave stand to gain if they can set a new industry standard. And in a tough biotech market, we believe the clinical laboratories performing the tests will be the first to appreciate from these trends. With its stock price trading near 52-week lows, Impath's technology and its market penetration can be had cheap. The company faces regulatory risk as well as exposure to government reimbursement, but that goes with the territory. With a core business in cancer diagnostics and a reputation for clinical excellence, Impath doesn't have a lot of downside. We believe the next move is up and the reason why we are adding Impath to our list.

The technology to fingerprint tumors has already arrived, and molecular diagnostics will change the way doctors practice medicine. It's just a matter of time before sophisticated molecular diagnostics make their way into every hospital and doctor's office. Companies like Millennium will find these new diagnostic markers; Third Wave's chemistry will make these tests possible; and Impath will get them there. And the practice of medicine will be permanently changed.

Scott Gottlieb, M.D.
Decmber 23, 2002

BIOTECH COMPANIES

COMPANY	TECHNOLOGY LEADERSHIP	REFERENCE DATE	REFERENCE PRICE	12/20/02 PRICE	52-WEEK RANGE	MARKET CAP
ABGENIX (ABGX)	ANTIBODY THERAPEUTICS	9/30/02	6.61	7.64	5.16 - 36.50	669.1M
CELL GENESYS (CEGE)	CANCER THERAPEUTICS	6/10/02	13.24	11.75	9.32 - 24.32	423.2M
COGENT NEUROSCIENCES (NONE*)	NEUROGENOMICS	5/2/02				
CURAGEN (CRGN)	CELLULAR SIGNALLING	3/13/02	17.67	4.55	3.40 - 23.80	224.3M
GILEAD SCIENCES (GILD)	RATIONAL DRUG DESIGN	12/05/01	33.88**	35.73	26.08 - 40.00	7.0B
HUMAN GENOME SCIENCES (HGSI)	CELLULAR SIGNALING	10/26/01	43.97	9.27	8.15 - 36.85	1.2B
IMPATH (IMPH)	HEALTHCARE DIAGNOSTICS	12/20/02	19.48	19.48	9.98 - 49.20	318.1M
ISIS PHARMACEUTICALS INC. (ISIS)	ANTISENSE THERAPEUTICS	7/9/02	7.30	6.50	6.0 - 23.41	358.4M
MDS PROTEOMICS (NONE*)	PROTEOMICS	2/05/02				
MILLENNIUM PHARMACEUTICALS (MLNM)	TARGETED DRUGS	11/29/02	10.01	8.73	7.13 - 28.00	2.5B
NANOGEN (NGEN)	BIOCHIPS	10/2/01	4.95	1.32	1.22 - 6.34	29.0M
OSI PHARMACEUTICALS (OSIP)	CANCER THERAPEUTICS	8/27/02	16.16	18.10	11.50 - 49.56	659.2M
QUOREX (NONE*)	RATIONAL DRUG DESIGN	12/05/01				
SEQUENOM (SQNM)	PHARMACOGENOMICS	1/09/02	9.00	1.75	1.25 - 11.44	68.9M
TRIAD THERAPEUTICS (NONE*)	RATIONAL DRUG DESIGN	4/9/02				
VERSICOR (VERS)	ANTI-INFECTIVES	10/29/02	10.00	10.20	7.65 - 25.40	269.1M
VERTEX (VRTX)	RATIONAL DRUG DESIGN	9/17/01	28.60	16.67	12.67 - 32.45	1.3B

* Pre-IPO startup companies.

** Split-adjusted price.

NOTE: This list of Gilder Biotech Report companies is not a model portfolio. It is a list of technologies in the 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.

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