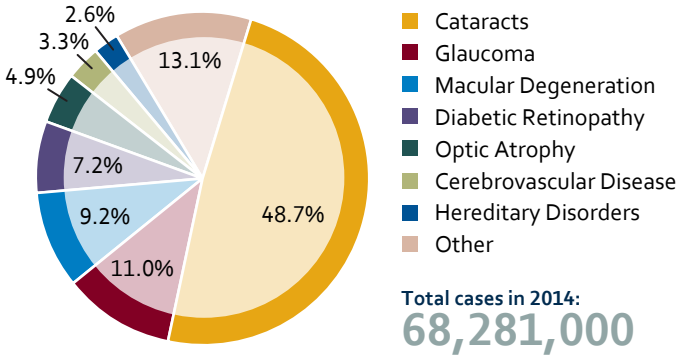
Eye Disorders Are Focus Of Novel Neurostimulation Technologies

by Michael Lachman

Medical devices that provide treatment using electrical neurostimulation technology have seen growing use in recent years for numerous applications, ranging from brain and movement disorders such as epilepsy and Parkinson's disease, to the management of chronic pain and hearing loss. (*See "Neuromodulation Market: Innovation Brings High-Growth Rewards"* — Medtech Insight, *March 2013 and "Emerging Peripheral Nerve Technologies Draw New Competitors To Neuromodulation Market"* — Medtech Insight, *April 2013.*) But the indications for this type of technology clearly are expanding, and ophthalmology has emerged as one of the more interesting areas of research in the neurostimulation field.

Exhibit 1

Global Burden Of Blindness And Partial Sight: Percent Of Cases By Cause, 2014



SOURCE: Life Science Intelligence Report, "Global Markets for Surgical Ophthalmology in 2013," published April 2013

Exhibit 2

Growth In Selected Sight-Threatening Conditions Worldwide, 2013–2017E (Numbers in thousands)

	2013	2014E	2015E	2016E	2017E	CAGR
Macular degeneration	6,166	6,284	6,406	6,524	6,649	1.9%
Diabetic retinopathy	4,729	4,909	5,072	5,231	5,388	3.3%
Glaucoma	7,456	7,529	7,604	7,676	7,733	0.9%

SOURCES: Life Science Intelligence Report, "Global Markets for Surgical Ophthalmology in 2013," published April 2013; Medtech Insight

In 2013, the US Food and Drug Administration approved **Second Sight Medical Products Inc.**'s *Argus II* Retinal Prosthesis System, an implantable neurostimulation device for the treatment of late-stage retinitis pigmentosa (RP). FDA approval of the Argus II was a high-profile event that brought renewed attention to the potential for neurostimulation applications in the ophthalmology arena; however, this device represents only the "tip of the iceberg."

There are now numerous corporate and academic programs around the world actively developing competing implants to address sight-threatening conditions such as RP and late-stage age-related macular degeneration (AMD). RP is a major cause of hereditary blindness and affects some 1.5 million people worldwide, while AMD is the third-leading cause of vision loss overall and, like many other vision disorders, is increasing in incidence as populations age.

In addition to sight-restoring electrical implants, implanted electrode technology also is being investigated for the treatment of moderate-to-severe dry eye disease, while others are working on noninvasive, externally delivered neurostimulation devices that aim to restore vision by revitalizing neurological communication pathways and reversing the cellular effects of degenerative eye diseases.

Second Sight Solidifies First-To-Market Status With Argus II FDA Approval

The Argus II System, in development since the company's founding in 1998, provides electrical stimulation of the retina to elicit visual perception in blind patients. The system has four components: a tiny camera and transmitter mounted on eyeglasses that capture and process an image, an implanted receiver that wirelessly receives these data and sends the signals through a thin cable to the back of the eye, an epiretinal implant consisting of an array of 60 electrodes that is secured to the retina and emits electrical pulses in response to the signals, and a wire-

less microprocessor and battery pack worn on the patient's belt that powers the entire device. The electrical pulses induce responses in the retina that travel through the optic nerve to the brain, which perceives patterns of light and dark spots corresponding to the electrodes stimulated. Patients learn to interpret these visual patterns into meaningful images and can gain the ability to achieve basic object recognition, identifying such things as doors, windows, and sidewalks.

In the company's FDA clinical study, all implanted patients achieved at least light perception, and those with the best outcomes could read large letters (1 inch to 2 inches in height). Most patients were able to perform mobility tasks and follow a white line, which is a surrogate for staying within a crosswalk while crossing the street. There were no product failures in the study, an achievement the company attributes to significant preclinical work in animals and long-term testing of the device in a simulated in vivo environment.

Although the Argus II received FDA approval in February 2013, the first commercial implants in the US did not occur until January of this year. In March 2013, Second Sight filed a supplement with the FDA to capture product improvements that had been implemented since the original premarket approval (PMA) submission in 2010. In addition, because the system uses radiofrequency (RF) transmission, approval also was needed from the Federal Communications Commission (FCC). Following receipt of both the FDA and FCC approvals at the end of last year, the product was launched commercially in the US, targeting 12 centers nationally that are currently accepting patient consultations.

There have been about 75 Argus II implants to date worldwide, including 30 in the FDA clinical trial, with 15 of those implanted in the US. The product received the CE mark in 2011 and also is being implanted in several European countries. Reimbursement has been established in Germany, where there are currently five implanting centers. In the US, Argus II has been approved by the Centers for Medicare and Medicaid Services (CMS) for both a new technology add-on payment (inpatient setting of care) and a transitional pass-through payment for the outpatient setting. (*See "Medicare Bonus Payments Awarded To Cook's Stent, Second Sight's Eye Implant"* — Medtech Insight, *August 2013*.) The device was named as a "Top Ten" innovation by the **Cleveland Clinic** last year. (*See "Six Devices, Diagnostics Among Cleveland Clinic's Top 10 Innovations For 2014"* — Medtech Insight, *December 2013*.)

Whereas the approved indication in the US is limited to RP with bare light perception, the label in Europe is broader, covering all outer retinal degenerations with severe-to-profound vision loss, which also includes late-stage AMD. The company estimates that there are over 100,000 patients who would be candidates for the Argus II in the US and Europe combined, based on currently approved indications. This year, Second Sight plans to initiate a feasibility study in patients with late-stage AMD, which represents a larger but older patient population compared to RP.

Second Sight is developing improved image processing software to enhance performance with the current 60-electrode array, while also developing a next-generation device with a higher density of electrodes. Longer term, the goal is to directly stimulate the visual cortex of the brain, rather than the retina, as this would allow treatment of blindness due to all causes, including glaucoma, without the need for an intact optic nerve.

Retina Implant AG To Commercialize This Year In Europe

The Argus II is currently the only retinal prosthesis with FDA approval; however, several competing development efforts, both corporate and academic, are underway. (*See Exhibit 3*.)

The most advanced of these is a wireless subretinal implant from **Retina Implant AG** of Germany, which received the CE mark in July 2013 for patients with retinal degeneration and no functional vision. Retina Implant will begin commercialization in Europe this year and is working to establish reimbursement in Germany and the United Kingdom.

The Retina Implant device is a 3-mm x 3-mm microchip containing 1,500 electrodes. Unlike the epiretinal Argus II implant, which is placed on top of the retina, the Retina Implant chip is implanted subretinally, underneath the macular region of the retina. And, rather than using a camera and transmitter to send an image to the chip, the eye's own optical system (cornea and crystalline lens) transmits images to the retina as in a normal sighted eye. To supply enough stimulation to the retinal nerve cells, the signal

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must be amplified, requiring that the chip receive power via an implanted power source. Patients can adjust the brightness and contrast of the system and store their personal settings. According to the company, blind patients in clinical trials have been able to recognize shapes of people and objects and read letters and words, although individual results can be quite variable.

Retina Implant was founded in 2003, and the first 10 patients were implanted with the device in a small pilot study that began in 2005. The pilot study involved a wired, externally powered system, and the devices were explanted after 30 days. In 2010, Retina Implant began enrolling a second clinical study to support CE mark approval. Thirty additional patients were enrolled in this study, which involved the first use of a longer-term implant and a wireless, internally powered system. Device longevity has been an issue, with devices implanted to date functioning only up to one year. Near-term development efforts will be focused on material processing to improve long-term stability of the system in the intraocular environment.

» Data from the first patients to receive Pixium Vision's implant are expected in 2014 and will form the basis of a CE mark application that could be submitted later this year.

The **Wills Eye Institute** in Philadelphia, which will be the lead clinical trial site for the Retina Implant device in the US, has been in discussions with the FDA regarding a US Investigational Device Exemption (IDE) clinical study, which could begin as early as this year.

Multiple Retinal Prosthetic Devices In The Pipeline

In addition to these competitors, there are several others moving forward in this field, including **Pixium Vision**, a French company; **Bionic Vision Australia**; **Nano Retina Inc.**, an Israeli joint venture of US-based nanotechnology developer **Zyvex Labs LLC** and Israel-based investor/incubator Rainbow Medical Ltd.; the Boston Retinal Implant Project, which has founded two companies, **Bionic Eye Technologies** and **Visus Technologies**, to commercialize its technology; and the CORTIVIS Project, a collaboration involving European and US researchers.

Founded in 2011, Pixium Vision is developing the *IRIS* (*Intelligent Retinal Implant System*) to treat patients who have lost their sight through degenerative conditions of the eye, such as RP and late-stage AMD. The company's technology was developed in collaboration with the Vision Institute at the National Eye Hospital in Paris.

The IRIS system utilizes a 150-electrode epiretinal implant that is surgically placed into the eye and attached to the surface of the retina. Similar to the Argus II, the IRIS system requires the patient to wear spectacles containing an integrated mini-camera and wireless transmitter. The spectacles are connected to a pocket computer, which processes the image captured by the camera into a signal that is transferred back through the spectacles and projected onto the retinal implant to stimulate the ganglion cells and generate images. The brain learns to interpret the signals it receives from the implant during a structured rehabilitation program undertaken by patients. Pixium Vision hopes to differentiate the IRIS system based on its novel camera technology, designed to capture visual information in a way similar to that of human eyes.

Pixium Vision has made rapid progress: the company was founded in late 2011, and its first implant system, the IRIS1, entered a clinical study in April 2013. Data from the first patients to receive the implant are expected in 2014 and will form the basis of a CE mark application that could be submitted later this year. Further into the future, Pixium Vision plans to commercialize a second-generation subretinal implant based on the Photovoltaic Retinal Prosthesis, which is under development by a group led by Daniel Palanker, PhD, at **Stanford University**. System prototypes have demonstrated functionality in in vitro and in vivo tests, and clinical trials could begin as early as 2016, with a CE mark possible by 2018 or 2019.

The Stanford prosthesis features several thousand electrodes that receive images acquired by a head-mounted video camera. The images are processed by a pocket computer and are then projected into the eye from video goggles using pulsed near-infrared light. The pulsed light is converted by each photovoltaic pixel into pulsed electric current that stimulates the nearby inner retinal neurons. Wireless retinal chips can be inserted in several modules, each about 1 mm in size. Since each photovoltaic pixel operates independently, they do not need to be physically connected to each other. Thus, small segments of the array may be separately placed into the subretinal space, "tiling" a large area while greatly simplifying the surgery.

Exhibit 3

Selected Companies/Institutions Developing Neurostimulation Devices For Eye Disorders

Company or Institution	Product/Description	Development Status
Retinal Implants for Retinitis Pigmentosa (RP) and/or Late-Stage AMD:		
Second Sight Medical Products	Argus II Retinal Prosthesis System Epiretinal implant that stimulates retina using processed image from spectacle-mounted camera	FDA approved February 2013; CE mark 2011; product commercialized in US and Europe
Retina Implant AG	Wireless, powered subretinal implant using image from eye's own optical system	CE mark July 2013; US IDE study could begin 2014–2015
Pixium Vision	Intelligent Retinal Implant System (IRIS) Epiretinal implant using processed image from external camera; subretinal second-generation implant	CE mark application estimated 2014–2015 for epiretinal implant
Bionic Vision Australia	Retinal implant using processed image from external camera	Initial human implants performed with prototype device
Nano Retina	Bio-Retina implant Retinal implant using image from eye's own optical system, powered by spectacle-mounted laser	Human implantation to begin as early as 2016
Boston Retinal Implant Project; Bionic Eye Technologies; Visus Technologies	Subretinal implant and external camera system	Implant in preclinical phase
CORTIVIS Project	Cortical Visual Neuroprosthesis Implant that stimulates visual cortex of the brain	Preclinical phase
Externally Delivered Neurostimulation for RP, AMD, Glaucoma, and/or Trauma:		
EBS Technologies GMBH	NEXT WAVE brain stimulation device Repetitive, transcranial alternating current stimulation for glaucoma or nerve/brain injury	Approved for sale in Europe; not approved for sale or investigational use in US
Okuvision GMBH	OkuStim Noninvasive, transcorneal microcurrent electrical stimulation for RP	Marketed outside the US; not approved for sale or investigational use in US
Acuity Medical International	TheraMac Noninvasive, transcutaneous microcurrent electrical stimulation for dry AMD	Marketed outside the US; not approved for sale or investigational use in US
ScyFIX	Noninvasive, transcutaneous microcurrent neuromodulation system for RP and/or dry AMD	Marketed outside the US; not approved for sale or investigational use in US
2C Tech Corp. Inc.	SeeQ Injected nanoparticle suspension that converts light into electrical stimulation	Phase I clinical study initiated in January 2014
Implantable Stimulation Device for Dry Eye Disease:		
Oculeve Inc.	Implanted electrode that stimulates lacrimal gland to restore tear production	Phase I clinical study underway

SOURCE: Medtech Insight

» BVA's Wide-View implant will be placed between the choroid and the sclera layers of the retina and will receive processed images captured from an eyeglass-mounted camera and transmitted via an external wire.

Bionic Vision Australia (BVA) is a consortium of Australian researchers, some of whom were instrumental in developing the cochlear implant marketed by **Cochlear Ltd.** The grant that established BVA came in late 2009, and since that time BVA has developed a 24-electrode early prototype device that has been implanted in three patients. For this device, a small lead wire extends from the back of the eye to a connector behind the ear. An external system is connected to this unit in the laboratory, allowing researchers to stimulate the implant in a controlled manner to study what patients are perceiving. Findings from this research are feeding back into development of two more advanced products: a Wide-View implant with 98 electrodes and a High-Acuity implant that will initially contain 256 electrodes and eventually contain 1,024 electrodes.

BVA's Wide-View implant will be placed between the choroid and the sclera layers of the retina and will receive processed images captured from an eyeglass-mounted camera and transmitted via an external wire. This system aims to restore vision to a degree that enables increased mobility and independence for patients. The High-Acuity device, which will utilize wireless data and power transmission and biocompatible diamond materials, aims to restore vision to a level where patients will be able to recognize faces and read large print.

BVA is not limiting itself to technologies developed in Australia. For example, the consortium is collaborating with Wolfgang Fink, PhD, of the **University of Arizona** and Erich Schmid, PhD, professor emeritus of the **University of Tübingen**, Germany, who are developing novel electrical stimulation strategies that could potentially improve vision to a greater degree than simply increasing the density of electrodes. These approaches include: (1) using variable electrode firing periods, including ultra-short bursts; (2) selectively firing the electrodes in specific patterns to better control the shape of electrical fields that are created; and (3) using some of the electrodes on the chip as return electrodes, so the stimulation can be more focused.

Nano Retina was founded in 2009 and is developing the *Bio-Retina* implant. Like the Retina Implant AG system, the Bio-Retina utilizes the optical system of the eye rather than an external camera to send images to the implant. The first-generation version of the device consists of 600 pixels, and the second-generation implant will feature 2,000 pixels. A rechargeable, battery-powered mini laser, situated on a pair of eyeglasses, powers the implant wirelessly.

The company hopes to differentiate its product based on simple, minimally invasive implantation, high resolution, low power consumption, and superior sealing of the implant to protect it from the intraocular environment. Nano Retina has validated system components in ex vivo and in vivo animal studies and is currently developing a human prototype. Human implantation of the Bio-Retina could begin as early as 2016.

The Boston Retinal Implant Project (BRIP) is another multi-institution, multidisciplinary effort to develop retinal implant technology. The project, which was initiated in 1988, is led by its two co-founders, Joseph Rizzo III, MD, of **Harvard Medical School** and Massachusetts Eye and Ear, and John Wyatt, PhD, of the **Massachusetts Institute of Technology**. As mentioned, BRIP has founded two companies to further develop and commercialize the key components of its system. Bionic Eye Technologies is developing a subretinal prosthesis that is still in the preclinical development phase, while Visus Technologies is developing "smart" glasses that incorporate wireless technology and embedded microcameras into a customized operational platform to provide visual information to blind patients through "sensory substitution." These glasses can be used alone as an assistive device or as the front-end driver of the subretinal implant.

The CORTIVIS Project is developing a microelectronic Cortical Visual Neuroprosthesis for the blind, which works by stimulating the visual cortex of the brain rather than the retina itself, using a processed image from a "bio-inspired" peripheral camera. Initiated in 2002 and led by Eduardo Fernández, MD, from **University Miguel Hernández** in Spain, CORTIVIS is a collaboration of researchers from at least five European countries as well as the US. This team decided to work on stimulation of the primary visual cortex because the neurons in higher visual regions of the brain often escape the degeneration associated with retinal diseases. If these higher visual centers can be stimulated with visual information in a format somewhat similar to the way they were

stimulated prior to the development of total blindness, a blind individual may regain limited but useful vision, including the ability to discriminate the shape and location of objects, navigate in familiar environments, and read enlarged text.

Most of CORTIVIS' current experimental work is being conducted in animals to improve biocompatibility and assure safety of the device. But researchers have also started acute implantations in human volunteers – patients who are already scheduled for significant brain tissue resection – to establish the safety of implanting multi-electrode arrays into human brain tissue. Preliminary results have been promising and short-term experiments in blind volunteers are planned for the near future.

Vision Restoration Through Externally Delivered Neurostimulation

Not every application of neurostimulation in ophthalmology requires the use of an implant. **EBS Technologies GMBH** of Germany has developed the *NEXT WAVE* brain stimulation device, which is designed to noninvasively revitalize selective communication pathways between neurological cells and expand the visual field of patients with impaired vision caused by glaucoma, optic nerve damage, brain injury, or stroke. The system delivers low-level electrical pulses via repetitive, transcranial alternating current stimulation (rtACS); the therapy is individualized to the patient and applied via externally placed electrodes. Although the system is approved for sale in Europe, it is not approved for sale or investigational use in the US.

Last year, EBS announced the results of a multicenter, 82-patient clinical trial of the NEXT WAVE device. About half of the clinical trial patients were given a 40-minute NEXT WAVE treatment for 10 consecutive days. Treated patients demonstrated an average increase of 24% in their total visual field, which was significantly better than patients in the control group who did not receive NEXT WAVE stimulation. All patients had vision impairment lasting at least six months prior to the clinical trial and had

exhausted all standard therapeutic options to improve their vision.

In addition to these efforts, a number of companies have developed systems to apply noninvasive, transcutaneous microcurrent electrical stimulation to reverse the effects of degenerative retinal diseases such as RP and dry AMD. These products are available outside the US, but are not FDA approved. For example, **Okuvision GMBH**, a subsidiary of Retina Implant AG, markets the *OkuStim* transcorneal electrical stimulation system, which is designed to reverse or halt the gradual effects of RP by activating neuroprotective growth factors in the retina. Patients place electrodes over their closed eyes to deliver the therapy in one 30-minute session per week.

» A number of companies have developed systems to apply noninvasive, transcutaneous microcurrent electrical stimulation to reverse the effects of degenerative retinal diseases such as RP and dry AMD.

Two US-based companies are marketing products outside the US that have mechanisms of action very similar to OkuStim. **Acuity Medical International Inc.** markets the *TheraMac* device with *V-RES* (Visual Restorative Electro-Stimulation) technology to restore vision in patients with the dry form of AMD. **ScyFIX LLC** markets a microcurrent neuromodulation (MCN) system for patients with either RP or dry AMD.

Meanwhile, **2C Tech Corp. Inc.** is pursuing a more sophisticated approach to retinal cell stimulation and rescue involving injection of nanoparticles into the vitreous of the eye rather than placement of electrodes onto the eyelids. A single injection of the company's *SeeQ* device constitutes billions of nanoparticles in a suspension. These nanoparticles produce electricity similar to that of a silicon solar cell and are activated by normal ambient light entering the eye without the need for an external power source. According to the company, this electrical stimulation induces diseased retinal cells to generate protective growth factors, which may prevent disease progression. However, periodic injections of SeeQ will likely be required to stop the retinal degenerative process. Because SeeQ particles deliver electrical stimulation in much closer proximity to retinal cells than do external electrodes, significantly less energy is required, and risk of corneal damage should be reduced. A Phase I clinical trial was initiated in January 2014 in Mexico, with the goal of achieving some functional vision improvement in late-stage RP and AMD patients.

Novel Implantable Stimulation Device Addresses Dry Eye Disease

In the field of therapeutics for dry eye disease, which is dominated by the prescription drug *Restasis* (cyclosporine ophthalmic emulsion; **Allergan Inc.**) and a wide range of over-the-counter lubricants and artificial tears, a novel device-based approach is under development by **Oculeve Inc.**, which was founded in 2011. The technology was conceived by researchers at Stanford University as part of a collaboration between the Biodesign and Ophthalmology departments.

The Oculeve implant is a tiny electrode that is placed via a minimally invasive, injection-like procedure through the eyelid and adjacent to the lacrimal gland. The device delivers small electrical pulses to the gland to stimulate and restore natural tear production. The Oculeve device could address the five million Americans with moderate-to-severe dry eye out of the roughly 25 million total US dry eye population. A Phase I clinical study of the device is underway. [A#2014700018]

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