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## Neuromodulation: Three Start-Ups To Watch

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### Executive Summary

The neuromodulation market is growing at a rapid pace and investors and strategics are paying close attention to early-stage innovators. We highlight Cardionomic, Nuviant and Pixium, three young companies that are listening to the brain, fixing broken hearts and making the blind see.

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- The US market for implantable neuromodulation devices is expected to reach \$3.3 billion in 2019, a 46% increase over 2014.
  - Innovative start-ups hope to share the ride. To date, companies focused on pain relief have been investors' favorites, raising some of the biggest rounds in medtech.
  - But other indications are gaining traction. New entrants are working to transform heart failure care, bring sight to the blind, and develop closed-loop deep brain stimulation, among many other therapeutic frontiers.

The US neuromodulation technology market, worth \$2.3 billion in 2014, is poised to grow 46% over the next five years, reaching \$3.3 billion in 2019, and potentially rivaling markets like that for coronary stents. (*See Exhibit 1.*)

Among the factors driving this expansion are large unmet need in many chronic conditions, an aging and increasingly aware patient population, and the potential advantages that neuromodulation devices may offer over conventional treatment. Technical advances, too, such as miniaturization, rechargeability and sophisticated externals are making new forms of treatment possible. Despite potential barriers like high up-front development costs as well as marketing costs for companies and an uncertain reimbursement landscape, new

applications for neuromodulation continue to be explored, while more traditional applications are being updated with newer technology.

## EXHIBIT 1

### Implantable Neuromodulation Devices, Market Forecast, 2014–2019



*Medtech Insight report #A594, "US Neurostimulation Devices Market," published June 2015*

Neuromodulation is one of the few bright spots in medtech investing. Neurology-focused device firms raised a total of \$1.6 billion between 2010 and mid-2015, according to Informa's *Strategic Transactions*, and companies with neuromodulation technologies claimed more than 55% of that amount. Most of that money went to firms focused on treating pain. (See "[Neuro Medtech Investors Have Time \(And Money\) For The Pain](#)" — *START-UP*, November 2015.)

But pain isn't the only game in town. In this issue, we look at three young companies outside the CNS arena. [Cardionomic Inc.](#) is developing a neuromodulation device for acute decompensated heart failure. **Nuviant Medical Inc.** has a next-generation deep-brain stimulation device potentially for Parkinson's, atrial fibrillation and other indications, and [Pixium Vision](#) is working on two kinds of bionic retinas.

#### Cardionomic: Targeted Neuromodulation For Acute Heart Failure

Heart failure is the number-one reason for hospitalization among US adults over age 65. The condition is common: some 5.8 million Americans suffer from heart failure, with over half a million newly diagnosed each year. By one estimate, acute decompensated heart failure (ADHF), the sudden worsening of HF symptoms, accounts for some 1.76 million hospitalizations annually; rehospitalizations occur in about half of those patients within six months.

For many years, standard treatments have included oxygen, diuretics, systemic vasodilators and inotropes (agents that alter the force of the heart's pumping) – approaches that either merely relieve symptoms or, in the case of inotropes, come with unwanted side effects, including higher mortality.

Minnesota-based Cardionomic is developing a neuromodulation device to treat the poor pumping action that underlies ADHF. It will be placed in the right pulmonary artery through the internal jugular vein, much like the Swan-Ganz catheter that is familiar to cardiologists and internists. Over several days of hospitalization, according to president and CEO Steve Goedeke, it will stimulate autonomic nerves that selectively control ventricular contractility without affecting heart rate, thus improving cardiac contractility and cardiac output without the dangerous systemic effects associated with inotropes. Improved cardiac output leads to better end-organ perfusion and a more favorable neurohormonal profile, combating the vicious cycle that so often develops in heart-failure patients when initially compensatory neurohormonal activation winds up worsening ventricular function. The company has so far raised \$22.3 million.

“Those of us in the field of heart failure are hard-pressed to answer the question, ‘What is the next compelling therapy in the heart-failure space, especially related to devices?’” Goedeke says. “I think Cardionomic has a great approach that starts with a solid mechanism of action, is reinforced by human clinical evidence and ends with better patient outcomes.”

Goedeke, an engineer, inventor and former senior director within [Medtronic PLC](#)'s Cardiac Rhythm Disease Management division, says patients treated with the device are also expected to tolerate higher doses of beta-blockers and ACE inhibitors upon discharge – a factor associated with improved outcomes.

In a first-in-human proof-of-concept study of 10 patients with stable (not decompensated) New York Heart Association (NYHA) Class III heart failure, a different embodiment of the device led to a 22.6% increase in left ventricular contractility without a statistically significant change in heart rate. The results were presented at the *2015 Annual Meeting of the North American Neuromodulation Society* and the *European Society of Cardiology's Heart Failure 2015* conference.

Goedeke declines to provide details about upcoming studies. “We’re pretty close to the vest on our clinical endpoints,” he says. “Heart failure studies are challenging, and we’ve put quite a bit of work into refining our endpoints such that we can successfully execute our pivotal trial, obtain favorable labeling and, most importantly, provide an effective therapy to those in need.”

Although the therapy is selective rather than systemic, Goedeke adds, the patient will experience positive systemic changes: “These attributes will be a significant advantage as we design and execute a successful trial.”

In working out trials and endpoints, the 10-employee company draws upon the expertise of [Ohio State University](#) cardiologist William Abraham, MD, who is chair of the company’s scientific advisory board and one of the world’s foremost experts on heart failure.

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“The beauty of this [is that] this is really targeted neuromodulation – this is taking advantage of everything we’ve learned over the past 50 or 60 years about neuroanatomy, and using it,” Abraham says. “That 20% increase in contractility would do all the right things in terms of improving blood flow to vital organs ... breaking this neural, hormonal and hemodynamic storm of acute decompensated heart failure.”

Cardionomic’s technology originated at the [Cleveland Clinic](#), where anesthesiologist Sandra Machado, MD, cardiologist Marc Penn, MD, PhD, and neurosurgeon and neuromodulation pioneer Ali Rezai, MD, developed a device to stimulate selected nerves surrounding the pulmonary artery that are responsible for cardiac contractility. They based it on research dating back to the 1980s that observed an increase in contractility with stimulation of nerves in this area. The inventors filed patents in the 2000s and early 2010s as the Cleveland Clinic Foundation and, as of 2011, as Cardionomic. In December 2013, New Enterprise Associates-backed incubator Denali Medical II licensed the Cardionomic technology from the Cleveland Clinic, testing it further with an off-the-shelf electrophysiology device.

Denali Medical II and Cardionomic closed on a \$20 million Series A round last October, merging to become Cardionomic Inc. (Denali then closed its doors.) The round was led by New Enterprise Associates, Greatbatch Inc. and the Cleveland Clinic Foundation, and was chosen for *START-UP*'s 2015 A-List. (See ["The A-List: The Trend-Shaping Series A Financings Of 2015" — START-UP, January 2016.](#)) [\[See Deal\]](#)

Goedeke attributes this fundraising success in part to a strategy of projecting labeling, clinical endpoints and the likely reimbursement landscape, a farsighted approach that gave investors a clearer sense of the likely endgame. “Clinical endpoints are key to the program’s overall economics and are particularly important drivers of product design,” he says. “Our efforts on endpoints allowed us to create an achievable product definition that will be effective in a large number of patients while generating meaningful profits.” With a modest penetration rate, Goedeke estimates, those investors could share in a US and European market worth well over a billion dollars.

Cardionomic’s intellectual property coverage includes placement of the device in the pulmonary artery and adjustment of the signal it sends.

Beyond the company’s primary mission, Goedeke sees a number of therapeutic extensions that should reduce the rate of ADHF hospitalizations. “We are creating a great opportunity for a stand-alone company or for an acquisition by a device company that wants to expand beyond CRT [cardiac resynchronization therapy], ICD [implantable cardioverter defibrillator], pacing [and] monitoring,” he says.

### **Nuviant: Closed-Loop Deep Brain Stimulation**

The future of neurostimulation, says Will Rosellini, is in closing the loop: to not only stimulate the nervous system, but also adjust that stimulation automatically based on signals received from the nervous system. Rosellini co-founded Nuviant Medical with that ideal in mind.

Equipped with an IP portfolio bought from Medtronic plus the assets of a bankrupt Belgian company that had developed a strong closed-loop stimulator for deep brain stimulation (DBS), Nuviant is developing a rechargeable, implantable neurostimulator and recording platform called *Synapse*. The device

offers two-way communication, the ability to record signals from surrounding anatomy and simultaneous stimulation of multiple targets. The company is planning to test it in several neuromodulation applications, including DBS, atrial fibrillation, overactive bladder and neurogenic dysphagia.

So far, one patient has been successfully implanted with Synapse, and Nuviant is planning a clinical study in Parkinson's patients.

Rosellini, a former minor-league pitcher, holds five master's degrees in addition to a law degree; he is a 15-year veteran of the neurotechnology space. He previously founded Microtransponder, which is developing a vagus-nerve stimulation device for the treatment of stroke and tinnitus. He also founded and led Sarif Biomedical LLC, a stereotactic microsurgery company, and Lexington Technology Group LLC, to successful exits.

In 2012, Rosellini left his position as CEO at Microtransponder after temporarily losing his voice to thyroid cancer. In March 2014, intent on building a new neurostimulation company, his incubator hedge fund, Rosellini Scientific, snagged 14 patents from Medtronic related to remotely monitored implantable devices.

That December, Rosellini acquired Synaptix, a venture-backed Belgian company that had developed a vertically integrated manufacturing company and what Rosellini calls a best-in-class closed-loop stimulation system. The device was CE marked for deep brain stimulation, but the firm had declared bankruptcy in March 2014. Rosellini then co-founded nUro Inc., in December 2014 with Synaptix's former CEO, Hartmut Spitaels. The company changed its name to Nuviant in May 2015.

Since inception, the company has been funded by a mixture of grants and investments from multiple private and government investors. It has raised a total of \$7 million, with its most recent fundraising round of \$250,000 from nXn Partners in Dallas. In January 2015 it was awarded a grant for €3.4 million from the Wallonia (Belgium) governmental initiative BioWin. Two months later, it announced a funding round consisting of over 60 investors, making it eligible to become a publicly traded company with OTC:QB. The firm in its various iterations has also won NIH Small Business Innovation Research grants to develop a wireless neuromodulation device for overactive bladder (as Rosellini Scientific, in December 2014) and for neurogenic dysphagia (as Nuviant, in December 2015).

Nuviant holds 13 patents with seven pending; these include protection of implanted, remotely managed, automated neuromodulation systems.

Now a 12-employee company, Nuviant plans to go public in Q3 2016, though Rosellini says the company is still weighing whether to file a Form 10 or S-1 registration statement with the Securities and Exchange Commission. It plans to make its decision and file in first-quarter 2016.

Synapse's key differentiators are its rechargeability and its ability to record local field potentials in the region of the brain immediately

**Synapse's key differentiators are its rechargeability and its ability to record local field potentials in the region of the brain immediately surrounding the implanted electrode.**

surrounding the implanted electrode. "Researchers using non-implanted devices have demonstrated that incorporating sensing into DBS systems and closing the loop can significantly improve DBS therapy," Rosellini says. "To make this a viable therapy you need to have this capability in a fully implanted device. Nuviant's Synapse system is the world's first fully implantable, rechargeable DBS system with sensing capabilities to receive the CE mark."

The device's rechargeability may draw patients with competing implanted DBS systems when it comes time to replace them; Rosellini points out that the market in spinal cord stimulators is already moving toward rechargeable devices.

Nuviant plans to swim in a pond with some very large fish, including Medtronic, [Boston Scientific Corp.](#) and [St. Jude Medical Inc.](#), all of which offer DBS products. The overactive bladder market is heating up as well.

But Rosellini says he built Nuviant to compete. Though the company is willing to explore licensing its platform and even to be acquired, that may not be necessary. "We expect to be able to get the cash flow break even by 2017, and we expect to scale the company with internal cash flows."

"One of the biggest risks in medical devices these days is reimbursement. Nuviant has de-risked this by targeting the \$600 million-plus DBS market where reimbursement is already established," he adds.

On February 16, the company announced that after a year-long selection and negotiation process, [GlaxoSmithKline PLC](#) (GSK) had selected Nuviant to provide implantable pulse generators and peripherals for GSK's own neuromodulation research.

### **Pixium's Bionic Retina**

Among companies still in the R&D and clinical stage, Pixium Vision holds the unusual distinction of already having gone public. The company is simultaneously developing two different approaches to retinal neuromodulation for blindness. Both stimulate the retina, which then sends signals to the brain through the optic nerve, allowing light and shape perception with bionic partial vision for people blinded by either retinitis pigmentosa (RP) or age-related macular degeneration (AMD). RP affects about 1.5 million people worldwide, whereas AMD affects more than 14% of white Americans over age 80; both result from degeneration of photoreceptor cells (rods and cones) in the retina.

For RP patients, Pixium's *IRIS II* Bionic Vision Restoration System (VRS) implants a miniature array of 150 electrodes on the surface of the retina (epiretinal), stimulating the superficial cell layer. This provides patients with light and shape perception, making it easier to navigate their environments; the device is also explantable. The previous-generation, 49-electrode IRIS I was first implanted in patients in 2013, while IRIS II was first implanted in January 2016 in a study anticipated to include up to 10 patients across seven European centers. The company also filed for CE mark in December 2015.

CEO Khalid Ishaque projects IRIS II will go commercial in the second half of 2016, depending on CE mark approval and reimbursement timing. The launch will take place in a phased fashion at a couple of dozen European centers of excellence that can offer long-term patient follow-up; thus a large sales force will not be needed.

“Surgery is a relatively minor part of this whole treatment – patients need to come in for reeducation and learn how to interpret artificial vision,” Ishaque says.

He estimates an average selling price of €100,000 in a potential billion-dollar market, one that will include a recurrent revenue stream of software upgrades, replacement patient external components and an outside warranty.

On the other hand, Pixium’s *PRIMA* bionic VRS, designed more specifically for AMD patients, is a miniature, passive, wireless subretinal implant that resembles tiny solar panels (2 mm or smaller). It replaces the damaged subretinal photoreceptor cell layer with several thousand modular electrodes that send electrical signals to more superficial retinal cells. Siting the electrodes in the subretinal area leads to better mimicry of natural visual signal processing than does the epiretinal method, according to Ishaque, enabling richer resolution for the patients to potentially progressively learn to distinguish faces. *PRIMA* is currently in the preclinical stage, and Ishaque expects a first-in-human trial this calendar year.

If *PRIMA*’s first-in-human trial is successful, a pivotal European trial in AMD patients is planned for 2017. However, after conversations with the FDA, Ishaque says the company may opt for the priority-review Innovation Pathway to accelerate introduction of *PRIMA* in the US.

“We might go for a pre-IDE, subject to what FDA is going to be requiring from us,” Ishaque says. However, he adds, “there’s no comparison [device] to [*PRIMA*] at the size of things we are talking about and how the implant will be stimulated. We are working with world experts in view also of FDA requirements, as to what standards become applicable when the implants are that miniature and for continuous use.”

Both systems interface via infrared or near-infrared signals with a proprietary camera sensor, built into sunglasses, that connects with a pocket computer. The computer’s software converts video signals into electrical signals that are delivered to each patient via customized stimulation settings.

According to Ishaque, IRIS surgery requires about two-and-a-half hours of general anesthesia. The goal for subretinal chips is implantation in a less than an hour-long surgery requiring only local anesthesia.

Founded in December 2011, Pixium raised €9.5 million six months later in a Series A round led by Omnes Capital that included Abingworth LLP, Global Life Science Venture and Polytechnos. At the same time, it acquired Intelligent Medical Implants AG (IMI), a Swiss company also working on an epiretinal device. A Series A extension in the amount of €15 million followed in 2013, led by Sofinnova Partners. Pixium also licensed wireless subretinal photovoltaic technology from the lab of Stanford professor Daniel Palanker, PhD, and adopted technology from the Paris Institut de la Vision. Having thus acquired both preclinical subretinal and more advanced clinical-stage epiretinal assets, the start-up found itself in the challenging position of deciding whether, and how, to pursue both. In June 2014, it made a bold move and went public. Its IPO raised €39.5 million on EuroNext.[\[See Deal\]](#) Less than a year later, it was awarded €6.9 million from the public-private R&D partnership Sight Again. The company now has 38 employees.

“We required funding to execute in

Is acquisition on the

parallel on two axes, which in a private financing realm, especially in Europe, was next to impossible to reach,” Ishaque says. In 2014, he recalls, “the market was hungry for opportunities in supporting medtech, which allowed us the opportunity to tell our story to investors.”

CEO Khalid Ishaque joined Pixium in March 2014 after 17 years at Boston Scientific, most recently as general manager of the International Neuromodulation division.

horizon? Pixium may be an awkward meal for existing neuromodulation players, which lack ophthalmology expertise, or for ophthalmology companies that are not involved in neuromodulation.

Is acquisition on the horizon? Pixium may be an awkward meal for existing neuromodulation players, which lack ophthalmology expertise, or for ophthalmology companies that are not involved in neuromodulation. Moreover, Ishaque says, the latter may not fully appreciate the patient service burden that follows implantation: “This is not a sell-and-forget environment.”

Though Pixium is in conversation with companies from both those categories, “I want to position the group to be a leader in vision restoration,” says Ishaque. “After that, of course, the board and shareholders decide what’s best.”

The company holds extensive IP, including some 250 patents. Ishaque expects a highly competitive field. “Like cochlear [implants], we think there will only be room for two or three players in this space,” he says.

An important current competitor is [Second Sight Medical Products Inc.](#), which received FDA approval in 2013 for its \$150,000, 60-electrode *Argus II* epiretinal prosthesis. Though Second Sight beat Pixium to the US market, it held its \$32 million IPO in November 2014, five months after Pixium went public. (Ishaque says IRIS II’s key advances are the 150-electrode implant, smart video sensor that mimics the eye and explantability in case of future upgrades.) [Retina Implant AG](#) is a German company, founded in 2003, that is developing a subretinal device based on cochlear-implant technology. Israeli start-up [Nano Retina Inc.](#), a company of investment and holding firm Rainbow Medical Innovation Ltd., is also working on a retinal implant.

Optogenetics, another frontier in low-vision research, may slow vision loss, but does not stop the death of photoreceptors, Ishaque notes. For people who are already blind, implants that speak to the brain may be the only solution. (See “[Optogenetics: Start-Ups Head For The Light](#)” — *START-UP*, [November 2014](#).) “The 21st century has to be about the brain,” he says. “We are really entering the brain-machine interface.”

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