vizient™

Spine and neuro technologies

Spine and neuromodulation devices

Technology Watch | 2016 Volume 2

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Introduction

The spine and neuromodulation marketplaces continue to be dynamic. An acceleration of innovative medical devices and manufacturing techniques are driving these markets forward. 3D printing is entering the spine marketplace. Several of the manufacturers are utilizing this process. The manufacturing process is providing vendors with both advanced design capability creating implants that enhance bone ingrowth and the potential capability to design customized patient implants. As of December 2015, the FDA has cleared over 20 3D printed orthopedic medical devices.

Implants to preserve motion are also entering the market. Despite a lag in the development of interspinous and artificial disc implants, it appears that an increasing number of vendors are once again investing in innovative technologies in these areas. The race to get U.S. FDA approval of an implant that closely mimics the spine's natural intervertebral disc is ongoing as well.

The neuromodulation market is also experiencing rapid growth and innovation. Magnetic resonance imaging (MRI) compatible devices have entered the U.S. market. The flexibility for neuro modulated patients to have future MRI scans is an exciting development. Additionally, new indications are being approved and are in development. The potential to utilize neurostimulation to treat new conditions and diseases is driving rapid investment and new company entry.

As health care changes, hospitals have an increasing need to focus their attention in these two markets. Prices are increasing while reimbursements vary. Excitement and caution are the key words for these markets.

Disclaimer The Vizient orthopedic staff attended clinical sessions at key orthopedic meetings through the year. The staff meets with suppliers, reviews new technologies and monitors key clinical trial data. The information is consolidated into this overview of product and practice trends in the various orthopedic segments. This document is intended to educate nonclinical hospital staff, providing them insight into new and innovative technologies. Vizient staff has no personal financial connections with the suppliers and has no conflicts of interest in the development of this document. The products presented are for educational purposes. Vizient does not endorse any of the products reported in this document.

Market watch

The 12-month price trend and current average market pricing by product segment is shown in the tables that follow.

Pricing trends

Spine products - lumbar

Category	Change (%)
Pedicle screw system	↑ 0.2
Plating system	↓ 2.6
MIS device	↑ 1.9
Interspinous system	↑ 0.4
Artificial disc	↑ 0.1
Vertebral compression device	↑ 2.1

Spine products - cervical

Category	Change (%)
Pedicle screw system	↑ 1.3
Plating system	↓ 3.1
Minimally invasive surgery (MIS) device	↑ 3.7
Artificial disc	↓ 3.4

Neurostimulation products

Category	Change (%)
Deep brain stimulators	↑ 1.7
Spinal cord stimulators	↑ 8.3
Vagus nerve stimulators	↑ 5.8
Sacral nerve stimulators	↑ 2.7

All prices in the tables that follow are the average prices for that category of products, not selling prices for specific products. Individual hospital pricing may vary given considerations such as rebates, quality, and volumes that are not included in these estimates.

Neuromodulation devices

Deep brain (DBS)

Supplier	Average price
Generators	
Medtronic	$12,980
Leads	
Medtronic	$1,445

Vagus nerve (VNS)

Supplier	Average price
Generators	
LivaNova	$21,080
Leads	
LivaNova	$6,590

Spinal cord (SCS)

Supplier	Average price
Generators	
Boston Scientific	$17,865
Medtronic	$15,130
St. Jude Medical	$13.920
Leads	
Boston Scientific	$2,710
Medtronic	$2,600
St. Jude Medical	$2,780

Sacral nerve (SNS)

Supplier	Average price
Generators	
Medtronic	$11,000
Leads	
Medtronic	$3,310

All estimated selling pricing is the averaged pricing over a category of products. This is not selling pricing for a specific product. Your pricing may vary given considerations such as rebates, quality and volumes that are not included.

Supplier watch

NuVasive, Inc.

NuVasive® is a growing force in the spine market. It focuses on developing minimally disruptive surgical products and procedurally integrated solutions for spine surgery. Since the company's inception in 1999, the company's commitment to Speed of Innovation® drives its sustained growth. NuVasive's ability to rapidly develop and commercialize innovative spine surgery products and procedures to fulfill an unmet clinical need has allowed the company to introduce innovative products and solutions.

An example of the company's innovation and their most recent introduction is the magnetically adjustable implant systems based on the MAGnetic External Control, or MAGEC®, technology platform.

MAGEC (MAGnetic Expansion Control) System

MAGEC rod system is comprised of two sterile, single-use, titanium spinal rods. Each innovative rod contains a small magnet and is surgically implanted using standard commercially available fixation components. The implanted MAGEC spinal rod is used to brace the spine during growth to minimize the progression of scoliosis. The MAGEC rods are available in 4.5 mm and 5.5 mm diameters. The internal magnets are controlled by an external remote controller.

Scoliosis is an abnormal curvature of the spine. While small curves do not typically cause medical problems, large curves can lead to complications. If untreated, scoliosis can progress at a rapid rate and cause breathing problems, as well as cosmetic disfigurement. Traditional treatments include casting, spinal bracing, and spinal fusion. To address the limitations of spinal bracing and fusion for treatment of severe scoliosis in young children, a distractible spinal implant called a growing rod was developed.

Traditional growing rods are surgically implanted across the spinal curvature. Lengthening of the growing rods occurs frequently, approximately once to twice a year. The average number of surgeries per patient is 12 over the course of six years. Lengthening of a traditional rod requires the surgeon to surgically reopen the incision site and lengthen the growing rod, which is a procedure that exposes a patient to increased risk. The MAGEC system can be lengthened without repeated surgeries and periodic lengthening of the rod can be performed in an office setting. The magnet allows the rod to lengthen without needing, enabling the surgeon to customize patient therapy with more frequent, noninvasive, device adjustments.

The system can be used in the treatment of skeletally immature patients under 10 years of age diagnosed with severe spinal deformities, such as scoliosis. The rod(s) can be implanted into children as young as two years of age.

Unique ICD–10–PCS procedure codes for the device were approved that include:

- XNS0032 (reposition of lumbar vertebra using magnetically controlled growth rod(s), open approach)
- XNS0432 (reposition of lumbar vertebra using magnetically controlled growth rod(s), percutaneous endoscopic approach)
- XNS3032 (reposition of cervical vertebra using magnetically controlled growth rod(s), open approach)
- XNS3432 (reposition of cervical vertebra using magnetically controlled growth rod(s), percutaneous endoscopic approach)
- XNS4032 (reposition of thoracic vertebra using magnetically controlled growth rod(s), open approach); and
- XNS4432 (reposition of thoracic vertebra using magnetically controlled growth rod(s), percutaneous endoscopic approach)

These new ICD–10–PCS procedure codes are effective on October 1, 2016.

The system maps to the following MS–DRGs:

- 456 (Spinal Fusion Except Cervical With Spinal Curvature or Malignancy or Infection or Extensive Fusions with MCC)
- 457 (Spinal Fusion Except Cervical with Spinal Curvature or Malignancy or Infection or Extensive Fusions with CC) and
- 458 (Spinal Fusion Except Cervical with Spinal Curvature or Malignancy or Infection or Extensive Fusions without CC/MCC)

The U.S. Centers for Medicare and Medicaid Services (CMS) has granted a new technology add-on payment (NTAP) for magnetically controlled growth rods. To qualify for an NTAP in the inpatient setting, NuVasive demonstrated a substantial clinical improvement relative to available alternatives. Under § 412.88(a)(2), new technology add-on payments are limited to the lesser of 50 percent of the average cost of the device or 50 percent of the costs in excess of the MS–DRG payment for the case. The reported

total operating cost of the MAGEC spine is $17,500 for a single rod and $35,000 for a dual rod. CMS set the maximum new technology add-on payment for a case involving the use of the MAGEC Spinal Bracing and Distraction System at $15,750.

This new add-on payment is effective on October 1, 2016 for fiscal 2017.

NuVasive has also incorporated their proprietary limb lengthening technology into the Precice® limb lengthening intramedullary nail used for lengthening of the femur and tibia to correct a congenital deformity or injury resulting in one leg being shorter than the other.

Technology watch

Spine market

The U.S. spine market is steadily growing. The U.S. spine market is now estimated to equal the size of the U.S. joint markets. The Becker Spine Report estimates the spine surgery market to be valued at over $7 billion and is expected to reach $11 billion by the end of 2020.[1] The experts project an overall market growth of 4-6% in compound annual growth through 2020.[234] Since the spine market is comprised of several smaller market segments, growth within the various segments will vary. The segments include:

Neurostimulation products

Market	Procedure	Products
Spinal fusion	Thoracic and lumbar fusion	Pedicle screws
	Cervical fusion	Interbody devices
	Interbody thoracic and lumbar fusion	Spinal plating systems
Motion preservation	Dynamic stabilization	Artificial discs
	Discs replacement	Interspinous process spacers
		Pedicle screw-based systems
		Facet replacement products Annulus repair devices
		Nuclear disc prostheses
Minimal invasive		Cannulated screws
		Interbody cages
		Rods
		Non-cannulated screws
Vertebral fracture repair & body replacement	Vertebral compression fracture treatment	Kyphoplasty devices
		Vertebroplasty devices

Motion preservation is a small piece of the spine market but where most of the innovative technology is being developed. In the other market segments like spinal fusion, products are approved for use by the U.S. FDA 510K process. Under this process, new products must demonstrate equivalence to products already approved in the market. Little clinical evidence of unique benefit is required. This has led to numerous suppliers entering the market with products that are similar, yet are at greatly varying prices. In the motion preservation segment, many products require stricter regulatory requirements before being approved for sales and use in the U.S. These stricter requirements have limited the number of suppliers and slowed technology development. In the future, advances in this segment will drive higher market growth. Motion preservation procedures include dynamic stabilization, artificial disc replacement, total disc replacement, annular repair and disc nucleus replacement. Development efforts and a favorable regulatory approval environment will increase the availability and innovation of motion preserving devices. However, unfavorable reimbursement for these devices has limited their utilization. This may change as the dynamic health care environment shifts to keeping patients healthy and improving outcomes.

Spine market

Market overview

Devices for the preservation of spinal motion are normally contained within the non-fusion segment of the spine market. Product development efforts have focused on the areas of interspinous, artificial disc replacement and prosthetic disc nucleus replacement devices. Each provides benefits and increase mobility from traditional fusion procedures. Despite years of development, the ultimate goal is to develop a prosthetic disc nucleus that closely mimics the composition and function of the intervertebral disc allowing for full freedom of spinal motion has yet to be fully achieved.

Motion preserving medical devices are unique within the spine market for their more restrictive regulatory requirements. Most spine products are cleared for U.S. market use through the U.S. FDA's 510K device clearance process. Through this process, a vendor demonstrates that a new device is "substantially equivalent" to a similar device already cleared by the U.S. FDA before 1976. Human data are usually not required for a 510K submission. The Premarket Approval (PMA) process requires a human clinic trial to prove safety and efficacy. The clinical trial must be approved by the U.S. FDA and the resulting data evaluated by a clinical panel of experts. The cost and time required to get a product approved through the PMA process is expensive. For most of the motion preserving devices, the PMA process is required allowing surgeons better information on the device.

The average success rate of a lumbar spinal fusion is approximately 75-80%.[5] Failure of the fusion to heal may be associated with continued pain. At one or more levels, spinal fusion will result in decreased spinal motion and possible complications in surrounding vertebra. This edition focuses on the spinal implants designed to increase patient movement and restore the spine to its original function.

Interspinous implants

Interspinous implants are used to treat lumbar spinal stenosis or facet joint arthritis. The aims of implanting interspinous devices are:

- to unload pressure from the facet joints and the intervertebral disc
- to restore foramen height, where the nerve endings pass away from the center of the spinal region and into the legs
- to provide stability especially in bending backward while still allowing motion

Interspinous devices may be categorized into interspinous fixation and interspinous spacing devices. Interspinous fixation (fusion) devices are being developed to aid in the stabilization of the spine. The devices range from paired plates with teeth to U-shaped devices with wings that are attached to the spinous process. They are intended to be

an alternative to pedicle screw and rod constructs to aid in the stabilization of the spine with interbody fusion. Interspinous spacers are small devices implanted between the vertebral spinous processes. After implantation, the device is opened to expand the foramen and decompress the nerves. Interspinous fixation devices are not intended for stand-alone use. Interspinous fixation (fusion) devices contrast with interspinous distraction devices (spacers), which are used alone for decompression and are typically not fixed to the spinous process.

Companies with US FDA PMA approved interspinous devices

Vendor name	Device name	Indicated use	FDA PMA #	Approved
Medtronic	X-Stop®	one or two level lumbar	P040001	2005
Paridign Spine	Corflex®	one or two level lumbar	P110008	2012
VertiFlex	Superion®	one or two level lumbar	P140004	2015

The list of U.S. FDA PMA approved interspinous devices is short. Many other interspinous devices are available having been cleared through the U.S. FDA 510K clearance process.

The lack of reimbursement in the U.S. by both private and government payers for interspinous devices has limited their use and development.

Companies developing interspinous devices

Vendor name	Product name	Regulatory status
Interspinous devices		
Medtronic	Diam™	Conformité Européenne (CE) mark, FDA declined
Non-Linear Technologies	NL-Prow	CE IDE on-going
Replication Medical	GelFix™	CE mark
DePuy Synthes	In-Space	CE mark, US IDE ongoing
BioAlpha	NovoMax™	In development
Aurora Spine	DynaZip™	In development
Globus Medical	Acadia®	CE mark, US IDE ongoing
Zimmer Biomet	UniWallis®	CE mark
Paradigm Spine	coflex™	CE mark
FDA approved	Corflex®	one or two level lumbar
Scient'x,	IsoBar	CE mark
Medtronic	Aperius PercLID	CE IDE on-going
Mikai S.p.A	Falena	CE IDE on-going
Scient'x	IsoBar TTL	In development
Innovative Spinal Technologies	TBD	In development

DynaZip™ interspinous implant (Aurora Spine)

The DynaZip interspinous implant is a minimally invasive posterior dynamic interspinous implant for motion preservation without the need for fusion. The implant features the Zip One-Step™ locking mechanism to allow surgeons the ability to secure the implant without the use of a set screw. The implant will be available in multiple sizes to accommodate variations in patient anatomy, with plate length sizes of 35 millimeters, 40 millimeters and 45 millimeters. The implants are not commercially available or for distribution in the U.S.

Acadia® facet replacement system (Globus Medical)

The Acadia facet replacement system is a bilateral implant system designed to restore and mimic the facet joints in the lumbar spine. The implant is constructed from cobalt chrome alloy with highly polished articulating surfaces. Portions of the implant are coated with hydroxyapatite to promote bone growth. It is secured to the bone with pedicle screws fastened with locking nuts. A crosslink offers added coupled and rotational support. It will be available in an assortment of sizes to fit patient anatomy. The device is currently an investigational device and is not commercially available or for distribution or sale in the U.S.

In-Space™ interspinous spacer (DePuy Synthes)

The In-Space is an interspinous spacer designed to interrupt segmental extension and for distracting the interspinous space. Implanted by percutaneous tissue approach, the device is currently an investigational device that is not commercially available or for distribution or sale in the U.S.

DIAM spinal stabilization system (Medtronic)

The implant is placed between the spinous processes (the visible ridges of the back) to act as a shock absorber that reduces loads on the surrounding vertebrae and restores the natural function of the joint. The core of the DIAM system is made of silicone, while the outer mesh and tethers are made of medical-grade polyester. The flexible properties of the DIAM materials may also protect the integrity of the spinous process. The device is currently an investigational device and is not commercially available or for distribution or sale in the U.S.

UniWallis® posterior dynamic stabilization system (Zimmer Spine)

The UniWallis implant offers surgeons the ability to perform surgery from a unilateral approach, preserving the supraspinous ligament. The device is currently an investigational device and is not commercially available or for distribution or sale in the U.S.

Companies in active clinical trials for FDA approval

Vendor name	Clinical trial name	Clinical trial #	Status
Globus Medical	Safety and effectiveness of the Acadia facet replacement system to treat spinal stenosis	NCT00401518	Active, not recruiting
Globus Medical	Safety and effectiveness of the Flexus interspinous spacer	NCT01156675	2012
FLEXUS IDE	Terminated	one or two level lumbar	2015
Medtronic	Treatment of lumbar spinal stenosis with X-Stop PEEK spacer in moderately symptomatic patients	NCT00517751 COAST	Terminated
Medtronic	Study of the safety and effectiveness of DIAM™ spinal stabilization system versus conservative care	NCT00456378	Active, not recruiting
Medtronic	Satellite™ PEEK Nucleus Replacement Retrospective Analysis	NCT01110967	Complete
Paradigm Spine	Post-Approval 'Real Conditions of Use' Study	NCT02555280	Active, not yet recruiting patients

Vendor name	Clinical trial name	Clinical trial #	Status
Spinal Simplicity	Minuteman Spinal Fusion Implant Versus Surgical Decompression	NCT01455805	Recruiting patients
VertiFlex	Safety and effectiveness of the Superion™ in spinal stenosis	NCT00692276	Active, not recruiting
Zimmer Biomet	Efficacy of the Aspen Spinous Process System in Anterior Lumbar Interbody Fusion	NCT01016314	Active, not recruiting

Artificial discs replacement implants

Artificial disc replacement is another segment of the motion preservation market. Similar to a hip or knee joint replacements, a disc replacement substitutes a mechanical device for the natural disc in the spine. The device is meant to restore motion to the spine by replacing the worn, degenerated disc. The disc replacement device is typically constructed of a softer material core with a ridged outer body. Artificial disc replacement initially gained FDA approval for use in the U.S. in 2004. After a lengthy regulatory lag, several new devices have been approved by the FDA for use in the United States mixed between lumbar and cervical indications. On the heels of these recent approvals are several others in the later stages of U.S. pivotal clinical trials. Artificial discs replacements registered a 7.3 percent increase to $244 million in 2013. There has been a significantly greater increase in the implant of cervical discs versus the lumbar discs. The economics of the devices are generally favorable when compared with a cervical fusion. Several manufacturers are currently researching, developing and testing total disc replacement for the U.S. market.

Companies with US FDA PMA approved artificial disc implants

Vendor name	Device name	Indicated use	FDA PMA #	Approved
DePuy Synthes	Prodisc®-L	Lumbar	P050010	2006
DePuy Synthes	Prodisc®-C	Cervical	P070001	2007
Medtronic	Prestige®	Cervical	P060018	2007
Globus Medical	Secure®-C	Cervical	P100003	2012
NuVasive	PCM®	Cervical	P100012	2012
LDR	Mobi-C®	Cervical	P110002 P110009	2013
Medtronic	Prestige® LP	Cervical	P090029	2014
Aesculap	activL®	Lumbar	P120024	2015

The lack of reimbursement in the U.S. by both private and government payers for interspinous devices has also limited their use and development.

Companies developing artificial disc implants

Vendor name	Product name	Target therapy	Regulatory status
Artificial disc implants			
DePuy Synthes	Discover™	Cervical	CE mark, US IDE ongoing
Dymicron	Triadyme-C™	Cervical	In development
Globus Medical	Secure® C3	Cervical	CE mark
Integra LifeSciences	eDisc™	Cervical	In development
Nuvasive	NeoDisc™	Cervical	CE mark, US IDE ongoing
Osimplant	Aramis™	Cervical	CE mark
RTI Biologics	NuNec™	Cervical	European study ongoing
Simplify Medical	Simplify®	Cervical	CE mark, US IDE ongoing
Spinal Kinetics	M6®-C	Cervical	CE mark, US IDE ongoing
SpinalMotion	Kineflex C®	Cervical	Terminated
Stryker	CerviCore®	Cervical	In development
University Hospital, Bordeaux	Axelle®	Cervical	In development
AxioMed Spine	Freedom®	Lumbar	CE mark, US IDE ongoing
Globus Medical	Triumph®	Lumbar	CE mark, US IDE ongoing
Medtronic	Maverick™	Lumbar	CE mark, US IDE complete
Nuvasive	XL TDR®	Lumbar	CE mark, US IDE ongoing
Spineart	Baguera®L	Lumbar	CE mark

Baguera®L lumbar disc prosthesis (Spineart)

The Baguera L lumbar disc is an artificial disc with a sloping anatomical design of the plates to optimize the fit between the device and the disc space, and to maximize the endplate coverage. The guided mobile nucleus is designed to prevent excessive constraints on the facet joints. It allows six degrees of freedom. The coated titanium plates reduce artifacts under MRI for a better postoperative control. The implants are not commercially available or for distribution or sale in the U.S.

Discover™ cervical disc (DePuy Spine)

The Discover cervical intervertebral disc is indicated for symptomatic cervical disc disease, with the aim of improving range of neck movement and reducing neck pain. The device includes titanium alloy endplates coated with porous titanium spray and hydroxyapatite, and a central ultra-high molecular weight polyethylene articulating core. It is available in a range of sizes and thicknesses. The implants are not commercially available or for distribution or sale in the U.S.

Discover artificial cervical disc (IDE Study)
Study Size: 500 patients
Prospective, randomized, multicenter, U.S. study

This multicenter, prospective, randomized controlled trial is designed to evaluate the safety and effectiveness of the Discover artificial cervical disc when compared with ACDF for the treatment of cervical

degenerative disc disease. The patients were randomized to total disc replacement or cervical fusion to determine the safety and efficacy at two years after surgery. This is the pivotal trial for FDA approval. Patient enrollment is complete. No data has been released.

Freedom® lumbar disc Interspinous Implant (AxioMed Spine)

The Freedom lumbar disc is a one-piece, viscoelastic, total disc replacement device, and is intended to relieve low back pain by replacing intervertebral discs that have been damaged by degenerative disc disease. The material characteristics of the polymer, in combination with the implant design, provide the three-dimensional motion that mimics the natural biomechanics of the spine. The implants are not commercially available or for distribution in the U.S.

Freedom lumbar disc pivotal trial
Study Size: 400 patients
Prospective, multi-center, randomized study

The Freedom lumbar disc trial is the company's U.S. pivotal trial to demonstrate the safety and efficacy of the device. The trial data are intended to be used to gain FDA approval for use in the lumbar spine. The study concluded patient enrollment in late 2014. No additional data are available at this time. The data will be used for AxioMed's pre-market approval submission to the FDA. The device was CE mark approved.

Maverick lumbar total disc replacement (Medtronic)

The Maverick lumbar disc is a metal on metal, cobalt-chromium alloy implant. The implant is designed to provide a posterior center of rotation allowing for functional stabilization and restoration to normal spinal kinematics. The outer surfaces of the implant are hydroxyapatite coated providing improved bone to device fixation and long-term implant stability. A unique feature of the system is the implant tool which combines four tools into one to simplify the implantation procedure. The device is investigational and not available for sale or use in the United States.

Maverick™ lumbar disc pivotal trial
Study Size: 577 patients
Prospective, randomized, multi-center, U.S. study

This large, prospective, randomized clinical trial of 32 participating U.S. hospitals is to assess the safety and effectiveness of the MAVERICK Total Disc Replacement as a method of treating patients with lumbar degenerative disc disease at one level from L4-S1. The trial is the company's U.S. pivotal trial. The study is complete. No additional data are available at this time. The data will be used for Medtronic's pre-market approval submission to the FDA. The device is CE mark approved.

Triumph® lumbar disc (Globus Medical)

The Triumph lumbar disc is an articulating artificial disc that consists of two cobalt chrome alloy components. The device has two endplates and a rotating core that are inserted as one piece. The outer, bone-contacting surfaces have multiple serrated keels for fixation into the vertebrae and a titanium plasma porous coating to permit bony growth. The device is designed to allow motion in flexion and extension up to 24 degrees (+/- 12 degrees), in lateral bending up to 24 degrees (+/- 12 degrees), and in axial rotation up to 29 degrees in either direction; however, motion is mediated by anatomic constraints which limit the axial rotation to about 3 degrees in either direction. The device is designed to be implanted through a posterolateral approach. The implants are not commercially available or for distribution in the U.S.

Companies in active clinical trials for FDA approval

Vendor name	Clinical trial name	Clinical trial #	Status
Aesculap	Activ-L Artificial Disc Treatment of Degenerative Disc Disease in the Treatment of Degenerative Disc Disease	NCT00589797	Active, not recruiting
ARO Medical	Safety Study of ARO Spinal System as an Adjunct to Lumbar Decompression	NCT01970514	Active, not recruiting
AxioMed LLC	Freedom Cervical Disc in the Treatment of Lumbar Degenerative Disc Disease (FLD)	NCT00775801	Active, not recruiting
DePuy Spine	Comparison of Discover Artificial Cervical Disc and ACDF for Treatment of Cervical DDD	NCT00432159	Active, not recruiting

Vendor name	Clinical trial name	Clinical trial #	Status
Globus Medical	Triumph Lumbar Artificial Disc IDE: A Pilot Study	NCT01198470	Active, not recruiting
K2M, Inc.	RHINE™ Cervical Disc Clinical Study	NCT02403453	Recruiting patients
NuVasive	Evaluating The Safety and Effectiveness of The NeoDisc™	NCT00478088	Completed
Nuvasive	XL TDR® eXtreme Lateral Total Disc Replacement for the Treatment of Lumbar Degenerative Disc Disease	NCT00927238	Completed
Simplify Medical	Investigation of the Simplify® Cervical Artificial Disc	NCT02667067	Recruiting patients
Spinal Kinetics	Restore CLINICAL TRIAL	NCT01609374	Active, not recruiting
Tetec AG	Safety and Efficacy With NOVOCART® Disc Plus Autologous Disc Chondrocyte Transplantation	NCT01640457	Active, not recruiting

Prosthetic disc nucleus implant

Spinal disc is a cartilaginous tissue located between the vertebras. The spinal disc acts as a flexible joint between the vertebra, allowing bending and twisting of the spine column. A disc nucleus replacement device is designed to replace only the inner portion of the disc (the nucleus). The ultimate goal in disc nucleus replacement development is the creation of a non-metal based prosthesis that closely mimics the natural function of spinal disc nucleus allowing multi-directional freedom of movement. Various materials have been utilized in the development of prosthesis including metals and ceramics, injectable fluids, gels, and elastic coils. The difficulty in the development of the prosthesis is that it must withstand repeated high stresses in very complex modes of deformation including combined bending, torque, shear and compression. It must act as an efficient shock absorber. It has been a complex design task. Many early pioneers have ceased development efforts or failed to demonstrate safety and efficacy. Yet others continue development efforts as listed below. To date no non-metal prosthetic disc nucleus implant is available in the United States.

Companies developing prosthetic disc nucleus implants

Vendor name	Product name	Regulatory status
Apollo Implants	TBD	In development
Arthro Kinetics	CaReS®	In development
Baxano Surgical	PNR	In development
Cambridge Polymer	TBD	In development
Clariance	NucleoFil	In development
Cryolife	BioDisc™	CE mark
DePuy Synthes	SINUX ANR	CE mark
DePuy Synthes	Hydrafil	In development

Vendor name	Product name	Regulatory status
Disc Dynamics	Dascor®	CE mark, US IDE ongoing
Dynamic Spine	IPD	In development
Gentis, Inc.	DiscCell™	In development
Interpore Cross Intl (Zimmer)	TBD	In development
RayMedica	Hydraflex™	In development
Replication Medical	NucleoFix™	In development
Stryker	Aquarelle™	In development
Zimmer Biomet	Newcleus	CE mark
Nuvasive	NeuDisc™	FDA approved
SpinalMotion	Kineflex™	In development
Spine Wave	NuCore™	In development
RTI Biologics	NUBAC™	CE mark, US IDE ongoing
Replication Medical	GelStix™	CE mark
TranS1	PNR	CE mark
Vertebral Technologies	InterCushion™	CE mark, US IDE ongoing
Zimmer Biomet	Regain	CE mark, US IDE ongoing

DASCOR disc nucleus replacement (Disc Dynamics)

The DASCOR is a disc nucleus replacement device. The implant replaces an abnormal disc nucleus with an artificial device that conforms to the disc nucleus space and is designed to perform like a natural healthy nucleus. It is different from an entire artificial disc replacement, where the entire spinal disc – not just the nucleus (the inner portion of the disc) – is replaced. Unlike total disc replacement, the procedure is minimally invasive and preserves the anatomy of the spine. The implants are not commercially available or for distribution/sale in the U.S.

GelStix nucleus augmentation implant (Replication Medical)

The GelStix device is a matchstick-sized implant placed into a degenerated disk using a small 18 gauge needle. After several hours, the gel absorbs body fluids swelling up to ten times its original volume, rehydrating and pressurizing the disc from inside the cavity. The hydrogel implant is an oxidized hyaluronic acid gelatin. The gelatin forms a cross-linked hydrogel when wet expanding to form crystalline clusters. The implant is investigational and not available for sales or use in the U.S.

NUBAC Disc nucleus replacement (RTI Biologics)

The NuBac implant system is a nucleus replacement device designed to provide physiological motion between the two adjacent vertebra. It utilizes the company's proprietary articulating P3™ technology which is based on an articulating inner ball and socket design to achieve spine load sharing and stress distribution. The implant is made of PEEK-OPTIMA®. The implant is not commercially available or for distribution/sale in the U.S.

Companies in active clinical trials for FDA approval

Vendor name	Clinical trial name	Clinical trial #	Status
RTI Biologics	Trial Evaluating the Safety and Effectiveness of NUBAC™ Disc Arthroplasty	NCT00931515	Complete
Replication Medical	Comparative Evaluation of Clinical Outcome of Degenerative Disc Disease Treated With the GelStix™ Nucleus Augmentation Device	NCT02763956	Recruiting patients
Vertebral Technologies	A Pilot Study of the InterCushion Disc Nucleus Prosthesis	NCT01652053	Recruiting patients
Seikagaku Corporation	A Study of SI-6603 in Patients With Lumbar Disc Herniation	NCT01941563	Active, not recruiting

Economic impact

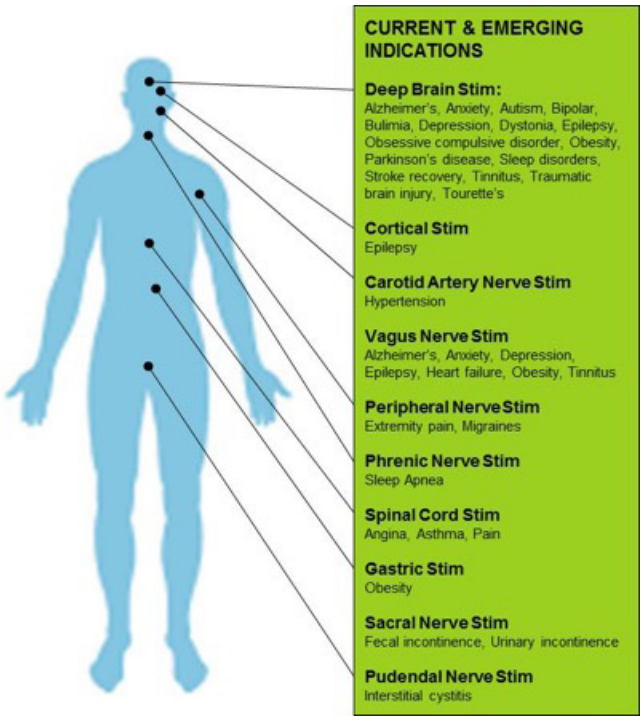
The economic impact of motion preserving spine devices is minimal due to their low utilization. Despite these devices being available in the U.S. for many years, use has been restrained by reimbursement challenges and limited long-term data. These hurdles are being overcome as enhanced device designs and long-term, larger patient clinical trials are conducted. Undaunted, suppliers are actively developing motion preservation devices. As reimbursement issue change and technology improves, this category of devices will slowly begin to impact the hospital budget.

Reimbursement

Reimbursement for motion preserving spine implant procedures is mixed. Artificial disc replacement is reimbursed while for interspinous devices reimbursement varies and disc nucleus replacement does not. Different Medicare contractors may have local coverage determinations that affect coverage for these types of procedures. Some third-party payers will reimburse, whereas others still consider these procedures investigational. Check with your payer to confirm its reimbursement policy.

Neuromodulation

The neuromodulation continues to expand rapidly in both procedures and indicated uses. The product category is characterized by implantable devices applying low-level energy to the nervous system to block nerve signals. Implantable neurostimulation systems are very similar to implantable cardiac pacemakers typically consisting of three implantable components (the extension, lead, and power source) and two external components (the control magnet and a handheld programmer). The extension is used to connect the lead to the power source, and the lead is used to deliver the electrical stimulation to the targeted nerve(s). During the past year, several new devices have been approved for both traditional and new indications. While only a handful of indicated uses for these medical devices have been U.S. FDA approved, the chart shows the success of neurostimulation and regulatory barriers are driving companies to investigate broader applications for the technology.



To date the U.S. FDA has approved the use of neurostimulation therapies targeting the following nerves and indications:

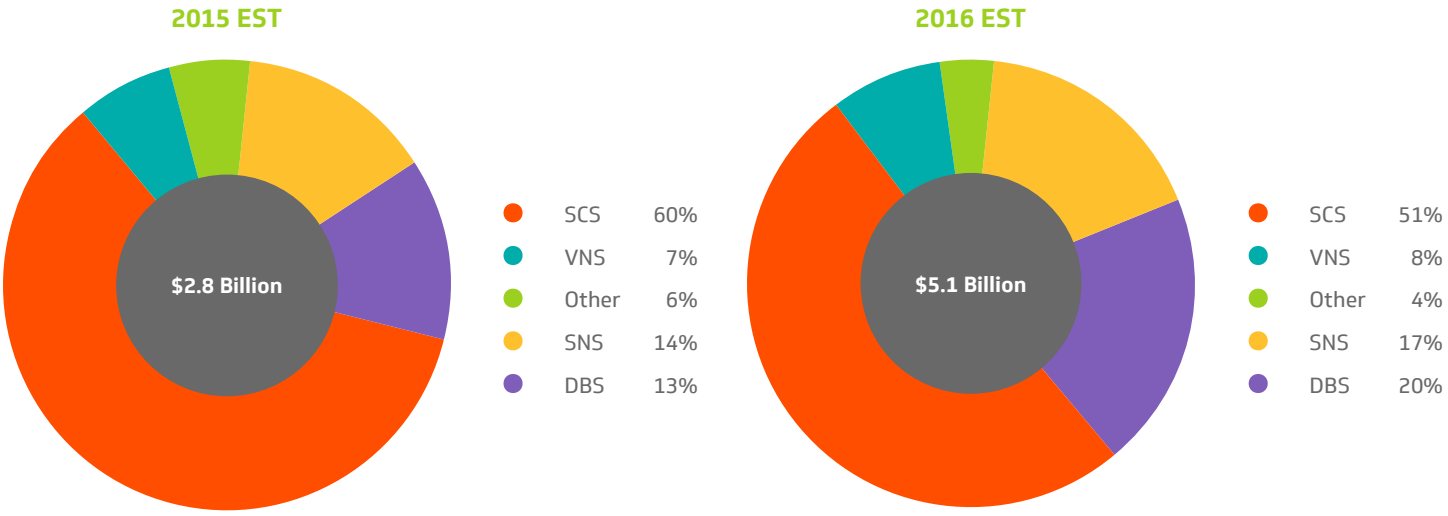
- Deep brain stimulation (DBS)
  - Essential tremors
- Parkinson's disease
- Epilepsy
- Spinal cord stimulation (SCS)
- Chronic pain management
- Vagus nerve stimulation (VNS)
- Epilepsy
- Sacral nerve stimulation (SNS)
- Overactive bladder

In the future, indicated uses for neurostimulation therapies may also include:

- Movement disorders
- Heart failure
- Stroke recovery
- Obesity
- Angina
- Traumatic brain injury
- Hypertension
- Sensory disorders
- And others

The 2015 U.S. neuromodulation market is estimated by Grand View Research, Inc. to be approximately $2.8 billion[6]. By 2020, the market is projected to grow at an aggregated rate in the mid teen to over $5 billion. Regardless of market segment whether chronic pain, deep brain vagus nerve or any other, all the segments are projected to grow at double digit rates through 2020. The chronic pain management is currently the largest therapy segment at 60%. This segment is projected to continue to remain the largest and grow with an estimated 45% over the next five year period. Growth of the other neurostimulation therapy segments will also grow as new indications and devices are approved by the U.S. FDA reducing the overall chronic pain market share.

Medtronic is the dominant market share player across all neurostimulation therapy segments. The chronic pain management segment dominates the therapy classes in both volume and number of competitors. Due to the ease of market entry and annual growth projections, the pain management segment will continue to increasing in both numbers of competitors and procedures. The pain management segment is also highly physician controlled. The pain management market dynamics of favorable reimbursement for conducting in-office trials, high sales representative physician support and an unfavorable reimbursement for generator implant will insolate this market from significant negative price pressures and sustain annual price increases. The other therapy categories represent significant market growth opportunity. Overall prices have increased approximately 7% in 2015. The market value, profitability and growth potential has attracted increasing numbers of companies to invest in new technologies to address the many conditions that neuromodulation may provide clinical benefits for. For many suppliers, their neuromodulation businesses are key to growth strategies.



Companies with US FDA approved neuromodulators

Vendor name	Chronic pain	Parkinson's	Epilepsy	Migraine headachs	Overactive bladder	Obesity
Advanced Uro					Nuro	
Bioness	StimRouter					
Boston Scientific	Precision Spectra					
Precision Montage MRI						
Cefaly Technologies				Cefaly II		
Cogentix.					Urgent PC	
EnteroMedics						Maestro
LivaNova			AspireSR VNS			
MainStay	ReActiv8					
Medtronic	RestoreSensor	Activa				
DBS			InterStim II			
NeuroPace			RNS			
Nevro Corp.	Senza					
Nuvectra	Algovita					
SPR						
Therapeutics	Sprint					
StimWave	StimQ Freedom-8A					
St. Jude Medical	Protégé Protégé MRI					
Proclaim Elite						

Recently approved neuromodulation devices:

Algovita® spinal cord stimulation system (Nuvectra Corporation)

The Algovita Spinal Cord Stimulation (SCS) System is the company's first device for the treatment of chronic pain of the trunk and/or limbs. The device features 24 channels, broad parametric ranges, bi-directional recharge and wireless telemetry. The unique Coil-in-Coil lead design allows the lead to be stretchable to reduce lead migration and breakage. This construction is available in all the 8 and 12 electrode leads. The device received U.S. FDA approval in November 2015.

Cefaly® II trigeminal nerve stimulation system (Cefaly Technology)

The Cefaly II is an external trigeminal nerve stimulation device for the prevention of frequent episodic migraine attacks. The device has a built-in rechargeable Lithium-ion Polymer 3.7 V battery. It is placed on the forehead for 20-minutes once a day, using a self-adhesive electrode and a magnetic connection. The device sends tiny electrical impulses through the skin to desensitize the upper branches of the trigeminal nerve and reduce the frequency of migraine attacks. The enhanced device is now three-quarters the size of the original, fits in the palm of your hand, is rechargeable, uses magnets to stay in place, and allows patients more control over the intensity of their therapy. The device costs $349 and comes with a 60-day money back guarantee. The device received U.S. FDA clearance in July 2016.

Precision Montage™ MRI spinal cord stimulation system (Boston Scientific)

The Precision Montage MRI System is cleared for full-body, 1.5 Tesla MRI scans when conditions of use are met. The device is indicated for chronic pain management. The device MultiWave™ Technology enabling delivery of multiple waveforms, including burst and higher rates, intended to help respond to changes in pain over time. The device utilizes the IlLumina 3D algorithm to create a computer model so physicians can target the source of the pain. The system was U.S. FDA approved in May 2016.

Proclaim™ Elite spinal cord stimulation system (St Jude Medical)

The Proclaim Elite is an upgradeable, non-rechargeable spinal cord stimulation (SCS) system for the treatment of chronic pain. The device utilizes Burst Stimulation, a proprietary neurostimulation waveform function that delivers closely-spaced pulses of electrical energy to a patient's spinal cord to manage chronic pain. The system also features conditional magnetic resonance (MR) labeling allowing patients to safely undergo head and extremity MRI scans. St. Jude Medical has further enhanced ease-of-use and familiarity for patients by leveraging Bluetooth® wireless technology and Apple™ mobile digital devices to improve familiarity and interaction with the control device. The device received U.S. FDA approval in November 2015.

Sprint™ peripheral nerve stimulation system (SPR® Therapeutics)

The Sprint Peripheral Nerve Stimulation (PNS) System is indicated for percutaneous peripheral nerve stimulation for the management of chronic and acute pain, including post-operative and post-traumatic pain. The device includes a threadlike lead and a small wearable stimulator. The lead is placed through the skin via a fine needle and connects externally to the wearable stimulator about the size of a watch. The device delivers electrical stimulation through the lead, activating peripheral nerves to achieve pain relief. In one study funded by the National Institutes of Health, the device was associated with a 72 percent reduction in average pain in post-amputation patients[7]. The device is completely reversible and minimally invasive. The company is marketing the device as a solution to minimize opioid over prescription. The device received U.S. FDA clearance in August 2016.

Many companies are entering the neuromodulation market investigating the use of the technology to treat a range of disorders, including obesity, depression, leg pain, resistant hypertension, sexual dysfunction, urinary tract disorders, heart failure and drug addiction.

Companies developing neuromodulation devices

Spinal cord stimulation

Vendor name	Product name	Target nerve	Target therapy	Regulatory status
Spinal cord modulation				
Boston Scientific	Precision Novi™	Spinal cord	Chronic pain	CE mark US IDE on-going
Mainstay Medical	ReActiv8™	Dorsal ramus	Chronic pain	CE mark US IDE on-going
Medtronic	Intellis RC™	Spinal cord	Chronic pain	In development
Medtronic	Prime ADVANCED	Spinal cord	Heart failure	In development
Nuvectra Corp	Algovita®	Spinal cord	Chronic pain	FDA cleared; CE mark
StimWave	StimQ	Peripheral nerve	Chronic pain	FDA cleared; CE mark
StimWave	Freedom-8A™	Dorsal ramus	Chronic pain	FDA cleared; CE mark
Spinal Modulation St Jude Medical	Axium™	dorsal root ganglion	Chronic pain	CE Mark US IDE on-going
St Jude Medical	Proclaim™ Elite	Spinal cord	Chronic pain	FDA cleared; CE mark

Axium neurostimulator system (St. Jude Medical)

The dorsal root ganglion (DRG) is believed to allow for more selective targeting of pain areas that are hard to reach, like the groin, lower leg, and foot. The ACCURATE study showed that DRG stimulation was better than traditional spinal cord stimulation (81.2 versus 55.7 percent) in providing pain relief. The system consists of the implantable generator, trial stimulator device, a programmer, a patient programmer, one or more leads which may be used in combination with a lead extension and the accessories and tools used for implanting the system. The system is non-rechargeable. The device is investigational and not available for use or sale in the United States.

Freedom-8A spinal cord stimulation system (StimWave Technologies)

Freedom-8A spinal cord stimulation is indicated for the treatment of chronic back and leg pain. It is the first wirelessly powered, fully-programmable, microtechnology neurostimulator. The device is based on an injectable microchip that delivers small pulses of energy to electrodes. The device's Wireless Pain Relief™ technology enhances the devices ability for chronic pain patients are able to have 3-Tesla full body magnetic resonance imaging (MRI) examinations. Other neuromodulation systems with MR conditional labeling typically limit exams to just the head or limbs, or to older 1.5T MRIs. It has an eight-electrode array, which provides additional programming and placement options for patients, including the use of high-frequency stimulation. The device received U.S. FDA approval in December 2015.

NeuSpera system (NeuSpera Medical)

NeuSpera Medical is developing a miniaturized chronic pain neuromodulation device. The implant is more than 100 times smaller than currently available neuromodulation devices. The device will be delivered through a miniaturized injectable technology. Its small form factor is expected to reduce procedure complexity and time as well as patient complications and post-surgical pain. The tech is powered by the company's MidField technology. The device is investigational and not available for use or sale in the United States.

Protégé MRI spinal cord stimulation system (St. Jude Medical)

The Protégé MRI system is the next evolution of the Protégé family for chronic pain management. The key feature is its FDA approval for MRI compatibility when used with the 60cm Octrode™ percutaneous leads. The system is the smallest MR-conditional SCS implantable pulse generator available in the United States, and is upgradeable. Upgradeable technology allows patients to access future technology, once approved, through software updates rather than surgical device replacement. The device was approved by the U.S. FDA in April 2015.

ReActiv8 neurostimulator (Mainstay Medical)

ReActiv8 is a small implanted device which stimulates the nerves responsible for contracting the multifidus muscle that stabilize the lower back. The device includes two leads which are placed bilaterally near the medial branch of the dorsal ramus nerve at the L3 vertebra, and are connected to a small battery powered implantable pulse generator. An external programmer communicates wirelessly with the generator and is used to customize stimulation. Therapy is delivered in twice daily, 30 minutes sessions and controlled via a handheld wireless remote control. The therapy activates the muscles in the lower back cycling between contraction and relaxation. The device is investigational and not available for use or sale in the United States.

Deep brain stimulation

Vendor name	Product name	Target nerve	Target therapy	Regulatory status
Deep brain modulation				
Aleva Neurotherapeutics	spiderSTIM™	Deep brain	Parkinson's	In development
Boston Scientific	Vercise™	Deep brain	Parkinson's	CE mark US IDE on-going
Deep Brain Innovations	TOPS™	Deep brain	Parkinson's	In development
Functional Neuromodulation	DBS-f	Deep brain	Alzheimer's	In development
Medtronic	DBS	Deep brain	Parkinson's	FDA approved
Medtronic	Activa® PC+S	Deep brain	Epilepsy	CE mark US IDE on-going
NeuroSigma	eTNS™	Trigeminal Ganglion	Epilepsy & Depression	CE mark
NeuroVista Corp	TBD	Deep brain	Epilepsy	In development
Newronika	TBD	Deep brain	Parkinson's	In development
Rio Grande	TheraCap™	Deep brain	Traumatic brain injury	In development
Sapiens SBS (Medtronic)	SureStim®	Deep brain	Parkinson's	CE mark US IDE on-going
St Jude Medical	Infinity™	Deep brain	Parkinson's	In development

Vendor name	Product name	Target nerve	Target therapy	Regulatory status

Deep Brain Stimulation (DBS) therapy (Medtronic)

Medtronic's Deep Brain Stimulation therapy is an expansion of indicated patients for the therapy. The therapy and device is now indicated for use in people with Parkinson's disease of at least four years duration and with recent onset of motor complications, or motor complications of longer-standing duration that are not adequately controlled with medication. This recent approval by the FDA was based on data from the EARLYSTIM clinical study, published in the New England Journal of Medicine in 2013, which found that patients treated with Medtronic DBS Therapy and best medical therapy reported a mean improvement of 26 percent in their disease-related quality of life at two years, compared to a one percent decline in patients treated with best medical therapy alone.[9] In a study of patients with longer-standing motor complications, DBS patients' quality of life improved 20 percent from baseline to six months compared to no improvement in the patients treated with best medial therapy alone. The expanded use of the DBS system was approval in February 2016.

Infinity deep brain stimulation system (St. Jude Medical)

The Infinity™ deep brain stimulation system is designed to support treatments for movement disorders including Parkinson's disease, tremor and dystonia. The system will be available in two different sizes and will be upgradeable. The product comes with Bluetooth® wireless technology that will connect the DBS platform with Apple digital devices, which will be used as patient and physician controllers. The iPod-like touch controllers will aid the patients in turning the device on and off and also to change modes. An iPad® Mini will be used by physicians to program the implant. The device is investigational and not available for use or sale in the United States.

Vercise PC DBS system (Boston Scientific)

The Vercise dbs system is indicated for the treatment of tremor, including the most common form of this movement disorder known as essential tremor. Tremor is characterized by involuntary and rhythmic shaking, usually associated with difficulty in an activity such as writing or holding and controlling items. The system utilizes a rechargeable, 25-year life battery and features multiple independent current control, which gives clinicians the ability to control stimulation precisely for a neural target to help minimize unwanted side effects. The device is investigational in the U.S., currently being evaluated in the INTREPID Study. The device is not available for use or sale in the United States.

Vagus nerve stimulation

Vendor name	Product name	Target therapy	Regulatory status
Vagus nerve modulation			
Cerbomed	NEMOS®	Epilepsy	CE mark
CerebralRx	FitNeS	Epilepsy	CE mark
LivaNova	AspireSR®	Epilepsy	FDA approved
LivaNova	Centro™	Epilepsy	In development
LivaNova	ProGuardian™	Epilepsy	CE mark
LivaNova	Vitaria™	Heart failure	US IDE ongoing
LivaNova	Equilia™	Heart failure	In development
electroCore	gammaCore™	Migraine headaches	CE mark

Vendor name	Product name	Target therapy	Regulatory status
EnteroMedics Inc.	Maestro®	Obesity	FDA approved
Microtransponder	Serenity®	Tinnitus	In development
Microtransponder	Vivistim®	Stroke rehabilitaion	In development
NeuroPace	RNS®	Epilepsy	FDA approved
SetPoint Medical	TBD	Inflammatory diseases	In development

AspireSR vagus nerve stimulation system (LivaNova)

The AspireSR VNS System is an FDA-approved medical device that offers unique cure for reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures and treating drug-resistant epilepsy and treatment-resistant depression. The device has incorporated a cardiac-based seizure-detection algorithm that can detect tachycardia (rapid heartbeat) and automatically trigger a defined auto-stimulation. The system consists of the implantable generator, lead, and external programming system used to change stimulation settings. The device was approved for use in the U.S. by the FDA in June 2015.

Equilia heart failure therapy system (LivaNova)

Cardiovascular disease has been shown to be associated with an imbalance in the autonomic nervous system that controls cardiac activity. The imbalance overstresses the heart and contributes to the worsening of heart failure. By stimulating the vagus nerve, the Equilia system is expected to improve heart function. The pulse generator acts similar to cardiac pacemaker. The device is being investigated in the Vanguard (Vagal Nerve Stimulation Safeguarding Heart Failure Patients) clinical study, which is designed to evaluate the device and therapy for heart failure patients. The device is investigational and not available for use or sale in the United States.

gammaCore vagus nerve stimulator (electroCore LLC)

The company is developing non-invasive vagus nerve stimulation therapy for the treatment of primary headaches (migraine and cluster headache. The device non-invasively stimulates the cervical branch of the vagus nerve. A sham-controlled pilot study on non-invasive vagus nerve stimulation (nVNS), recently published in Neurology (August, 2016), reported that nVNS therapy can reduce the number of headache days per month for chronic migraine patients[10]. The company is guaranteeing the device with a full refund should the therapy not work. The company is partially funded by Merck. The device is investigational and not available for use or sale in the United States.

VITARIA heart failure therapy system (LivaNova)

The Vitaria system utilizes Autonomic Regulation Therapy to treat chronic heart failure by restoring autonomic balance via low level, natural frequency vagus nerve stimulation. The system's pulse generator acts similar to cardiac pacemaker. The generator is computer-controlled and battery powered, and stimulates the vagus nerve in the neck through the electrodes sending signals to the heart and brain. The generator is 8 cc and weighs 16 g. With normal use, the lithium carbon monofluoride battery has a 5-8 year life expectancy. The device is investigational and not available for use or sale in the United States.

Other nerve stimulation

Vendor name	Product name	Target nerve	Target therapy	Regulatory status
Other nerve modulation				
Allergan	Oculeve™	Lacrimal gland	Dry eye disease	CE mark US IDE ongoing
Advanced Uro-Solutions (Medtronic)	Nuro System	Tibial nerve	Overactive bladder	FDA approved

Vendor name	Product name	Target nerve	Target therapy	Regulatory status
Atrotech	Atrostim PNS™	Phrenic nerve	Respiratory muscle paralysis	CE mark
Autonomic Technologies	Pulsante™	Sphenopalatine ganglion	Cluster headaches	CE mark
Avery Biomedical	TBD	Phrenic nerve	Breathing therapy	FDA approved
Axonics Modulation	Axonics SNM™	Sacral nerve	Urinary and fecal dysfunction	CE mark US IDE ongoing
Bioness	StimRouter™	Peripheral nerve	Chronic pain	FDA approved
BlueWind	OAB-1000™	Tibial nerve	Overactive bladder	CE mark US IDE ongoing
CVRx	Barostim neo™	Carotid baroreceptors	Heart failure	CE mark US IDE ongoing
CVRx	Barostim neo legacy™	Carotid baroreceptors	Resistant hypertension	CE mark US IDE ongoing
EndoNovo	tPEMF™	Tibial nerve	Neuro inflammation	FDA approved
ImThera Medical	aura6000™	Hypoglossal nerve	Sleep apnea	CE mark
InCube Labs	TBD	Tibial nerve	Bladder function restoration	In development
NeuImpulse	Lightpulse 100	Peripheral nerve	Chronic pain	CE mark
nUro Inc.	TBD	Tibial nerve	Overactive bladder	In development
SPR Therapeutics	Sprint™	Peripheral nerve	Chronic pain	FDA approved
Synapse Medical	NeuRx DPS®	Diaphragm muscles	ALS and other breathing problems	FDA approved

Navigated Brain Therapy® (NBT) (Nexstim plc)

Nexstim is a medical technology company developing a navigated non-invasive brain stimulation system. The NBT system is a device that uses navigated transcranial magnetic stimulation (nTMS) for use in stroke rehabilitation. The NBT technology is an advanced navigated transcranial magnetic stimulation system with the capable to model the electric field in the brain. E-field and EMG response based navigation enables enhanced accuracy, repeatability and dose control. This unique way of applying non-invasive magnetic stimulation pulses in combination with electromyography (EMG) measurement can be used to obtain an input-output curve and estimated motor threshold in one fast scan lasting 60 to 90 seconds. The device is investigational and not available for use or sale in the United States.

Barostim neo legacy system (CVRx, Inc.)

The Barostim neo legacy system is an implantable device used to stimulate the baroreceptors of the carotid sinus. The company theorizes at the human body has its own mechanisms for sensing changes in blood pressure and other blood flow changes. This natural system is largely located in the brain, as well as the walls of the carotid arteries. Pressure sensors, called baroreceptors, are found on the carotid artery and in the carotid sinus. These sensors measure and report blood flow to the brain, which compares it to the body's needs. Providing high-frequency,

minute electrical impulses to the carotid sinus nerves and the receptors can provide positive feedback to the brain and reduce blood pressure. The device is investigational and not available for use or sale in the United States.

Nyxoah obstructive sleep apnea system (Nyxoah)

Nyxoah is developing on a neurostimulation-based therapy for obstructive sleep apnea. The system combines a small implant inserted at the back of the tongue. The implant then causes a slight motion of the tongue, thus preventing obstruction to the airway during sleep. The implant is energized using a stick-on battery patch that is placed on the chin over the implant site. The implant is 20 mm in diameter and 2.5 mm thick. The implant is estimated to last 12 years. The device is investigational and not available for use or sale in the United States.

tPEMF TheraCap system (Endonovo - Rio Grande Neurosciences)

The tPEMF TheraCap system is a baseball cap-like device that utilizes a proprietary FDA-cleared tPEMF (Pulsed Electromagnetic Field) technology for the treatment of postsurgical neuroinflammation. The therapy is a non-invasive, portable treatment that inductively delivers a weak electrical therapeutic field to the brain. The treatment is administered by the TheraCap and is used to address pain and edema. The company is also studying the device to treat traumatic brain injury and other indications that include neuroinflammation, including concussion and multiple sclerosis. The device is investigational and not available for use or sale in the United States.

A large number of neurostimulation related clinical trials are underway worldwide to investigate the stimulation of various nerves to treat a wide variety of diseases and conditions. Most of these are academic centered based. There are also supplier funded device related clinical trials underway or are in development to treat a range of disorders including: epilepsy, obesity, Parkinson's disease, depression, sexual dysfunction, cardiovascular disorders, movement disorders, gastrointestinal disorders, urinary tract disorders, sensory disorders and drug addiction. This opens up a wider market of applications for neurostimulation devices. The list below focuses on those supplier funded clinical trials.

Companies in active clinical trials for FDA PMA approval

Vendor name	Clinical trial name	Clinical trial #	Status
Axonics Modulation	Treatment of REfractory Overactive BLadder With the AXonics Sacral Neuromodulation System	NCT02620410 RELAX-OAB	Recruiting patients
BioControl Medical	INcrease Of VAgal TonE in CHF	NCT01303718 INOVATE-HF	Terminated
Boston Scientific	Deep Brain Stimulation (DBS) for the Treatment of Parkinson's Disease	NCT01839396 INTREPID	Recruiting patients
Boston Scientific	Deep Brain Stimulation With the VERCISE™ System: Vercise DBS Registry	NCT02071134	Recruiting patients
CVRx, Inc.	CVRx Barostim Hypertension Pivotal Trial	NCT01679132	Active, not recruiting
EndoStim	Investigation of the EndoStim® Lower Esophageal Sphincter (LES) Stimulation System for the Treatment of Reflux	NCT02749071	Recruiting patients
LivaNova	Vagus Nerve Stimulation Clinical Outcomes Measured Prospectively in Patients Stimulated	NCT01281293 V-COMPAS	Recruiting patients
ElectroCore LLC	Vagus Nerve for the Treatment of Cluster Headache	NCT01792817	Complete
Medtronic	Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy	NCT00101933 SANTE	Active, not recruiting

Vendor name	Clinical trial name	Clinical trial #	Status
Medtronic	A Pilot Study of Deep Brain Stimulation to the Lateral Habenulae in Treatment-Resistant Depression	NCT01798407	Recruiting patients
Medtronic	DBS for TRD Medtronic Activa PC+S	NCT01984710	Recruiting patients
Medtronic	DBS Therapy for Treatment Resistant Depression	NCT02046330	Recruiting patients
Metavention	COMPLEMENT Study- A First in Human Study of Metabolic Neuromodulation Therapy	NCT02278068 COMPLEMENT	Recruiting patients
MicroTransponder Inc	Vagus Nerve Stimulation (VNS) With Rehabilitation for Upper Limb Function Improvement After Stroke	NCT01669161 VIVISTIM	Completed
Scion NeuroStim	A Non-Invasive Neuromodulation Device for Treatment of Migraine Headache	NCT01899040	Active, not recruiting
Scion NeuroStim	Caloric Vestibular Stimulation for Parkinson's Disease	NCT02134795	Complete
Soterix Medical	Targeted Electrotherapy for Aphasia Stroke Rehabilitation - Phase II Multi-Center Study	NCT02540109 TEASER	Recruiting patients
St. Jude Medical	A Multi-Centre RCT of the Axium® Neurostimulator for the Treatment of Chronic Inguinal Pain Following Surgery (SMASHING)	NCT02349659 SMASHING	Recruiting patients
St. Jude Medical	Chronic Pain of the Trunk and/or Limbs	NCT02143791 PRODIGY-1	Active, not recruiting
Uroplasty, Inc	Prospective, Multicenter Trial to Investigate the Safety and Efficacy of Percutaneous Tibial Nerve Stimulation for the Treatment of Fecal Incontinence	NCT01666405 URGENT-PC	Terminated

Economic impact

The economic impact of neurostimulation devices is becoming increasingly complex. Reimbursement pressure exists both in the form of tighter reimbursement or no reimbursement at all. At the same time, suppliers are increasing device prices annually creating a squeeze of hospitals. With the rapid projected growth procedures and indicated uses, the economic impact of using neurostimulation devices will continue to worsen for hospitals. These devices are very similar to pacemakers in functionality. Yet, the average price for a neurostimulators is approaching that of a cardiac resynchronization therapy (CRT-D) device. In the chronic pain management segment, hospitals must align better with physicians to begin to control pricing or the payers will do it.

Reimbursement

Reimbursement exists but varies by payer and by therapy. Neurostimulation for chronic pain management is reimbursed whereas neurostimulation for other indicated uses may not be. Strict controls on the medically necessary policy criteria are in place so hospitals must coordinate patient care with the physician to insure appropriate hospital reimbursement. For example, reimbursement exists for spinal cord stimulation while the Centers for Medicare & Medicaid Services (CMS) concluded earlier this year that coverage for the treatment-resistant depression indication is not reasonable and necessary. In the longer term, the continued positive clinical data and changing health care environment point to expanding coverage but potentially at lower reimbursement rates.

Reimbursement rates for procedures has remain relatively constant (<0.5% increase for 2016). The location of the procedure becomes important to profitability as seen with the differences in the implantation of the lead(s) DRG023 at $31,590 vs implantation of the generator DRG518 at $17,275. If the lead is implanted in a different setting from the generator, the hospital may realize a loss on the generator implant procedure.

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