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IN VIVO

Neuronetics Brightens Outlook For Neuro Devices

The neuromodulation company spent its first five years developing, testing and obtaining FDA approval for its transcranial magnetic stimulation system as a treatment for depression. Now, the company is applying the same steadfast approach to getting insurers to pay for the treatment.

By Tom Salemi / [Email the Author](#) / [IN VIVO May 2012, Vol. 30, No. 5](#)
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Executive Summary

Neuronetics Inc. forged a new specialty of sorts, the interventional psychiatrist. Unlike other interventional approaches, the externally applied *NeuroStar* delivers transcranial magnetic stimulation to the precise area of the brain responsible for intractable depression. The device is changing the lives of psychiatrists who launched “TMS” clinics, hoping to capture the early success, and potentially creating opportunities for medical devices designed to treat other brain-related disorders.

- For over a decade, researchers have hinted that transcranial magnetic stimulation of the prefrontal cortex could alleviate the symptoms of many diseases of the mind, including depression.
- Neuronetics was founded to develop a reliable TMS system that could prove, once and for all, that magnets can repeatedly and reliably help depression patients who don't respond to drugs. The company's *NeuroStar* system cleared the FDA in September 2008.
- With FDA approval behind it, Neuronetics has sold more than 400 systems to psychiatrists, including many who have built new practices around the promise of TMS and the potential of a new specialty, interventional psychiatry.
- Now the company is trying to reach more physicians and the US and is considering its options internationally. To broaden its US base, Neuronetics will need to continue to change the mind of insurers who have been slow to adopt payment policies for TMS.

A medical device, on occasion, can spawn a new specialty. A clever engineer designs a device or implant small enough to be deployed by those skilled with a guidewire and catheter, enabling an interventionalist to reach an organ previously accessible only through surgery. Over the past decades, these advances have helped minimize the physical impact of treating a blocked artery, fractured vertebrae or a dangerous spot of cancer. [Neuronetics Inc.](#) is an unlikely contributor to this movement. The nine-year-old neurostimulation company created a device capable of safely reaching one of the most remote areas of the body – the brain. And, in doing so, the company created a new specialty of sorts, one that carries a somewhat contradictory tag – the

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interventional psychiatrist.

Unlike other interventional approaches, Neuronetics' *NeuroStar TMS Therapy System* doesn't require an entry incision to access its targeted organ. Instead, the externally applied NeuroStar delivers transcranial magnetic stimulation, alternative waves of magnetic pulses, to the precise area of the brain responsible for deep, intractable depression, the kind of disease that's resistant to medication. (See "[Neuronetics Inc.](#)" — *START-UP*, February 2005.) In those drug-resistant depression cases, Neuronetics reports seeing success roughly half the time, with one-third of TMS recipients going into complete remission. In this case, the "interventional" approach isn't an alternative to highly invasive surgeries – as most interventional movements tend to be – but rather a successful treatment that replaces a lifetime dependence on anti-depressants and other pharmaceuticals, which come with side effects and dependencies that offer their own sets of risks. TMS also may help stave off invasive electro-shock therapy treatments and their deleterious side effects.

Neuronetics finds itself sitting at an interesting intersection of drugs and devices. Having sold some 400 capital equipment devices in the US over the past three years, Neuronetics has famously changed the lives of thousands of patients, earning it reels of free publicity. It was recently featured, for example, on the nationally syndicated Dr. Oz show. But the device also is changing the lives of psychiatrists. Many have left their traditional practices and launched "TMS" clinics, hoping to capture the early success and optimism surrounding a treatment that promises lasting – and perhaps permanent – relief for an often debilitating disease. The creation of these clinics – owned and staffed by psychiatrists with an eye toward using devices to treat mental illness, potentially creates opportunities for medical devices designed to treat depression, migraines or other brain-related disorders.

Neuronetics itself, while keeping its eye on the ball with unipolar depression, also has future designs on using TMS energy to help cure tinnitus, pain, and other conditions. But the future of the company – rather than just the future of its business – is perhaps more compelling. With revenues building and reimbursement agreements beginning to line up, Neuronetics is positioned well as a potential acquisition by a large medical device company. Just over the past year, two companies – [Greatbatch Inc.](#) and [Boston Scientific Corp.](#) – have acquired device companies with implantable deep brain stimulation technologies, NeuroNexus Technologies Inc., a privately held producer of neural mapping technology and stimulation leads, and Intellect Medical Inc., the developer of a DBS programming system that promises to improve the targeting precision of its Vercise DBS therapy, respectively. [[See Deal](#)][[See Deal](#)] (See "[Deep Brain Provides Stimulating Market](#)" — *START-UP*, March 2012.) These are implantable products requiring the expertise of specialized neurosurgeons. But with a non-invasive therapy, the company could draw interest from another class of acquirer entirely. Pharmaceutical giant [Pfizer Inc.](#) co-led the company's \$30 million Series E round last year, making Neuronetics one of only two device companies in which it's invested. [[See Deal](#)] ([NovoCure Ltd.](#) is the other.) [[See Deal](#)] Barbara Dalton, head of Pfizer's corporate venturing unit, says, "These are definitely novel, interesting and very different approaches to provide patients with therapeutic benefits. Those of us in the pharma industry need to be paying attention to these areas to see how they are going to grow and merge potentially with our historic businesses or become the businesses of the future."

As the old saying goes, Neuronetics could be acquired but it isn't for sale. Founded in 2003, Neuronetics is now beginning to hit its stride. The company has raised \$128 million over five rounds of capital investment over the past nine years. With that money, the company has successfully run its Neurostar device through a complicated interaction with the FDA, obtaining approval in 2008. (See "[Neuronetics' FDA Nod Opens Doors to New CNS Market](#)" — *START-UP*, November 2008.) With a non-surgical device, Neuronetics has earned the distinction of being the first of the class of venture-backed neurostimulation devices to obtain regulatory approval. In fact, nearly four years later, it remains the only company to secure FDA approval, underscoring the challenges that the other, implantable devices face in targeting diseases that have largely been served by drugs. The company continues to blaze new trails, securing reimbursement codes from the American Medical Association for TMS treatments for drug-resistant depression. The final test may be the largest; convincing insurers – including Medicare – to pay for the treatment. But the company is reporting enough progress in that area to conclude that broad reimbursement approval may not be a matter of if, but a matter of when.

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The Power Of TMS

With a growing list of willing insurers, Neuronetics is close to completing the journey it embarked upon 10 years ago when the Innovation Factory acquired the proprietary rTMS technology from [Neotonus Inc.](#), which began in a different disease. Neuronetics' coil design was invented by neurologist Charles M. Epstein, MD, PhD at [Emory University](#). Neotonus had licensed the technology with an eye toward developing a treatment for incontinence. But the Innovation Factory saw a larger opportunity in drug-resistant depression. For years prior to the company's founding, researchers had tested and touted TMS' role in treating depression. Mark Demitrack, MD, chief medical officer for Neuronetics, says more than 1,000 patients with depression had been involved in more than two dozen randomized studies testing how they might benefit from TMS, with the largest trial involving only 60 patients. "Research in the use of TMS in depression began in earnest starting in the early 1990s," recalls Demitrack, a psychiatrist and former senior executive at Wyeth.

By the time Neuronetics started, the early researchers had drawn several conclusions. First, the most effective dosing required larger field strength with multiple pulses over a longer period of time. The left pre-frontal cortex of the brain was pinpointed as the ideal target. "Neuroimaging provided significant evidence that it actually led to metabolic changes in the relevant structures in the brain that were presumptively involved in mood regulation. These data provided important circumstantial biological evidence to support the claim that it's actually doing something to the brain." Demitrack says the only component missing from making a compelling clinical case was a large, well-controlled trial with an FDA-approved design.

Neuronetics set out to refine Epstein's TMS technology and undertake such a study. Dan Sachs, a partner at Investor Growth Capital, worked with Bruce Shook, now President and CEO, to create Neuronetics and develop the Neotonus technology, thus supplying the final missing clinical piece. The company raised a \$16.5 million Series A, a reasonable sum to carry the product into clinical trials. Shook says the total spoke to the "quality of the opportunity, the magnitude of the unmet need, and the fact that we had a running start in the sense that we already had some data to look at." The design of the trial took some time as the FDA didn't have much experience with device therapies for depression. Electroconvulsive therapy (ECT), of course, had existed for years, but it's a treatment of last resort that uses electrical current to induce seizures in the brains of anesthetized patients. In fact, Neuronetics used ECT as a predicate for pursuit of its 510(k) notification.

[Cyberonics Inc.](#) also had a brief foray into neurostimulation treatment of refractory depression. The company used its implanted Vagus Nerve Stimulator to deliver mild electrical pulses to the vagus nerve in the neck. In 2005, after spending considerable time and money conducting clinical studies in the area, Cyberonics became the first company to gain FDA approval for the use of an implantable neurostimulation therapy to treat chronic, refractory depression (eligible patients must have failed four or more antidepressant treatments). Like Neuronetics, the precise mechanism of effect wasn't known, but it was believed to impact serotonergic neurons in the brain to regulate mood and improve response to antidepressant drugs. However, Cyberonics struggled to get insurers to pay for the procedure. (See "[Cyberonics' Two-Front War](#)" — *IN VIVO*, March 2006.) In 2007, Cyberonics restructured its business and made the decision to refocus its sales and marketing resources on epilepsy instead, a testament to the difficulty of a neurosurgical approach to depression. (See "[New Avenues in Neuromodulation](#)" — *Medtech Insight*, June 2010.)

Huge Market For Depression

The size of the depression market certainly is significant. According to the [US Department of Health and Human Services' National Institutes of Health](#), 21 million American adults (nearly 10%) will struggle from depressive illness. Depressive episodes may last up to two years, and antidepressants treat only a minority of those patients, sometimes bringing along debilitating side effects. According to the World Health Organization, depression is the fourth most disabling illness worldwide and will be the second leading cause of disability by the year 2020. The NIH projects that 10 percent of men and up to 25 percent of women will experience depression in their lifetime, which will leave them performing poorly at work, in social situations and at home. With depression accounting for 70% of psychiatric hospitalizations and about 40% of suicides, the cost of depression in the United States in the year 2000 was estimated to be \$83 billion, including both

\$26 billion in costs of treatment and \$57 billion in losses such as absenteeism, reduced productivity at work, and the value of lifetime earnings lost due to suicide-related deaths, according to the NIH.

Neuronetics and the FDA agreed upon a pivotal trial, begun in 2004, involving more than 300 patients at 23 sites (20 in the US). Neuronetics' efforts were aided by Demitrack, who had been recruited from the pharmaceutical industry to become the company's seventh employee and chief medical officer. Demitrack had served as assistant vice president of neuroscience at Wyeth, where he directed post-marketing clinical development in support of the *Effexor XR* brand of antidepressants. Before joining Wyeth, he was medical director for the antidepressant efforts at Lilly Research Laboratories. He oversaw the registration development and NDA submission of duloxetine. "He had a wealth of experience designing and running depression trials," Shook says. "He made everybody confident that we could pull this off. "

Demitrack says he didn't leave the pharmaceutical industry lightly. But Neuronetics presented a "paradigm-shifting" opportunity to treat depression. Existing depression medications are variations on a theme, he says, either re-uptake inhibitors or receptor antagonists. "They deal largely with tried and true mechanisms of action," he says. TMS, on the other hand, is a novel therapy with novel mechanisms of action.

Neuronetics' NeuroStar system employs a magnetic coil that sits atop the patient's head. (Actually, the coil rests upon a disposable layer called the *SenStar Treatment Link*, providing Neuronetics with a steady revenue stream.) The NeuroStar repeatedly fires small electric currents in the prefrontal cortex of the brain, using magnetic energy comparable to that of a magnetic resonance imaging device. The currents depolarize local neurons, causing the release of neurotransmitters, and activating distant areas of the limbic system. The stimulated regions also show an increase in blood flow and a rise in glucose metabolism; and all of these effects are implicated in improving mood. The evidence of success goes beyond good feelings that patients report. Neuroimaging studies have revealed changes in the cortical metabolic activity in tissue directly stimulated by TMS and in distal networks known to be involved in mood regulation, according to the company. NeuroStar does all this without the typical side effects brought on by antidepressants.

Clinical Challenges In Drug-Resistant Depression

Clinically validating a novel device therapy with a novel, dose-dependent mechanism of action hasn't been easy in drug-resistant depression, particularly since that disease is complicated even when it comes to the well-accepted pharmacological therapies. Neuronetics' initial pivotal trial was a bit of a disappointment. TMS failed to show effectiveness in the overall study population of 301 patients who had failed to benefit from anywhere between one to four antidepressant medication treatments. However, a retrospective view of the patients in the trial revealed that TMS did help 164 patients who had previously failed only one drug regimen in their most recent bout with depression lasting up to three years. Of these patients, 22.1% experienced an average reduction in their depression symptoms compared to a 9% average reduction of depression symptoms in patients receiving a sham treatment.

Once efficacy had been established in the controlled trials, results of open label studies helped to clarify the potential magnitude of clinical success in practice, say company officials. Demitrack noted that while randomized controlled trials are the gold standard to establish definitive evidence that a new treatment works, these studies generally underestimate the potential magnitude of effect in the real world because of the artificial nature of the blinded conditions of the controlled study. To provide a more accurate estimate of what to expect in routine practice, he continues, researchers typically observe the outcomes in open label studies, which are much more reminiscent of real-world clinical practice, where both patient and physician are openly aware of the treatment being used. Demitrack suggests open label studies better reflect the actual medical experience. "In the real world, when you go into the doctor's office, you know what you're getting," he says. "The doctor is hopeful that you're going to get better. You're hopeful you're going to get better, everybody's hoping for improvement. So generally, in real life, you get the benefit of both the intrinsic effect of whatever treatment you're getting, and also the additional beneficial non-specific effects of the doctor's bedside manner and your hope for the future, and that sort of thing." In the open label study conducted by Neuronetics, roughly half of the patients reported

improvement while one third of them went into complete remission at the end of six weeks

The Neuronetics cause got some help from another NIH study – the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study. The NIH's [National Institute of Mental Health](#) funded the nationwide trial to determine the effectiveness of antidepressants in patients who haven't responded to an initial treatment with an antidepressant. The NIH billed the seven-year, 4,000-patient study as the "largest and longest study ever done to evaluate depression treatment." According to Demitrack, each patient in the Star-D trial started with the generic drug, citalopram (manufactured by [Forest Laboratories Inc.](#)). Patients who didn't respond then could choose up to four medications from a menu of additional medicines. There are roughly 20 different types of antidepressants as well as several styles of counseling used to treat depression. STAR*D, Demitrack says, was one of the first national efforts to shine a light on the issue of treatment resistance. "There wasn't a lot of data on the use of treatments in people who were treatment-resistant, which is exactly the types of patients we were studying," he says. "It really underscored the inadequacies of currently available treatments." Just under 30% of the patients achieved remission with *Celexa*, the first line of treatment, and the remission rates downright plummeted in patients who were switched to their second, third and fourth rounds of drugs, dropping to 21%, 15% and about 7% respectively. For a company with a device that might help those non-responsive populations find relief, the trial sent a powerful signal. "The STAR*D data came out right when we were in the midst of our FDA review. And you can well imagine we made sure the FDA reviewers were aware of the data as it was coming out so that they could really have a reasonable benchmark to gauge the results we were seeing with TMS. It was a very, very useful study to us."

Still, the 510(k) notification didn't come easily. Neuronetics seemed to embody the medical device struggles with the agency, particularly concerning innovative technologies and approaches that didn't fit neatly into existing niches. Leslie Bottorf, general partner at Onset Ventures, says she anticipated Neuronetics would need only a 510(k) notification when she invested in the company's first round. Bottorf says the company knew clinical trials would be necessary at some point. The company would either need clinical data to convince the FDA to issue approval, or it would need the clinical information to sell the idea to psychiatrists. "It was maybe even harder and took more time and money than we thought," Bottorf says. "Depression trials are not easy." Bottorf says the early syndicate lists were long, because "we knew it was going to be a big and challenging trial, so we syndicated it widely, and we were able to do that trial successfully."

Neuronetics sought the 510(k) citing electroconvulsive therapy (ECT) as a predicate. As noted, ECT is seen by physicians as the last potential treatment for patients suffering from intractable depression. In ECT, physicians use electrical current to induce seizures in patients under anesthesia. As with TMS, the physical impact of ECT on the brain isn't understood, but the procedure can lift patients from their depression.

Karl Lanocha, MD, a neuropsychiatrist, spent 20 years administering ECT before opening his own practice with a NeuroStar device. Lanocha says the side effects of ECT are a concern, with the two most worrisome being amnesia (both retrograde and anterograde) and a potential drop in IQ. "ECT is a great treatment, and I did it for 20-some years, but it is not benign," he says.

Neuronetics initially positioned TMS as a safer alternative to ECT, although admittedly less effective. Bottorf says Neuronetics asked the FDA – which would convene an advisory panel – to rule on the risk-reward benefits of TMS vs. ECT. Eventually, the advisory panel couldn't reach a decision, so the FDA directed Neuronetics to file for a de novo 510(k), a relatively new path created in 1997 for devices with no clear predicate but a demonstration of safety. CEO Bruce Shook says the FDA approved TMS for patients who have undergone at least one round of antidepressants in the most recent bout of depression. That was all the opening Neuronetics needed to begin selling the device.

Creating A New Kind Of Psychiatry Practice

Many psychiatrists had long been waiting for TMS. Karl Lanocha, the neuropsychiatrist who now owns a TMS clinic, had been medical director for psychiatric services at a New Hampshire hospital. He handled inpatient flow, wrote prescriptions, administered ECT; he did it all. He says he first became aware of TMS in the mid-1990s when he read about early research in an ECT

journal. "I kept an eye on that research and eventually it became clear that it was just a matter of time before TMS would become a routine part of clinical psychiatry," Lanocha says. At his urging, the hospital placed an order for a NeuroStar. In fact, Lanocha says he was responsible for the first order placed in 2006. That year he trained at the Berenson-Allen Center for Noninvasive Brain Stimulation in Boston, an affiliate of Beth Israel Deaconess Medical center, expecting the device to be cleared by the FDA sometime that year. The back and forth with the FDA extended into 2008, but Lanocha finally got his machine. "We took delivery of the device, got the training, and struggled to find patients to treat," he recalls. TMS was still new, and, without insurance coverage, it was expensive.

But the patients started to come, including some people with very resistant depression that he'd been treating for years. After treatments with NeuroStar, things improved. "I was frankly astounded by the results that I was seeing," he says. "I very quickly came to realize that TMS is not just an incremental improvement over what we already have. It's not like a new antidepressant that comes out every couple of years."

Lanocha says he wanted to spend more time administering TMS, but the treatment schedule is largely incompatible with a general practice. TMS patients spend an hour in a chair, receiving the magnetic treatments. They're required to come in daily for a month or so to ensure the changes take hold. This is a significant departure from the standard psychiatric visits, which involved a 15-minute appointment every few months to adjust medications. Lanocha says his responsibilities at the hospital wouldn't allow it. The psychiatric clinic was short-staffed, and his partner of the previous eight years left to pursue a more attractive field of medicine. "My hospital position didn't allow me to devote the type of time and energy to TMS that I thought it deserved," Lanocha explains. So he discussed the particulars with his wife, and then decided to go out on his own.

To device executives and investors, such a move might seem commonplace. But it's not so for a tenured department chairperson. "You have to understand how much of a gamble this was," he says. "I was leaving a very well paid position that I had held for 20 years. I was chairman of the department. I did some demographic research and determined that I had to locate this practice in a city 60 miles from where I live, where I had no presence in the medical community. I would be offering this new treatment that no one had ever heard of, which was expensive and not covered by insurance, and I still had two kids in college. So it was a real gamble." Then why do it? "Because in the 25-plus years (at the time) that I had been practicing psychiatry and in a setting where I had a lot of exposure to patients with treatment-resistant depression, this was the most effective treatment that I'd ever seen, in terms of it not only allowing patients to get better, but to actually get well."

The NeuroStar has liberated psychiatrists who have been bound to a single style of delivering medicine. Dr. Randy Pardell calls TMS, "a breakthrough in my practice." Prior to the introduction of NeuroStar, he was "a very busy psychopharmacologist seeing lots of patients." Since the approval of NeuroStar he splits his time between prescribing medication and delivering TMS. He now operates two centers in upstate New York, each equipped with its own NeuroStar machine. Like Lanocha, Pardell says the early days were grim. But today, "From the business standpoint, I think it's something that has been beneficial to my bottom line as well. I'm not losing money; I'm making some money in doing this, and I've expanded to the point where now I've opened up a second place in Saratoga Springs. So it is an exciting time. It's helping patients in a different way than in the past, giving patients a level of vitality and clarity that you don't see with antidepressant medications."

With reimbursement not widely available, Neuronetics would appear to have an easier job selling to private practices able to draw clients capable of paying several thousand dollars out of pocket. Ian Cook, MD, director of the UCLA Unipolar Depression Research and Clinic Program, started using a NeuroStar in 2009, soon after it was approved. But he says many larger psychiatric institutions simply aren't equipped to make and manage large capital purchases. "We don't have devices," he says. "We don't have diagnostic equipment. We don't have endoscopes or use CT scanners. We don't have the kind of infrastructure that can comfortably support buying capital equipment." Private practices can sit down with a spread sheet, run the numbers and determine if they can make a go of it, he says.

Kevin Bitterman, general partner at Polaris Venture Partners, which co-led the Series D with

Pfizer, says Neuronetics clearly had reached a “tipping point” last year when the two investors stepped up to lead the round. Polaris certainly was aware of Neuronetics’ efforts to raise earlier rounds but didn’t commit until last year when it saw “the perfect confluence of an enormous market, enormous unmet need, great ground-breaking, first-in-class technology” coupled with the validation from outside sources including the NIMH study. “The clinical community had turned a corner,” he says. Psychiatrists saw TMS as an important piece in their arsenal, he says. “When we were doing our due diligence and talking to docs – because more devices had gotten out there and more patients had started to get treated – you just heard these wonderful stories of patients that had failed six, seven, eight, nine drugs. They were on their way to electroshock therapy and had lost all hope, and TMS is the only thing that worked on them. We heard that again and again. We thought that this was just an incredible opportunity to get behind the company and it’s exceeded our expectations in the year since we’ve been involved.” With investors and physicians fully on board, Neuronetics faces the task of convincing one final – and integral – player: payors.

Getting The Codes

Neuronetics is seeing some success. In January 2011, the AMA assigned two category 1 CPT codes and a third in 2012. (See Exhibit 1.) Previously, the AMA had assigned the more general CPT 3 tracking code that gave patients a chance at getting reimbursed for treatment, but it was a slight chance since insurers were more inclined to refuse payment. Even the CPT 1 code doesn’t guarantee payment. Mary Hailey, vice president of health policy and government relations of Neuronetics says success involves three clear steps: coding, coverage, and payment. “Just because you get codes doesn’t mean you have coverage and payment,” she says. “The codes are a great step in the right direction. But what we’re really working on now is the coverage and payment, and that is an educational process.” Neuronetics is meeting regularly with medical directors at third party payors, explaining how efficacious TMS has been in battling depression.

Hailey comes to Neuronetics after years at Kyphon, and later [Medtronic Inc.](#) following that company’s acquisition of the spinal company. Demonstrating the value of behavioral health treatments is more of a challenge, she says. The company can present data showing that patients perform better following a TMS procedure and they can also supply the imaging studies that back those results up, but the inertia of just using prescription medication is strong. If the medical director at the insurance company isn’t trained in behavioral health, they may be reluctant to adopt technologies that upset the standard treatments. Insurers have been paying upon appeal. Neuronetics provides general reimbursement support to physicians and patients in the reimbursement process.

EXHIBIT 1

TMS Codes Issued By The American Medical Association For Medicare Patients

(Private insurers negotiate their own rates.)

| CPT Code | Description | 2012 Total RVUs (1) | 2012 Conversion Factor(2) | 2012 National Payment(3) |
|----------|---|---------------------|---------------------------|--------------------------|
| 90867 | Therapeutic repetitive transcranial magnetic stimulation treatment; initial, including cortical mapping, motor threshold determination, delivery and management | 11.04 | \$34.04 | \$375.77 |

| | | | | |
|-------|---|-------|---------|----------|
| 90868 | Subsequent delivery and management, per session | 5.33 | \$34.04 | \$181.42 |
| 90869 | Subsequent MT re-determination with delivery and management | 13.64 | \$34.04 | \$464.27 |

(1) Medicare pays for physician services based on RVUs. There are three types of RVUs: practice expense, work and malpractice that, when summed, add up to the total RVUS for the service

(2) The conversion factor is the dollars associated with each RVU.

(3) This is national physician payment rate.

Neuronetics

Insurers clearly are worried about costs. Going by the AMA CPT codes, a round of treatments with NeuroStar could cost over \$4,000, a considerably higher cost than a round of drug treatments. "There is a real fear that if we open up the floodgates, everyone is going to be a TMS patient," Hailey says. "We tell them that not everyone meets the criteria for treatment." But physicians could use the device on patients who don't fit the criteria laid out by the FDA, which allowed Neuronetics to say TMS was effective on patients who failed only one previous round of drugs in their current bout of depression, as clinical trial data suggested. But psychiatrists say the follow-up study by the NIMH combined with the Neuronetics trial shows TMS can have an impact on patients with up to four failed drug trials. "Most of my patients have had multiple trials of antidepressant medications (up to 20 failed medicine trials) without success prior to starting TMS," explains Dr. Pardell in an email. "We are finding that [two-thirds] of our patients are having a significant response to Neurostar TMS therapy with over 40% of responders experiencing complete remission of symptoms. This level of response and remission is replicated at TMS centers throughout the country."

In 2008, a Neuronetics-supported study reported that TMS provided an incremental cost-effectiveness ratio of \$34,999 per quality-adjusted life year. This compares favorably to the \$50,000 "willingness to pay" standard for other depression treatments. The report says the total dropped even further when factoring in productivity gains brought on by depression relief. Bottom line, the report concludes, "TMS is a cost-effective treatment for patients who have failed to receive sufficient benefit from initial antidepressant pharmacotherapy. When used at earlier levels of treatment resistance, significant cost savings may be expected relative to the current standard of care." Neuronetics is also collecting durability data demonstrating how long the effects last. At six months, most patients are still well, Shook explains. "We are in the process of completing a 12-month follow-up study and will have those results early next year," he says. Clearly, insurers haven't embraced this conclusion, but they may do so with encouragement.

The company clearly is building momentum. NeuroStar was showcased on Dr. Oz, the show hosted by New York cardiothoracic surgeon Dr. Mehmet Oz, which gave it enormous visibility. During the segment, Dr. Oz watched as a patient received a TMS treatment and marveled at the effects seen in patients that had been previously been treated successfully. (the treatment effect is not immediate). He asked the audience if everyone had even heard of TMS. No hands went up. "This device has been available since the show launched and not a single person here as even heard about it. How can that be?" Oz asks. Tarique Perera, MD, the psychiatrist controlling the NeuroStar machine on the televised segment, explained that insurers were only covering the device on a case-by-case basis upon appeal. "If I can go from 20 medications to nothing, and feel like I'm better, I would have that conversation with my insurer," Oz encourages. TMS-equipped psychiatrists reported a slight bump in referrals following the Dr. Oz episode, but public discussions like those are more likely to help with insurers.

Neuronetics is gaining momentum. (See Exhibit 2.) In fact, Neuronetics secured its first Medicare contract in March from NHIC, which covers five New England states (excluding Connecticut). Priority Health, a private insurer in Michigan, also issued coverage. Blue Cross Blue Shield of Nebraska also agreed to pay for TMS, following a one-doctor campaign to get the treatment covered. “We laid the groundwork and the foundation by educating them about the technology,” Hailey says. “But he clearly needed to educate them on why it was needed by the beneficiaries of the plans.” Highmark Medicare, which covers Pennsylvania, New Jersey, Delaware, Washington, DC, and Maryland, has a draft coverage policy that hasn’t been finalized yet while several more insurers have agreed to review individual requests for coverage. But cost is a concern. “It’s just tougher and tougher for new technologies,” Hailey explains. “But it’s moving along. We’re starting to educate the larger players. Will they say yes right now? Maybe. Maybe not. But you just have to keep going back in.”

EXHIBIT 2

Insurers Agreeing To Cover TMS

| Insurer | Status | Date of Acceptance |
|--|--------|--------------------|
| NHIC - Medicare contractor covering five New England states (excluding Connecticut.) | Final | March 2012 |
| Blue Cross Blue Shield of North Dakota | Final | May 2011 |
| Priority Health, a private insurer in Michigan, also issued coverage. | Final | February 2010 |
| Highmark Medicare -Covers Pennsylvania, New Jersey, Delaware, Washington, DC, and Maryland | Draft | TBD |

Neuronetics

Future With Competition

Neuronetics’ persistence will ultimately pay off, and not just for the company. The inroads will be in place for a convoy of other companies developing TMS approaches to depression, like **Cervel Neurotech Inc.** and **Brainsway Ltd.** and possibly other diseases as well. In depression, Eric Meier, CEO of Cervel, says the company currently is running clinical trials on its “steerable TMS,” a technology platform licensed from **Stanford University**. If successful, the company’s TMS system would be able to reach deeper parts of the brain, he says, enabling it to treat depression and other conditions as well. Meier credits Neuronetics for educating physicians, patients and insurers. “We believe it’s opened the way for other companies such as ours,” he says. “There are plenty of opportunities for good companies to succeed here.”

Time will tell, but it’s clear Neuronetics will need to keep pushing forward to keep its hold in the market. Cervel and Brainway both may enjoy a technological advantage if they get their systems onto the market. Yiftach Roth, Ph.D., one of the founders of Brainsway, says its deeper TMS can reach points four of five centimeters into the brain, versus one to two centimeters by more superficial systems “The cortex on the medial prefrontal cortex, which is the target for many psychiatric disease, can’t be reached with standard TMS,” Brainsway’s Roth told our sister publication, *START-UP* magazine. Shook acknowledges there is “much discussion about deep TMS. Neuronetics reaches 3 cm, he says. But he says there’s still no clear benefit to going deeper. He also suggests the deeper approach might bring on more side effects, such as seizures. “Bottom line,” Shook says, “the jury is still out on this approach.”

Neuronetics also is pursuing other potential treatments with TMS. Last month, the company

released the *NeuroStar Xplor*, a TMS system that will come with multiple coils, including a sham coil. The upgraded coils could be used by academic institutions and researchers to test TMS against other conditions including pain, tinnitus, hallucinations, even Parkinson's.

Neuronetics' hold on the TMS market also could be threatened by a company that comes out with a cheaper system, or at least a system that doesn't require a \$100 disposable for each use. Lanocha, who says he placed the first order for a NeuroStar, says he's committed to the system. But, "if there were a company that was able to offer a machine of comparable quality at half the cost, and if I was just starting out, then that might be a different story," he says. Kevin Bitterman, the investor from Polaris, says Neuronetics clearly is the leader. "But the company is operating in anticipation of others entering the market, keeping an awareness that we're not always going to be an only-in-class technology here and a focus on making sure that we're always the best-in-class technology." This will be realized in terms of the quality of the actual product, the quality of customer service, and in terms of innovation, he says. "We want to make sure that Neuronetics stays on the cutting edge, and when others enter the market, that we're still the company that folks turn to for TMS. I'm more than confident that the company is going to be able to do that." Neuronetics also is eyeing a move into international markets, including Asia and Europe.

But, above all else, Neuronetics customers say they want the company to work harder to raise the profile of TMS. "I'd like to see more of a national marketing campaign where they get the word out," Pardell says, "so you can see it in periodicals like *People* magazine and *Ladies Home Journal*." The campaign should raise awareness of TMS, he says, while dispelling any concerns over safety. Neuronetics, however, continues to take a more indirect route to advertising, employing web sites and social media. Shook says Neurostar's budget is too small to promote TMS in mainstream media. Small companies can't afford the national ad campaigns used routinely by pharmaceutical companies, "which is what our customers are used to seeing." Suzanne McMonigle, vice president of marketing, says the company is concentrating on its website, ensuring that it is up-to-date and able to answer questions about TMS and NeuroStar. Its exposure to social media is limited, but advertisements running on Facebook have proven to be a good source of traffic. Neuronetics also is coordinating webinars where physicians and patients can discuss the TMS experience. "We have an unbranded site called 'The Depression Hope Center' that allows people to share their stories, and search through those stories to find others like you, to understand what their experience is like. I think that there's definitely opportunity moving forward for that exchange to be two-ways. We'll be looking at tapping into that moving forward."

Neuronetics and TMS may be relatively unknown to the general public, but they've caught the eye of potential partners and acquirers. The company clearly has fans at Pfizer. The pharmaceutical company's Specialty Care Business Unit, which reviews external opportunities for Pfizer, recommended the company to Pfizer's corporate venture unit, according to Barbara Dalton. "We're a strategic-oriented fund and we like to look at adjacencies," Dalton says. "Neuromodulation is a growing area both in utilization and adoptions." Michael Ehlers, senior vice president and chief scientific officer for Neuroscience at the company, states "The transcranial magnetic stimulation technology being developed by Neuronetics holds promise for brain disorders including depression. We may see a future where the combined use of device-mediated and drug-based therapies leads to breakthrough improvements in treating neurological and psychiatric diseases." Pfizer is probably not the only pharmaceutical company to think this way, giving Neuronetics potential leverage against traditional buyers like Medtronic and Boston Scientific, which also could be interested in adding to their neuromodulation line.

Neuronetics could find itself fitting into many organizations, particularly as it helps create a new specialty though which other devices might be sold. Dr. Perera, the psychiatrist appearing on the Dr. Oz show, noted that Neuronetics finally gave psychiatrists a biology-based tool to treat depression. Speaking to Dr. Oz, who happens to be a cardiothoracic surgeon, Perera says, "now we can go in and treat the brain just like you treat the heart." Neuronetics could be blazing a trail for other device companies to follow.

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