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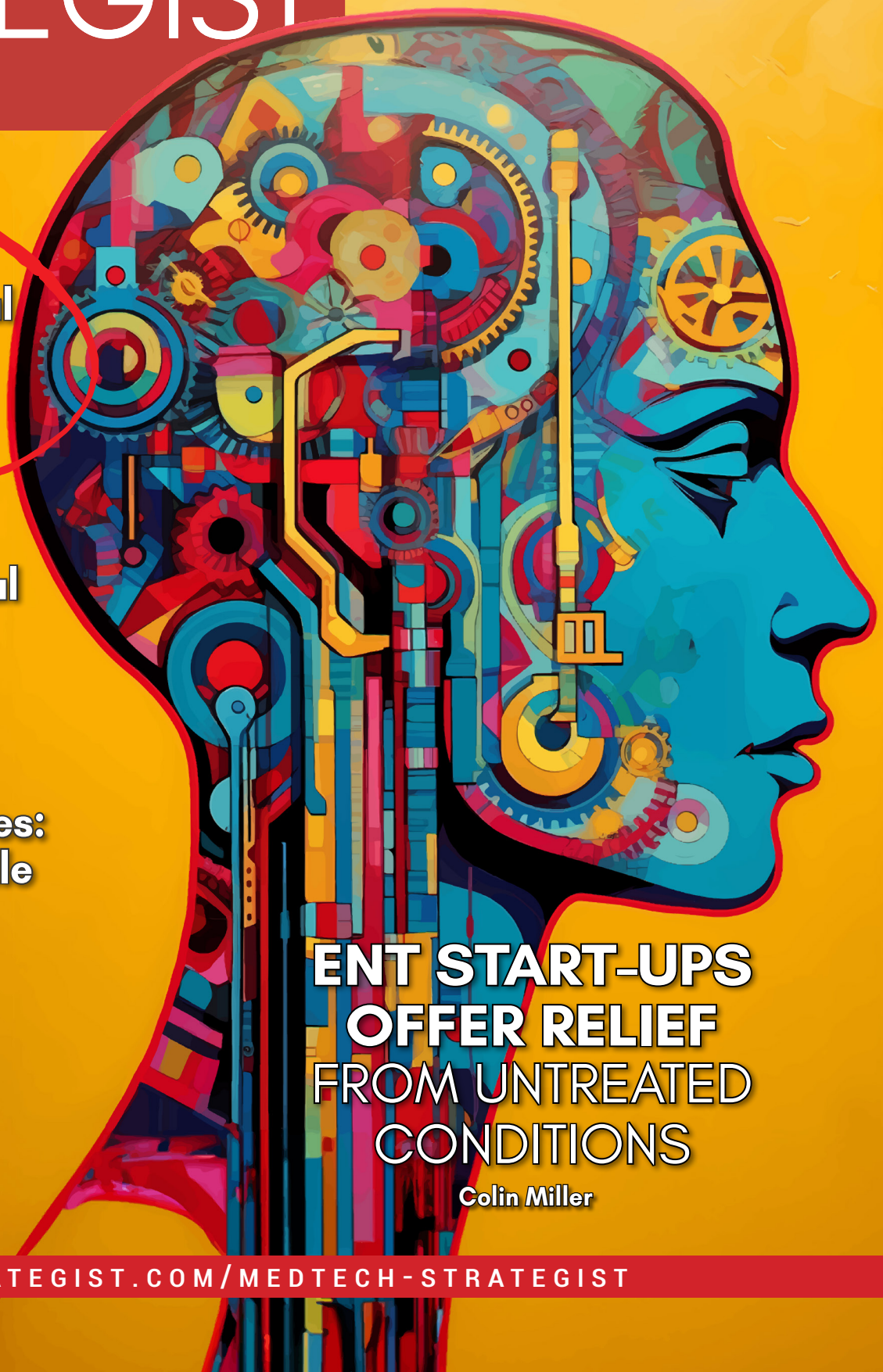

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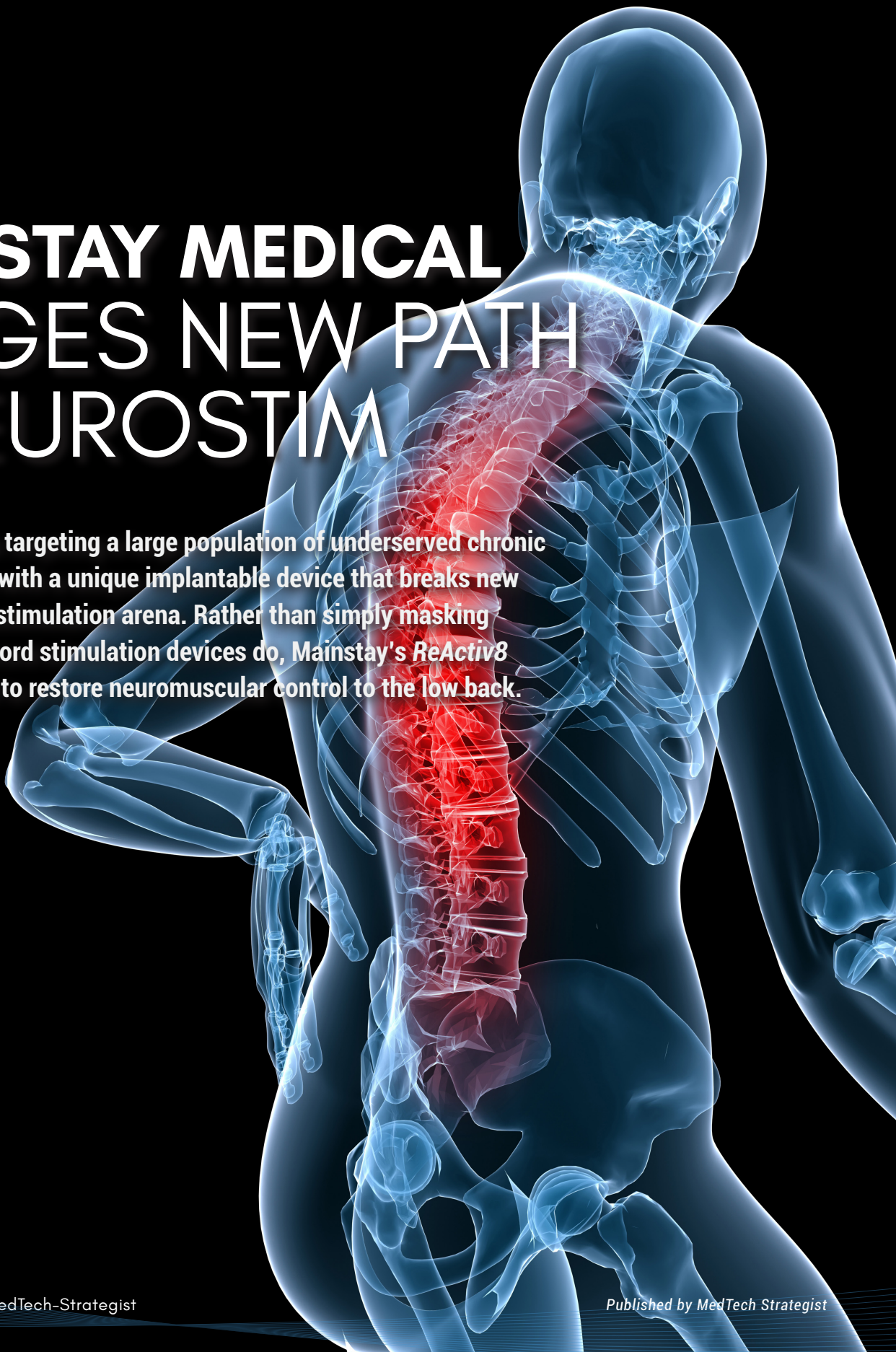

Mainstay Medical is targeting a large population of underserved chronic back pain sufferers with a unique implantable device that breaks new ground in the neurostimulation arena. Rather than simply masking the pain, as spinal cord stimulation devices do, Mainstay's *ReActiv8* therapy is designed to restore neuromuscular control to the low back.

▶ MARY THOMPSON

As one of several young companies innovating in the crowded neurostimulation space, Dublin, Ireland-based **Mainstay Medical** is differentiating itself by offering a unique approach to treating chronic low back pain caused by mechanical (muscular or joint) dysfunction. Rather than simply masking the pain, as medications and other therapies such as spinal cord stimulation (SCS) devices do, Mainstay's *ReActiv8* system is the first implantable neurostimulation device designed to treat the root cause of the pain by rehabilitating the underlying muscle that stabilizes the spine.

According to Chief Financial Officer Matt Onaitis, this approach enables Mainstay to tap into a large, underserved market opportunity encompassing chronic back pain sufferers who are not candidates for surgery and have limited effective treatment options today. However, as is the case with any new, unfamiliar therapy, Mainstay has a challenging road ahead to get both physicians and payors on board.

Mainstay received FDA PMA approval for *ReActiv8* in June 2020 and initiated its US commercial launch in late 2021. The system is also CE marked and is on the market OUS in Germany, the UK, and Australia (where it launched in January 2021). Physicians have implanted more than 1,000 *ReActiv8* devices to date, but with millions of people suffering from chronic back pain, that's only scratching the surface of the potential total addressable market.

The company appears to be well situated financially to support the ongoing rollout; Mainstay announced a $108 million equity financing in February 2021, co-led by Ally Bridge Group and Sofinnova Partners through its Crossover Fund, and including an unnamed "large, global medical device company." The company later refinanced its existing debt through a $50 million debt facility.

Educating Stakeholders

As Mainstay gears up commercially, one of its most pressing tasks is to educate stakeholders about the therapy and the differences between the *ReActiv8* system and more familiar neurostimulation devices such as SCS. According to Onaitis, *ReActiv8* therapy differs from SCS in two fundamental ways: it focuses on mechanical (muscle or joint-related) pain, rather than neuropathic pain, and the goal is rehabilitation, not palliation.

Although both types of devices have implantable pulse generators and leads, SCS leads are implanted inside the spinal canal to disrupt pain signals going to the brain, whereas the leads for Mainstay's system never enter the spinal canal. Rather, they are placed on either side of the spinal column to target the L2 medial branch of the dorsal ramus nerve as it crosses the transverse process at L3.

The dorsal ramus nerve controls a muscle group called the multifidus that resides deep in the back on either side of the spine and functions to stabilize the spinal vertebrae. As Onaitis explains, if someone has a facet joint problem or an injury to a muscle in their back, the brain will respond by reducing electrical signaling to the painful area, similar to the injury response in other areas of the body. However, when this pain response affects the multifidus, reducing its function, it leads to even less stability and creates a vicious pain cycle.

Studies show that the majority (an estimated 80%) of people with chronic low back pain that is mechanical in origin have a dysfunctional multifidus. But because the multifidus is a deep, involuntary muscle, it is difficult to isolate with physical therapy or at-home exercises, or with transcutaneous stimulation devices. Thus, it is relatively unresponsive to traditional rehabilitative therapies alone.

By stimulating the dorsal ramus, *ReActiv8* therapy directly targets the multifidus, causing it to contract. The stimulation is delivered in pulses to elicit 10 seconds of muscle contraction twice per minute, which Onaitis describes as "painless, slow, smooth contractions of the multifidus muscle that users say feels like a firm massage of the low back." Patients begin by using the device for two 30-minute sessions per day (typically in the morning and evening). The therapy is designed to rehabilitate the dysfunctional multifidus, thus restoring neuromuscular control and improving spinal stability so that the vertebrae are not moving beyond their normal range of motion. Over time, says Onaitis, this enables pain from the underlying injury to lessen.

In the US, *ReActiv8* is approved for use in adults with intractable chronic low back pain due to diagnosed multifidus dysfunction who have failed other therapies, including pain medications and physical therapy, and are not candidates for spine surgery. Mainstay trains healthcare providers on two mechanical tests clinicians can use to diagnose patients with multifidus dysfunction, or they can be diagnosed using MRI—the presence of marbled fat in the multifidus on MRI is indicative of a dysfunctional, atrophied muscle.

Pros and Cons

Three-year outcomes from Mainstay's 204-patient randomized, active sham-controlled, double-blind pivotal trial, published in September 2022 in the journal *Neuromodulation*, showed

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that the majority of *ReActiv8* patients experienced substantial improvements in pain and/or disability at three years. And 71% of those who were taking opioids at baseline reported voluntarily eliminating or reducing their opioid use (*see Figure 1*). There was a low incidence of serious adverse events (3.9%), and notably, there were no cases of lead migration over the three-year follow-up. Four-year data, presented at the 2023 North American Neuromodulation Society (NANS) meeting, demonstrated sustained improvement in pain and disability scores and continued reduction of opioid use. Moreover, 91% of patients at four years said they were "definitely satisfied" with the treatment.

The FDA approval was based on four-month and one-year follow-up data from the pivotal trial. The study failed to meet its primary endpoint—a comparison of the response rate (defined as a 30% or greater reduction in pain) between the treatment and control groups at 120 days—an outcome the company says was due to an "unexpectedly high" sham response. However, additional evidence led FDA to approve the device, including an analysis of the cumulative 120-day responder rate (taking into account the full range of response levels), continued improvements in pain out to one year, and the therapy's secondary benefits (subjects in the treatment group reported a greater reduction in low back pain, improvement in disability, improvement in overall quality of life, higher treatment satisfaction, and more favorable impression of change compared with controls).

Although the overall evidence was positive, the results suggest it can take many months of *ReActiv8* therapy before some patients achieve significant pain relief. That makes sense since this is a rehabilitative process, and muscle rehabilitation takes time, depending on the condition of the muscle to begin with. But that also highlights an important potential drawback for patients and physicians considering this implantable device: it does not provide instant pain relief, and the best outcomes require the patient to commit to dedicated, daily use for an extended period.

That said, *ReActiv8* does offer a much-needed treatment alternative for chronic back pain sufferers who have failed other therapies and whose pain severely impacts their quality of life, including their mobility. Patients such as these likely have the motivation to comply with daily use, and for the majority of those who do, the data suggest there is an eventual payoff, in some cases with complete resolution of their pain. In fact, a handful

Figure 1

ReActiv8: Pivotal Clinical Trial Outcomes to Year Three

Outcome	1 Year (N=176)	2 Years (N=156)	3 Years (N=133)
50% or greater reduction in Visual Analog Scale (VAS) pain intensity score	64%	72%	77%
More than 20-point reduction in Oswestry Disability Index	57%	61%	63%
VAS score <2.5	52%	65%	67%
Patients reporting they were "definitely satisfied" with ReActiv8 treatment	78%	80%	86%
Patients taking opioids at baseline who voluntarily eliminated or reduced opioid use	48%	60%	71%

Source: Mainstay Medical

of patients (seven in the pivotal trial by year three) have had the device removed due to pain resolution.

Conversely, a certain percentage of *ReActiv8* patients do not obtain adequate response even after extended use and are considered therapy nonresponders. A total of 25 patients in the pivotal trial had their devices explanted within three years (about 7-9 per year) due to inadequate response to therapy, a removal rate that the study authors point out is "in line with SCS reports." Although the company has yet to uncover a common thread that would explain inadequate therapy response, there is no current evidence that it is device- or procedure-related.

Challenging the Status Quo

Because patients who are eligible for *ReActiv8* have failed first-line treatments such as physical therapy, and they are not eligible for surgery, their treatment alternatives are limited and primarily palliative, including pain injections, radiofrequency nerve ablation, and/or opioid drugs. And, since they are not typical surgical patients, they are not the best candidates for SCS, which is used most often to treat lingering neuropathic pain following spine surgery (so-called failed back surgery syndrome; FBSS). Rather, *ReActiv8* is intended for people who have a joint or muscle injury that is primarily localized in the lower back, but unlike SCS patients, the majority of their pain is not radiating down the legs, which is a hallmark of nerve involvement.

That distinction is an important one, since payors have been reluctant to cover SCS for back pain patients who have not had or are not eligible for surgery, although that could change in the future. At this year's NANS meeting, SCS competitor **Nevro** released positive two-year data on nonsurgical back pain (NSBP) patients that could help drive payor coverage for SCS, and **Abbott** and **Boston Scientific** also have reported positive results with SCS in the NSBP patient population.

Nevro was the first company to obtain an FDA-approved NSBP indication for its SCS devices, in January 2022, and Abbott followed, with approval granted in May of this year. Abbott's approval was based on the 270-patient DISTINCT trial, which the company says is the largest randomized controlled trial ever conducted of SCS in nonsurgical back pain patients. Both companies are eager to tap into the huge NSBP opportunity, which Nevro estimates at $11.4 billion annually (total addressable market), with a current penetration of only 5%. (*See "Recently Launched Patient-Responsive SCS Is Another First for Nevro,"* MedTech Strategist, *May 17, 2023.*) According to Abbott, some 16 million US adults suffer from chronic back pain and 10 million have high-impact pain.

Although Nevro and Abbott are keen to gain a foothold among nonsurgical back pain patients, and they have formidable sales and marketing operations, Mainstay doesn't view them as an existential threat to its business. In fact, according to Onaitis, they're not competing for the same patients as Mainstay. "They're not looking at treating mechanical pain [in their studies]," he says, "they're enrolling patients with neuropathic pain who haven't [yet] had surgery." Beyond SCS, there are several other companies with peripheral nerve stimulation (PNS) devices that are targeting back pain—including **Curonix** (formerly StimWave) and **Nalu Medical**—but the focus of those systems, like SCS, is on blocking/masking pain signals, rather than on rehabilitation.

> Three-year outcomes from Mainstay's 204-patient pivotal trial showed that the majority of *ReActiv8* patients experienced substantial improvements in pain and/or disability.

This gives Mainstay a potential first-mover advantage among chronic, mechanical low back pain patients who are not eligible for surgery and are seeking more than palliative relief. However, that advantage also comes with some handicaps for a small company tasked with educating physicians and payors about a novel treatment option, particularly one with substantial up-front costs (on par with other implantable neurostimulation devices).

Given the challenges, Mainstay has made steady progress on reimbursement in the short time *ReActiv8* has been on the market, although there is much more to do, particularly in the US. The therapy is currently covered in all three of the company's OUS markets (Germany, the UK, and Australia) and it is covered by a US Medicare national coverage determination using existing PNS CPT codes. Among US private payors, however, coverage is currently limited to a few regional areas amounting to about three million covered lives. The first US private payor coverage decision, by Blue Cross Blue Shield of Alabama, was announced in Q4 of last year.

In addition to emphasizing its "rigorous" clinical trial data, something Onaitis says sets the company apart from others in the PNS field, Mainstay is also working to collect economic data to bolster its argument with payors. In March, researchers from Duke University and Brigham and Women's Hospital/ Harvard Medical School published an economic analysis

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in *Neurosurgery* showing that the majority of patients in the *ReActiv8* clinical trial who had high-impact back pain at baseline (meaning pain that substantially impacted their ability to work, socialize, and care for themselves) had transitioned to low- or no-impact pain within two years of beginning *ReActiv8* therapy. At baseline, 71% of the patients were classified with high-impact back pain, and after two years this had fallen to 10%, with 85% reporting no- or low-impact pain.

This suggests that *ReActiv8* therapy can significantly lower healthcare utilization and direct and indirect healthcare costs associated with chronic low back pain, according to the study authors, who point out that chronic low back pain is a leading cause of disability (and days of work missed) and "often a determinant for chronic opioid use."

Education Is Key

Because Mainstay is introducing a new type of therapy into the market with a different type of referral pattern, the launch also requires a lot of physician education. Although physiatrists (physical medicine and rehabilitation doctors) and physical therapists (PTs) are well versed in rehabilitative medicine and the multifidus muscle, many spine surgeons, and some pain doctors, are not. Still, says Onaitis, this is not a new therapy target—there are published articles on the multifidus and its involvement in the downward cycle of back pain "going back decades."

Under an ideal scenario, he adds, "the treating general practitioner, physical therapist, or other healthcare provider would refer the patient directly to a trained *ReActiv8* implanting physician after multifidus dysfunction is evidenced by physical assessment and/or imaging, and after the patient has tried and failed conservative treatments such as physical therapy and pain medications." Mainstay is aiding the process by helping *ReActiv8* implanters host education events so that local PTs, GPs, and other referral sources can learn about the device and how to identify the right patients for the therapy. And the company is particularly interested in multidisciplinary groups—with PTs, pain specialists, and spine surgeons all under the same roof. "Referrals at those centers are much more seamless," Onaitis says.

Within the next few years, the company expects to launch a next-generation version of *ReActiv8*, which will have a much smaller pulse generator, be more user friendly, and utilize smartphones as controllers, thus offering greater functionality, including the possibility of compliance reminders. All of that may appeal to a wider population of back pain sufferers who might otherwise shy away from an implantable device, and it also could help expand the therapy's indications.

In the meantime, Mainstay continues to deal with the challenges and incremental gains that come with launching a novel device-based therapy. The company has already proven it has staying power: founded in 2008 with little more than an idea, it took 13 years for Mainstay to achieve US approval and launch. As Onaitis points out, developing a complex medical device from scratch is a lengthy process, particularly for a "research and data-driven company" like Mainstay. Now that the company has achieved commercial launch, "getting the word out will take time," he acknowledges, "but we're making progress." MTS

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