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Target: The Brain

A major reorganization of the biotech and pharmaceutical industries is underway, leading to another huge value shift toward drug therapy and the overthrow of Wall Street's long-established methods for covering the industry and conventional wisdom on where to seek profits.

In June of 1991, Craig Venter published a landmark article in the journal *Science* under the syntactically challenged title: "Complementary DNA Sequencing: Expressed Sequence Tags and Human Genome Project." Whereas most other genome research reports trumpeted the discovery of a gene or two, Venter published the identity of more than 330, all active in the human brain. Venter employed a radically new approach to gene discovery that would propel him to stardom and create **Celera Genomics**. Venter's formula became the secret sauce of the genomic revolution.

It was no accident that Venter chose the brain as the testing ground for his new techniques. More genes are active in the brain than in any other organ: as many as one-half of all the genes in our bodies. The entire central nervous system may use some 80 percent of human genes. More than one-quarter of the 5,000 known genetic diseases affect the nervous system. The brain is a target-rich environment for genomics.

Genomics may have its most powerful impact on diseases of the central nervous system and vice versa. Genomics will drive the care of the central nervous system. And research on central nervous system diseases such as Alzheimer's, Parkinson's, and stroke, will drive—and fund—much of genomic research. This new field, applying genomics to diseases of the central nervous system, even has its own newly minted name: *neurogenomics*.

Neurogenomics is not yet on the radar of most top investors, or Wall Street. But it will be. Neurogenomics will not only transform the lives of tens of millions suffering from central nervous system disorders, it will force a restructuring of the drug industry entailing enormous shifts of value and huge new markets for drug sales and genomic research. Investors who are early to understand this will have a crucial edge.

Dr. Scott Gottlieb

"Neurogenomics will transform the lives of tens of millions suffering from central nervous system disorders and force a restructuring of the drug industry..."

INSIDE:

In the drug industry as elsewhere, form follows function. When most drug research was focused on about 500 known molecular "targets," which could impede the progress or symptoms of disease, it was not only possible to use the old labcoat-and-beaker, trial-and-error approach to drug discovery, it was also possible for most large drug firms to be active in most disease areas—though in some, like central nervous system disorders—relatively little progress was made by anyone.

But over the next decade or so, drug researchers will be confronted with tens of thousands of molecular targets. Disease remedies will often involve not just single targets, but interactions among them. This vastly more complex playing field will overwhelm not only the old research techniques, but also the very idea that every drug company can do everything, at least on the R&D side. That is already happening, with young biotech companies serving as research partners for Big Pharma. The trend will accelerate and the industry will begin to sort itself out by disease and molecular target sets. Wall Street will follow, patterning its coverage accordingly. Covered diseases and companies will attract broader investor attention.

Right now, in Wall Street's view, the "biggest" disease, and the one getting the most focused attention, is cancer, followed by heart disease. As genomics yields ever more specific, effective, and tolerable cancer-fighting drugs and diagnostic tools to guide their use, this trend will accelerate, a sub-industry of companies focused on the genomics of cancer will bloom, and there will be a boom in cancer investment.

Even bigger will be neurogenomics, creating entire new markets as new drugs displace despair over diseases we are now essentially powerless to treat. But precisely because the central nervous system is so rich genetically, companies successfully focused on this sector will overflow with intellectual property that may turn out to be crucial to other diseases as well.

Diseases of the central nervous system are particularly harsh. They can rob victims of their memories, control of their lives and emotions, and their powers of thought and speech. They're also therapeutically elusive. Current drugs can ameliorate symptoms, but there are no pills that can halt or reverse the progressive decline of sufferers from Alzheimer's and Parkinson's.

Seventy-three million people in the United States suffer from central nervous system (CNS) disorders, ranging from the common to the rare. Many are believed to involve a combination of hereditary and environmental factors. They fall into two broad categories: neurodegenerative (Alzheimer's disease, Parkinson's disease) and psychiatric (depression, schizophrenia, anxiety). Pain, stroke, and head-and-neck trauma span both categories. Alzheimer's disease alone, which already affects 5 million Americans, costs the health care system (Medicare/Medicaid and private insurance) $100 billion, and 22 million people worldwide will have it by 2025. Depression afflicts 20 million and costs the health care system $30 billion. An estimated 1.5 million Americans are affected by Parkinson's disease, including one in every 100 persons older than 60. Huntington's disease affects about one in every 10,000 people. In the U.S. alone, 30,000 people have the disease. Taken together, the direct cost of CNS disorders to the health care system comprised nearly 20 percent of all health care spending and it's rising.

In many brain diseases, the cost of custodial care is far higher than the amount spent on medications and represents a significant reservoir of latent demand for new drugs and treatments. In fact, the few existing CNS drugs boasted sales increases of almost 50 percent in the last five years, compared to 31 percent for drugs that treat every other disease.

So far, drug companies have had the most success developing therapies for psychiatric illness, with huge

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revenues. Scientists have been able to identify key receptors and inhibitors that affect them, such as the selective serotonin reuptake inhibitors (Prozac). Yet even these successful psychiatric drugs largely treat symptoms rather than underlying pathology and can't stop the progression of some dangerous diseases.

Because most CNS diseases arise from multigenetic origins as well as environmental factors, the CNS drug discovery process is particularly unpredictable. The success rate of phase 2 clinical trials in infectious disease is 85 percent, but in CNS it is not more than 50 percent. Companies often don't know if their drugs will work in humans until phase 3 trials, which is why so many CNS drugs have blown up in late stages, helping sour investors on the sector.

Genomics provides the optimal way to tackle the underlying mechanisms of these diseases. But genomics research for CNS faces special challenges. Many of the "functional genomics" tools that biotech companies are currently using to validate the genes they find are based on research on invertebrates like roundworms and fruit flies that lack the highly complex nervous system found in vertebrates or the complex genes that support them. CNS research is increasingly relying on mice, which do have complex central nervous systems like ours. But even so, there are limitations on gauging behavioral effects. How do you measure mouse depression? As for human tissue samples, they are harder to come by in brain research.

In the past, these shortcomings led to disaster in late-stage clinical trials, even for serious, well-funded efforts. Companies are beginning to compensate for all these difficulties by designing better animal models and incorporating computational, in silico models to make sense of the vast amounts of data emanating from their target identification programs.

Two of the best technology plays in this space are **Elan Pharmaceuticals** [ELN] of Dublin, Ireland, which has an industry-leading IP position in Alzheimer's disease, and **Cogent Neuroscience** of North Carolina, which is at the leading edge of applying genomics and in silico tools to the discovery of novel brain targets.

To see why we like Cogent and Elan, you must appreciate all these things that make the brain a special pharmaceutical challenge. Even the best in silico tools need to be coupled with good wet lab biology to allow companies to test drug leads in real biological environments. Only actual cells can provide certain critical information, which has been a real challenge for brain research.

Even the best in silico tools need to be coupled with good wet lab biology

Classic cell culture—getting cells from the body to multiply in a test tube so there are enough to experiment on does not work for the brain. Brain tissue is post mitotic—meaning it has stopped dividing—so you can't create a culture from brain cells unless you turn them into non-natural brain cells. And neural cell lines bear only a passing resemblance to bona fide neurons, and are of limited value anyway, because they lose some of their original gene expression patterns, distorting the disease process.

In other parts of the body, similar cells clump together, but in the brain, similar cells are relatively isolated from each other and yet are extremely interconnected to the many different cell types surrounding them. Because these cells are dependent for their function on that wiring, studying single cell types in isolation is not very helpful. So studying things in one cell type isn't predictive of the real environment. Neuroscience has suffered from the lack of models than can simulate the interactive environment in which brain cells operate.

Enter Cogent Neuroscience, which shows how these long-standing R&D weaknesses can be turned around with smart biology and genomics. Cogent is developing ways of analyzing intact cells in living tissues. The company has configured a brain slice system that allows it to rapidly screen potential drugs against living brain tissue. The company believes it is the first company to preserve living brain tissue intact, allowing it to work with individual cells in heterogeneous, dynamic structures. Cogent's brain slices are taken from mice, and while mice brains are bad at predicting the human behavioral effects of drugs, they work well for predicting biology.

When a person suffers a stroke, neurons deprived of oxygen die immediately. As these neurons die, they trigger other neurons to die as well, causing the stroke to spread. By the time the average patient enters the emer-

gency room, neurons have been dying for days.

Cogent, unlike other research groups, is looking not for the etiology of stroke, but for novel modulators that interrupt this serial cell death and mediate neuronal repair. Cogent adds individual expressed human genes to its living brain assays and tests them for their ability to prevent neurons from dying. When they do, they sequence the gene, and at the end of the day have a validated drug target. By leaving the sequencing as the last part of the process, the company is able to move quickly. With a traditional gene sequencing and expression assay approach, the best you can do is determine that a gene is somehow associated with a disorder, but not generate a validated target right on the spot.

In stroke, Cogent is analyzing the entire expression genome to better understand what blocks the cascade of cell death. The company is hunting for regulatory gene sequences that have some control over the brain's behavior, in effect creating a functional genomic map of the brain. They're looking for the nodes that turn disease on and off. So far, it has identified more than 50 novel gene targets, some of which it may develop into lead compounds and take through preclinical studies before seeking partners.

In April, Cogent raised $15 million in a private placement to support its search for genes that protect neurons during stroke—twice as much money as it originally sought. Now Cogent is out shopping for partnerships in pharmaceuticals and in information systems to develop a bioinformatics system to warehouse and analyze the vast amounts of regulatory data generated by the program. The goal would be to produce a computational map of gene regulation in the brain, similar to something **GeneLogic** [GLGC] is pursuing.

Parkinson's disease, characterized by the selective demise of specific neurons in the brain, impairing motor functions, is another area of focus for Cogent. Effective drugs might well turn on neurodegeneration, the same principles at play in stroke. The disease affects only a small cluster of neurons localized in a narrow band deep in a part of the brain called the substantial nigra. When these neurons don't work, they fail to release the neurotransmitter dopamine, which aids in smooth muscle activity. Symptoms include uncontrollable episodic trembling, rigidity, lack of balance, and slowness of movement. By the time these symptoms are made manifest, more than 75 percent of crucial motor neurons are lost.

The current treatment is to deliver dopamine to the brain. But these drugs have severe side effects,

The State of the Market

The market has been rough on biotechnology stocks in recent months and unkind to our three favorites: **Sequenom**, **Vertex Pharmaceuticals**, and **CuraGen**. Meanwhile, their technology has only grown more compelling.

CuraGen's stock has steadily eroded ever since we picked it at around $17 and recently tumbled as low as $7.50 before recovering a bit. Wall Street has soured on the technology leader, largely because the company is in such early stages of its search for new drugs. With nothing but preclinical news ahead for at least the next six months and maybe as long as a year, Wall Street figures that CuraGen's shares will be trading in line with overall negative sentiment on genomics companies. CuraGen's book value is $6.90, and the company is trading at cash value.

Vertex Pharmaceuticals has been on a roller coaster ride this past month, first shooting to over $30 per share over two weeks, and then sliding back under $20 in just a matter of days. The moves in both directions were driven by a product called pralnacasan. First, Wall Street bid up Vertex's shares on rumors of impressive results from a phase 2 study. Then investors dumped shares after the study's results appeared underwhelming. Actually, the results were the predictable outcome of several trial-specific parameters, rather than the drug's activity. The study proved pralnacasan's safety, pharmacokinetics, and efficacy. Our long-term view of Vertex, or the drug, hasn't changed. You don't buy Vertex for any one product, but a deep pipeline and demonstrated ability to generate novel compounds and move them into the clinic. Vertex still has the best technology.

Sequenom's stock price has been battered down because one of its venture investors, in need of cash, has been dumping shares. Meanwhile, Sequenom just moved its first product into clinical development,

reverse symptoms only temporarily, and slow but don't halt progression. Eventually, patients develop resistance, making the drug less effective.

Cogent, employing its functional analysis of genes active in the brain, is seeking to isolate the pathways involved in the activation and demise of these dopamine-producing brain cells. The company has already identified 400 genetic regulatory sequences in living brain tissue, some implicated in Parkinson's, and is making provisional patent filings on more than 200 of them.

Long term, Cogent plans to develop its own proprietary products. Near term, it is charging Big Pharma companies to use its industrial scale high throughput system for their own R&D. And mid-term, it is building a drug discovery program centered on the eye. Turns out, the genomics of the eye and brain are similar; in embryo, a part of the developing brain juts out to form the eye. Cogent has focused on the genomics of glaucoma, which, like stroke, is an ischemic disease. The eye could benefit from the same neuroprotective interventions that Cogent is designing for stroke, and it's a more druggable body part than the brain because it's more accessible. That makes it a more feasible near-term market for a small company.

One of the best applications of neurogenomics is Alzheimer's. That leads us to our other favorite company, Elan Pharmaceuticals.

Alzheimer's is becoming a bright spot in a field that has resisted substantial clinical progress for more than a decade. Scientists have already characterized a number of genes and proteins they believe are involved in Alzheimer's (Elan has done many of them). The gene *apoplipoprotein* (ApoE) is a major risk factor for the disease. Venter revealed in the *New York Times* recently that he has the gene and that he's now taking the cholesterol-lowering drug Lipitor to decrease his chance of contracting the disease. Scientists have also developed better animal models of Alzheimer's. As a result, several treatments are close to or in clinical trials.

Unlike most CNS diseases, Alzheimer's has a rare familial form, making the implicated gene easier to isolate and study. Yet even this bright spot illustrates the inadequacies of our current treatment paradigms. Sales of drugs for treating Alzheimer's were $853 million in 2000, almost all of it due to one class of medications that work by inhibiting cholinesterase, which in turn blocks the breakdown of the neurotransmitter acetylcholine. Lack of acetylcholine is believed to be the main cause of

which we believe is the first drug ever to be developed purely from population genomics. Sequenom's genotyping technology remains the industry's platform of choice. While many of its peers are suffering from a slowdown in spending on instruments, Sequenom continues to exceed expectations. The company is still sitting on the most diverse set of clinically well-characterized populations. Wall Street has barely shrugged.

CuraGen, Vertex, and Sequenom are all young companies that have made significant progress in a short time. The price pressure is a measure not of the companies, but of Wall Street's determination to dump any biotech companies that are not already generating steady earnings or lack a bevy of products in the late stage of clinical development.

By contrast, we look for companies with core technologies that will power sustainable products over time. We look at their pipeline in large part as a measure of the long-term potential of their technology. With Wall Street so focused on product, this platform story is out of vogue.

One reason we like CuraGen and Vertex is the meticulous process by which they develop and validate their drug leads. The best thing they can do is to take their time with their most promising candidates. Rushing a compound into clinical development might satisfy Wall Street in the short term, but it will hurt much worse later if a product blows up in trials. Much of the point of rational drug design is to avoid wasting money in costly trials on unqualified prospects. The deliberate methodologies employed by Curagen and Vertex will result in more and better drugs down the line. We don't want them to hurry that process.

For us, the real news from the Street is that some of our favorite companies are trading at discounts, even as their technology is being borne out in the clinic. That's a compelling story. **B**

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Elan's Alzheimer's Milestones

- October 1988: First description of the amyloid protein precursors comprising characteristic plaques found in the brains of patients with Alzheimer's.
- September 1989: Determines that the newly discovered amyloid precursor protein turns out to be a previously characterized protein called protease Nexin II.
- March 1990 and June 1990: Elan describes the process by which these proteins are processed by the body.
- June 1990: Co-discovers one of the first mutations in the gene that is responsible for production of the protein and known to cause disease.
- February 1992: Describes an early description of the toxicity of this protein when it's administered to cultured neurons.
- September 1992: Describes the surprising discovery that the protein is produced by all cells at low levels and is secreted into cerebrospinal fluid, blood, and media of cultured cells. This finding heralded the beginning of drug discovery for inhibiting its production.
- November 1992: The first description of the inflammation which is invariably seen in the brains of patients with Alzheimer's dementia.
- December 1992: Describes the fact that patients who have the so-called "Swedish mutation in APP" will likely get Alzheimer's dementia because they are overproducing the protein. This is heralded as a very important finding that supports the amyloid hypothesis. The results are published in the journal *Nature*.
- January 1993: Elan researchers found evidence that there is a clip in the gene needed to release the protein. Elan researchers coined the name for this cleavage as "secretase." These results are also published in the journal *Nature*.
- February 1995: Elan researchers successfully characterized a genetically engineered mouse that overproduces the mutant protein and produces Alzheimer's dementia pathology in mice. This is also published in the journal *Nature*.
- June 1995: Elan researchers discover the reduction of A42 in the cerebrospinal fluid of patients with Alzheimer's disease.
- March 1996: Elan introduces the first Alzheimer's-specific tests to aid neurologists in the differential diagnosis of the diseases, redefining the diagnostic protocol.

cognitive impairment in Alzheimer's. These drugs do no more than slow the progression of symptoms and can bring severe side effects. Yet the dramatic climb in sales of Aricept, the classic drug treatment, reveals the demand for anything that can help.

Elan Corporation [ELN] has made some of the most significant Alzheimer's discoveries to date. In the January 2001 issue of the *Journal of Neurochemistry*, it described a novel class of compounds that demonstrate an in vivo reduction of the protein beta-amyloid peptide. The buildup of beta amyloid in the brain is believed to be responsible for the disease. The inhibitor that Elan has contrived offers the most promising avenue for treating this disease yet to emerge.

Ever since Enron became the Betty Crocker of cooked books, Elan's stock prices have been battered by concern over its own accounting practices. Elan's net income has grown largely through a combination of purchase acquisitions, circular joint ventures, and other sources of lower quality revenue. More than 50 research-and-development joint ventures allowed Elan to simultaneously shift R&D costs off its balance sheet and book revenue long before the ventures developed any products. In one typical deal, Elan invested $20 million in a joint venture partner and the joint venture itself, which immediately paid Elan $15 million for a "medical technology license." The $15 million was booked as costless revenue; the $20 million showed up as a balance sheet asset. Sound fishy? The Street hates it and short sellers have had a field day. Also unhelpful was the suspension of one of Elan's advanced clinical trials for a highly touted Alzheimer's vaccine, after four of 97 patients in France were reported to have clinical signs consistent with inflammation in the central nervous system.

Elan has to straighten out its accounting and its PR. But current earnings, phantom or otherwise, or even one vaccine, are not the reasons to buy Elan. The company Elan is sitting on a mountain of intellectual property, which is why we're interested. (See the accompanying chart for their major discoveries). It is a leader in the geography of the brain, region-specific processing in the brain, and cellular aspects of neurogenesis and degeneration. Now might be a good time to pick up this IP while it's cheap.

Elan is collaborating with **Pharmacia** and **Upjohn** to develop blockers of beta secretase, the enzyme believed responsible for the buildup of the

protein beta amyloid, believed responsible for Alzheimer's. (**Vertex** [VRTX] is also working on a beta-secretase inhibitor). Elan is also heavily invested in neurogenomics, having collaborated with the two leading start-ups in this space: Cogent and **Neurome**. (Keep your eye on Neurome. It's a privately held California biotechnology company that is building databases that quantify the molecular patterns of the brain, region-by-region, and circuit-by-circuit. We like their technology, but they're not as close to developing drugs as others.)

Elan already has products on the market and steady revenue. Its multiple sclerosis drug Antegren is currently in phase 3 trials in collaboration with **Biogen**. Elan plans to file for approval in 2004 and just invested $60 million in a biopharmaceutical plant in Southern Ireland for its manufacture, a welcome expression of confidence.

Elan's first quarter results, released May 2, were below Wall Street's expectations, with earnings per share at 22 cents versus estimates of around 34 cents. While Elan's key brands performed well, its MyoBloc botulinum toxin continues to sell poorly, and the results of its new launch of Frova into the crowded migraine market remains to be seen. The near-term new product pipeline also remains skimpy, all additional reasons why Elan's stock price continues to remain under pressure.

One of the big things weighing on Elan's stock is a debt instrument that's convertible for stock in the next year. Some investors believe this could strap the company with a liquidity crisis, so they're staying away. But Elan's new management should be able to take aggressive action to buy the debt back or swap it for some stock before it faces a squeeze, and they have the cash on their balance sheet to do it. Wall Street should react favorably to such a move.

But we are interested in Elan not for its near term pipeline, but for its rich intellectual property position in the neurology market, which will become perhaps the hottest of all biotech sectors in the next few years. All the companies, Big Pharma and biotechs alike, are developing pockets of expertise in specific disease areas—cancer, neurology, and cardiology, among the largest. The drug industry is reorganizing itself by such disease categories. Gone are the days of one big pharmaceutical company developing products in dozens of different diseases and indications. In the near future, patented data such as proteins and genetic markers will be the mother's milk of drug research. Companies will identify themselves according to where they own the most IP.

In neurology, we believe Elan has a commanding position. All the negative news has left it with a compelling valuation. Wall Street remains wary. We agree there are some bumpy stretches ahead, including a pending SEC investigation. Most of the bad news is priced in. Long-term, Elan's commanding IP is going to make it a leader.

The frequent claims of victory by the gene-sequencers of the Human Genome Project have produced genome fatigue. Investors and the public have grown tired of hearing about the genome's promise, and some investors have switched from pumping what they don't understand to dumping it.

Wise investors will not lose perspective. The sequencing of the human genome is both the cause and effect of a technological revolution that is sweeping through biotechnology and will fundamentally alter medical care. For the past decade, neuroscientists—using techniques such as functional magnetic resonance imaging, brain mapping, and electrodes—have been making slow progress in understanding the anatomical and functional structures of the brain, as well as the electrical circuitry. All that effort hasn't translated into a deep understanding of the molecular level of disease, or the development of new therapies for some of the most devastating CNS disorders. But the tools and IP being developed by Cogent and Elan are unthinkably smarter, faster, and more sensitive than anything available to biologists only a few years ago.

The drug industry is reorganizing itself by disease categories

Consider the drug industry's inherent vitality. The world's appetite for useful pharmaceuticals shows no limits. It is only the old methods of drug development that are limited. Big Pharma may hit a slow growth patch as they retool development and marketing to make up for pipelines notoriously lacking in blockbuster drugs. But they will enjoy a demographic tailwind in the United States and most other developed countries for decades. Extended life span means people stay older, longer, and they'll rightly demand all the drugs that help them exercise their God-given right to a pain-free, fun-filled, life.

Genomics will provide answers to problems that haven't been resolved by more traditional methods and lead to drugs that halt disease and even reverse it. The technological leaps that enabled the sequencing of the genome parallel the miniaturization of electronics from the vacuum tube to the first microprocessors.

We launched this letter last year because we believed it was finally time for biotech, enabled by the progress of Moore's law and the abundance of genomic research on which to apply in silico tools, to deliver real results. In no area is this more true than neurogenomics. Without genomics, neuroscience has been stalled because the brain is the most complex biological process in the body. That very complexity is the reason to expect that genomics will provide the key to understanding and to cures. Neurogenomics is finally here and the rewards for our patients and our species will be truly profound.

Scott Gottlieb
May 8, 2002

BIOTECH COMPANIES

Company	Technology Leadership	Reference Date	Reference Price	5/2/02 Price	52-Week Range	Market Cap
Cogent Neurosciences (none*)	Neurogenomics	5/2/02				
CuraGen (CRGN)	Cellular Signalling	3/13/02	17.67	8.70	8.43 - 41.34	424.7M
Elan Corp. (ELN)	Neurogenomics	5/2/02	$11.15	$11.15	10.40 - 65.00	3.6B
Gilead Sciences (GILD)	Rational Drug Design	12/05/01	33.88**	33.10	22.50 - 39.00	6.41B
Human Genome Sciences (HGSI)	Cellular Signaling	10/26/01	43.97	15.45	14.75 - 77.00	1.94B
MDS Proteomics (none*)	Proteomics	2/05/02				
Nanogen (NGEN)	BioChips	10/2/01	4.95	3.64	3.00 - 10.60	79.4M
Quorex (none*)	Rational Drug Design	12/05/01				
Sequenom (SQNM)	Pharmacogenomics	1/09/02	9.00	5.70	5.15 - 18.70	213.6M
Triad Therapeutics (none*)	Rational Drug Design	4/9/02				
Vertex (VRTX)	Rational Drug Design	9/17/01	28.60	20.75	15.50 - 52.25	1.52B

* Pre-IPO startup companies.

** Split-adjusted price.

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.

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