EPIRETINAL IMPLANTED RETINAL PROSTHESIS: USING ELECTRICAL STIMULATION TO TREAT VISION LOSS IN PATIENTS WITH RETINITIS PIGMENTOSA

Katherine Dunkelberger, ked98@pitt.edu, Mahboobin 4:00 pm, Evan Kaseman, ejk50@pitt.edu, Mahboobin 4:00 pm

Abstract — Patients with retinitis pigmentosa, a degenerative outer retinal disease affecting 1.5 million people, experience progressive vision loss due to damage in an area of photoreceptors in the retina. To help combat this disease, epiretinal implants utilize an embedded electrode array on the surface of the retina that stimulates retinal cells to partially restore functional vision. The Argus II, an innovative epiretinal prosthetic used to treat retinitis pigmentosa, received Food and Drug Administration (FDA) approval to market in February 2013 under the Humanitarian Use Device Exemption. Epiretinal implants are important at this time because without any viable cure for this genetically inherited disease, patients with retinitis pigmentosa have little hope of regaining sight. Technical topics covered in this paper include degenerative eye diseases and retinal prosthetics, specifically the Argus II. The retinal prosthetics information contains explanation of the functioning of the Argus II system, the importance of the microelectrode array, and the significance of device placement. This paper then discusses ethical implications including a risk-benefit analysis and the sustainability of treatment. Related future research of epiretinal prosthetics is explored to evaluate advancements of the technology. Finally, Dr. José-Alain Sahel, Chair of the Department of Ophthalmology at University of Pittsburgh Medical Center, provides expert insight on current vision restoration research.

Key Words — Argus II, degenerative eye disease, epiretinal prosthetic, microelectrode array, neuroprosthetic, retinitis pigmentosa, vision restoration

RETINAL PROSTHETICS: THE LEADING INNOVATION IN VISION RESTORATION

Navigating the world without sight is a frightening thought for most people. The 1.5 million people affected by retinitis pigmentosa (RP), however, may face this reality as their disease progresses, according to the article “Visions of a Bionic Eye” by Nigel Lovell and Gregg Suaning in IEEE Pulse [1]. A degenerative eye disease, retinitis pigmentosa affects the part of the eye that translates light into neural signals. No cure exists for retinitis pigmentosa, though researchers are currently investigating treatment methods. Since modern medicine falls short in curing RP, patients in late-stage RP go completely blind.

Retinal prosthetics (RPS) provide hope for patients suffering from degenerative eye diseases. This pioneering technology aims to translate images of the world to the brain via a microelectrode array, thus restoring functional vision. The most recent RPS involve surgically implanted electrode arrays. Epiretinal, subretinal, and suprachoroidal placement of the array are being tested, but epiretinal prosthetics (ERP) deserve increased attention. The epiretinal prosthetics have a greater amount of successful clinical research as explained by Ashish Kishore Ahuja and Matthew Behrend in their article “The Argus™ II retinal prosthesis: Factors affecting patient selection for implantation” [2]. The Argus II is an especially successful and well-tested epiretinal prosthetic capable of partially restoring functional vision. In their presentation at an International IEEE conference, David Zhou, Jessy Dorn, and Robert Greenberg explained the milestones in the Argus II’s history. A long-term clinical trial of the Argus II began in 2007. It became the first commercially available treatment for RP in 2011, and gained Food and Drug Administration (FDA) approval to market in the United States in February 2013 [3].

The Argus II has proved a major breakthrough in the treatment of retinitis pigmentosa. However, it is not a perfect solution and has notable risks. Later sections will discuss ethical and societal concerns of the Argus II and other ERP. Any medical treatment requires risk-benefit analysis, and this particular technology requires additional analysis of longevity and research methods. Through this analysis, the sustainability of RPS will be evaluated with respect to the following definition: a sustainable medical technology is one that effectively treats a medical condition and effects lasting improvements for the patient. Despite obstacles, ERP remain a promising innovative treatment option for degenerative eye diseases, particularly retinitis pigmentosa. Future research could improve the safety of implantation, resolution of visual stimuli, and similarity to natural vision. Dr. Sahel’s insight relates the direction of future research to the challenges of evaluating the sustainability of an evolving field.
OPHTHALMOLOGY: AN OVERVIEW OF EYE ANATOMY AND DEGENERATIVE DISEASES

In order to understand the mechanics of ERP, one must understand certain eye structures and functions. Eyes process light from our environment and produce mental images. Important steps in this complicated process occur in the retina. Different types of retinal prosthetics attach at different layers of the retina. Degenerative eye diseases such as retinitis pigmentosa affect cells in the retina. Retinal prosthetics offer hope for patients with incurable degenerative eye diseases.

Important Eye Structures and Functions

Our sense of sight works by translating wavelengths of light into neurological signals which the brain interprets to form the images we see. The article “Layers of the Retina” from the Discovery Eye Foundation describes the anatomy of the eye in detail [4]. Light enters the eye through the pupil, a small hole in the front of the eye. The light then passes through a lens which sits directly behind the pupil and into the vitreous cavity—the fluid-filled inside of the eye. Small muscles adjust the size of the pupil and the shape of the lens to focus the light onto the back of the eye called the retina. The retina is made up of rods and cones—photoreceptor cells that are activated by light. The area of the retina where vision is focused, called the macula, is the most sensitive area of the retina and is located at the back of the eye. Photoreceptors send signals to retinal neurons which in turn transmit those signals to the optic nerve, the neurological highway for visual information heading to visual processing centers in the brain [4]. See Figure 1 below, from the article “Facts About Age-Related Macular Degeneration” published by the National Eye Institute, for a depiction of important eye structures.

Mimicking the function of the eye structures is key for restoring sight for patients with retinitis pigmentosa and is a goal for retinal prosthetics. The article “Artificial Vision Through Neuronal Stimulation” appearing in the journal Neuroscience Letters outlines the key anatomical areas for retinal prosthetic research including the epiretinal surface, subretinal space, and suprachoroidal space. The epiretinal surface is the surface closest to the entering light in the eye. The subretinal space is behind the epiretinal surface. The suprachoroidal space is behind the subretinal space [6].

From an article by Rodrigo Fernandes, Bruno Diniz, Ramiro Ribeiro, et al. titled “Artificial Vision Through Neuronal Stimulation,” Figure 2 below depicts the possible placements of retinal prosthetic microelectrode arrays.

Each placement area corresponds to certain advantages and disadvantages. How the electrodes interact with retinal cells is vitally different among the microelectrode placements. In Figure 3 below from Susan DeRemer’s article “Layers of the Retina,” notice that the rods and cones, the photoreceptor cells stimulated by light, are underneath other retinal cells.
Katherine Dunkelberger  
Evan Kaseman

to retinal neurons located toward the surface of the retina. This striation of the retina seems counter-intuitive: light passes through layers of cells before activating photoreceptors, which then send corresponding signals back through those same cell layers. The signal is eventually transmitted back along the optic nerve to visual processing centers in the brain. The crucial relevance of this retinal anatomy is that subretinal electrodes connect to the most basic retinal cells that can still function, as the article “Artificial Vision Through Neuronal Stimulation” appearing in the journal Neuroscience Letters explains. ERP, however, target retinal neurons on the other side of the retina. These retinal neurons, when healthy, receive signals from lower order retinal neurons. Such signals are generated originally by photoreceptors, the cells most damaged by degenerative eye diseases. Thus, epiretinal prosthetics are the optimal treatment for patients with degenerative eye diseases because they stimulate retinal neurons further along the visual processing chain. This bypasses damaged photoreceptors and has proven to be effective in restoring functional vision [7].

Degenerative Eye Diseases Addressed By Visual Prosthetics

Retinal prosthetics have been clinically tested for various eye ailments, primarily degenerative eye diseases. The vast majority of clinical trial subjects suffer from progressive retinal dystrophies since retinal prosthetics were designed with this type of pathophysiology in mind. The term retinal dystrophy covers a wide range of inherited disorders affecting the retina. Progressive diseases begin with mild symptoms and worsen over time. Many subgroups of retinal dystrophies exist, but the most common disease, retinitis pigmentosa, is the most relevant for epiretinal prosthetics.

Peter Francis details in his article “Genetics of Inherited Retinal Disease” that instead of a specific mutation causing one specific set of symptoms, retinitis pigmentosa is a common set of symptoms among diverse combinations of genetic mutations. Over one hundred genes can contribute to RP and the disease can follow multiple inheritance patterns [8]. Francis further describes that retinitis pigmentosa typically affects rods—one type of photoreceptor cell. The rods die by programmed cell death because of genetic mutations. In the late stages of retinitis pigmentosa, the other type of photoreceptor, cones, are indirectly affected and degenerate as well. The disease progresses from symptoms of night-blindness, shrinking visual field, loss of visual acuity, and certain characteristic patterns of pigmentation in the retina to eventual complete blindness [8].

Retinal prosthetics have been used to treat other degenerative eye diseases including macular dystrophies, rod-cone dystrophies, and choroideremia—a degeneration of the nutrient layer of the eye resulting in retinal degeneration as explained by the article “Choroideremia” from the National Library of Medicine [9]. The article “Retinal Prostheses in the Medicare Population” commissioned by the Agency for Healthcare Research and Quality presents summaries of clinical trial data for RP testing. The review claims “blindness from RP has much higher direct medical and societal costs than other common causes of vision loss” because RP onsets earlier in life, therefore requiring more treatment years and resources [10]. The review includes RP trials, AMD trials, and trials including other degenerative eye diseases. Because RP is common, lacks treatment options, and onsets at an early age, retinal prosthetics have the most impact for RP. Thus, ERP may have significant benefits for other patient populations aside from RP, but patients with RP should be the main focus of ERP.

RECREATING VISION THROUGH RETINAL PROSTHETICS

Retinal prosthetics have progressed significantly to restore vision for patients with degenerative eye diseases, specifically retinitis pigmentosa. Since degenerative diseases primarily affect the photoreceptors, leaving the remaining original visual pathway intact, RPS are an ideal treatment for RP, according to the article “Retinal Prostheses in the Medicare Population” by Joann Fontanarosa, Jonathan Treadwell, David Samson, et al., because the devices utilize the remaining inner retinal cells to transmit images to the brain [10]. Compared to other current treatments, including gene therapy, low vision aids, and vitamin A supplements, RPS provide a more effective treatment due to their connection with existing retinal cells. The placement of the microelectrode array on the epiretinal surface of the eye, as in the case of the Argus II, is less invasive and is a more direct connection to the optic nerve fibers than subretinal or suprachoroidal retinal prosthetics as illustrated in the article “Artificial Vision Through Neuronal Stimulation” in the Neuroscience Letters journal [7].

How Retinal Prosthetics Compare to Other Treatments

Most treatments for RP focus on maximizing existing vision rather than restoring lost vision, from special lenses to magnify central vision to daily doses of 15,000 international units of vitamin A palmitate attempting to slow the progression of RP, as explained in the article “Facts About Retinitis Pigmentosa” published by the National Eye Institute [11]. However, these treatments do not benefit those patients with late-stage RP, as they are designed for patients that have not reached the point of complete blindness. Blind rehabilitation exists for those fully deprived of sight in order to maintain the patient’s independence and maximize quality of life, but this type of treatment only aims to manage the disease, not reverse the effects.

Conversely, the goal for retinal prosthetics is to restore lost vision due to retinitis pigmentosa, age-related macular degeneration, and other degenerative eye diseases. Utilizing an artificial means of detecting light, such as a camera, the
light energy is converted into an electrical signal. A multielectrode array implanted either on the epiretinal, subretinal, or suprachoroidal surface delivers the signal to the retinal neurons still remaining in the eye. In “Retinal Prostheses: Current Clinical Results and Future Needs,” an article written by James Weiland in the Ophthalmology journal, Weiland details how the application of an electrical charge from the multielectrode array in close proximity to a neuron can depolarize the neuron. Through the depolarization, action potentials are created in the extracellular fluid of the eye that results in a change in membrane potential and sends the signal through the optic nerve to the brain [12]. Through this connection with the original visual processing pathway, retinal prosthetics provide a treatment that restores vision rather than maximizing existing vision like the aforementioned alternative treatments. During these short periods of electrical stimulation, patients can identify rough images such as letters and shapes, significant progress for patients with complete blindness.

Furthermore, the ability for retinal prosthetics to restore vision during late-stage RP sets the treatment apart from another popular method—gene-based therapy. In an article published in the Technology Assessments journal titled “Retinal Prostheses in the Medicare Population,” the drawbacks of gene-based therapy are highlighted compared to RPS when Fontanarosa, the article’s author, notes that, “gene therapy appears to work best at rescuing failing tissue and does not appear to be as effective once all function is lost” [10]. Unlike RPS, gene-based therapy targets each of the 100 individual mutated genes responsible for RP to reverse the progression of the disease, but after the onset of complete blindness, this treatment is not viable. In addition, gene therapy has not been developed for every mutation that contributes to RP and not all contributing mutations are currently known. Hence, RPS are the most effective and adaptable present treatment for all stages of RP because the multielectrode array’s connection with the original visual pathway can help restore vision in patients with late-stage RP, with the epiretinal placement of the array providing the most direct connection.

**Placement of the Microelectrode Array: Benefit of Epiretinal Location**

While the multielectrode array can be placed in multiple locations—epiretinal, subretinal, or suprachoroidal—the epiretinal placement has proven most effective in partial restoration of visual function compared with the other two locations. Detailing the locations of each type of placement, the article “Chapter 1-Restoring Vision to the Blind: The New Age of Implanted Visual Prostheses” in the Translational Vision Science & Technology journal by Eberhart Zrenner and Bradley Greger analyzes the three types relative to each other and the comparable functional benefits as follows. Epiretinal placement of the multielectrode array is the furthest inside the eye, on the intraocular retinal surface located above the optic nerve fibers and ganglion cells, for a more direct control of the output signals of the retina. Conversely, the subretinal implant is placed directly in contact with degenerated photoreceptors, coupling the microelectrode array with photodiodes to detect light and ensure the device mimics natural eye movements. A less invasive technique, the suprachoroidal placement puts the multielectrode array between the choroid and sclera of the eye [13]. All three placements can be seen relative to each other in Figure 4 below from Zrenner and Greger’s aforementioned article.

![FIGURE 4 [13] Locations of multielectrode arrays relative to retinal cells and visual pathway](image)

In the visual imaging processing pathway, a complex connection between neurons exists, with retinal degenerative diseases such as RP affecting the first order photoreceptor neurons—the rods and cones. Subretinal and suprachoroidal prosthetics target the second order neurons of the pathway—the bipolar cells—which are the earliest viable target for vision restoration by visual prosthetic. See Figure 5 at the top of the next page, from Zrenner and Greger’s aforementioned article for a breakdown of the visual pathway.
A breakdown of the visual pathway into five orders of neurons:

Through this method, the prosthetic can take advantage of remnant retinal neurons close to the degenerated area and preserve some original processing. However, according to an article by Ashish Ahuja in the *Progress in Retinal and Eye Research* journal, the lack of an external power supply limits the array’s ability to properly stimulate the bipolar cells and optic nerve fibers for visual processing. Furthermore, degeneration of the first order photoreceptor neurons leads to anatomical remodeling and glial sheath formation between the target neurons and the electrodes of the multielectrode array for subretinal implants. Thus, the placement of the microelectrode array on the epiretinal surface is optimal because it is less invasive than the subretinal placement and targets photoreceptor neurons that are further along the visual processing pathway, leading to a more direct transmission of images from the device to the brain.

Some adverse effects discovered in clinical trials challenge the ethical legitimacy and longevity of the device.

### Breaking Down the Process of Image Transmission to Brain

Without the use of the damaged photoreceptors due to retinitis pigmentosa, the original visual pathway from the light initially entering the eye to the image being processed by the visual cortex in the brain is severed. Thus, the alternative treatments such as gene therapy and vitamin A supplements cannot restore vision to the patient because of the break in the pathway. However, the Argus II successfully restores functional vision by bypassing the damaged photoreceptors and targeting the third order neurons, the ganglion cells.

Ashish Ahuja describes the transmission process of the Argus II in detail in his aforementioned article, moving from external processing to internal processing of the modified pathway. The Argus II captures images of the environment in front of the user with a small camera with a resolution of 510x492 mounted in the center of the glasses. Connected by a wire to the patient-worn video processing unit (VPU) and battery, the camera transmits the image to the VPU, which digitizes the image in real-time and converts it to a 6x10 pixelated grid for the multielectrode array. Furthermore, the VPU generates a series of stimuli based on configurations made by the Argus II Clinician Fitting System software that are customized for each subject. Through the software, clinicians can control, for each electrode, the amplitude, pulse-width, and frequency of the stimulation waveform, allowing for the customization and adaptability of the device for different patients.

ARGUS II: A PIONEERING EPIRETINAL PROSTHETIC

Receiving a Humanitarian Device Exemption from the Food and Drug Administration in 2012, the Argus II, developed by Second Sight Medical Products, is the only commercially-approved treatment for late-stage RP in the world, according to David Zhou in his peer-reviewed article “The Argus II Retinal Prosthesis System: An Overview.” Utilizing a multielectrode array implanted on the intraocular epiretinal surface in combination with a virtual processing unit and camera mounted on a pair of glasses, the device is able to transmit images to the visual cortex. With over 120 subject-years in clinical trials, the Argus II is a pioneer in ERP and has shown significant ability to restore vision in patients with degenerative eye diseases. However, the two external portions of the device are pictured in Figure 6 below.

Once the information obtained by the camera is converted in the VPU, the signal travels back up the wire to an inductive radio-frequency (RF) coil link attached to the glasses. The coil wirelessly transmits the signal to a receiving...
Katherine Dunkelberger  
Evan Kaseman

and transmitting inductive RF coil secured to the outer surface of the eye under the rectus muscles by a scleral band around the eye. An electronics case, housing electronics needed for stimulation through the multielectrode array, is also secured by the scleral band and houses the implanted inductive RF coil. To connect the electronics case with the intraocular multielectrode array and transmit the signal, a metalized polymer cable penetrates the sclera with a pars plana incision. See Figure 7 below from the aforementioned article by Zhou, Dorn, and Greenberg for a depiction of the intraocular components of the Argus II.

![Internal components of the Argus II, demonstrating the structure and location of pars plana incision](image)

FIGURE 7 [3]  
Internal components of the Argus II, demonstrating the structure and location of pars plana incision

Once the signal reaches the intraocular region, the multielectrode array will receive the converted 6x10 pixelated grid image and stimulate the appropriate electrodes to produce the image. The implanted multielectrode array, made of a flexible polymer thin-film that allows the array to follow the curvature of the retina, is attached to the epiretinal surface over the macula with a retinal tack. Covering approximately 20 degrees diagonally of the visual field, the array has 60 platinum based electrodes organized in a 6x10 grid, with each electrode 200 μm in diameter and having a horizontal and vertical pitch of 525 μm. Sending controlled electrical impulses through the multielectrode array stimulates and depolarizes the remaining retinal ganglion cells, causing action potentials through the optic nerve. In his article “The Argus II Retinal Prosthesis: Factors Affecting Patient Selection for Implantation,” Ahuja reasons that when higher order visual pathway neurons are stimulated, the Argus II is able to transmit the image taken in by the camera on the glasses to the visual cortex in the brain [3].

![Demonstration of image produced by the Argus II transmitted to the patient](image)

FIGURE 8 [3]  
Demonstration of image produced by the Argus II transmitted to the patient

Scenarios similar to the one pictured above were utilized in the over 120 subject-years of clinical trials for the Argus II. The effectiveness of the device to restore vision to patients with RP and the durability of the device was tested in the clinical trials. The tests including Square Localization, requiring subjects to locate and touch a square that appeared in random locations on a black touch screen, and Direction of Motion, evaluating the patient’s ability to track and determine the direction of a white bar as it moved across the black touch screen at a random angle [3]. Unfortunately, many patients experienced intraoperative and post-implantation adverse effects. Such findings challenge the efficacy of the Argus II, requiring analysis of the relative benefits of the device as well as possible complications.

THE ETHICAL AND SOCIETAL ISSUES OF EPIRETINAL PROSTHESES

Vision restoration through ERP would improve the quality of life for potentially millions of patients affected by degenerative eye diseases. However, ERP have associated risks and uncertainties that raise doubt for ERP as an optimal treatment option. As with any surgical procedure, implanting an ERP device could have complications and side effects. These potential side effects are weighed against positive results obtained during clinical trials to evaluate the efficacy of the product. Other issues could arise since inorganic and synthetic materials of the device directly interact with the body, thus the degree of biocompatibility of the device and the human body contributes to the safety of the device. Moreover, the body is a hostile environment to foreign objects or substances including ERP. The durability and longevity of the device when implanted should be accounted for when determining the value ERP as a treatment for RP and other degenerative eye diseases.

Other ethical concerns regarding ERP involve research methods. A multitude of tests for measuring vision
improvement have been devised, so clinical trials rarely use the same testing methods. Furthermore, the low number of clinical trial subjects per study increases the uncertainty of results. Without a unified analysis across studies and because of small sample sizes, improvements in RPS may be difficult to identify and so research is not as efficient as it could be. Improvements regarding societal issues, specifically concerning the sustainability of ERP, are a top priority. Though ERP are currently the most successful treatment of retinitis pigmentosa, as a medical technology they raise sustainability concerns pertaining to effectiveness and longevity.

**Surgical Complications and Other Adverse Events: Is the Benefit Worth the Risk?**

Implanting ERP can restore functional vision but has the potential to damage the eye. In the study “Retinal Prostheses in the Medicare Population” commissioned by the Agency for Healthcare Research and Quality, 10 out of 11 major RPS clinical studies reported “adverse effects” [10]. Implantation surgical complications were reported in 6 of these studies, while 2 studies reported no surgical complications. Of the studies reporting complications in removal surgery, two-thirds reported some complications. After implantation, some patients experienced inflammation, changes in pressure within the eye, eye-scratching, bleeding, and limited eye-movement [10]. In the most serious cases, patients experienced trauma to the optic nerve. For this reason, the Argus II was granted the Humanitarian Device Exemption by the FDA, as mentioned before, because the device has not proven to be 100% effective but has shown that the possible benefits of the technology outweigh the health risks. The adverse effects cannot be ignored and must be addressed with future research to improve patient visual acuity as well as the stability and longevity of the implant.

While the aforementioned adverse events may detract from the efficacy of the device, the Argus II has shown promise for vision restoration in patients with RP. In addition to the FDA exemption, of which the Argus II is the only retinal implant to receive this distinction, the device received the CE Mark in Europe that made it the first commercially available implant in the world, according to the article “Artificial Vision Through Neuronal Stimulation” written by Rodrigo Fernandes [6]. The results of over 120 subject-years in clinical trials provided sufficient evidence that the Argus II was a viable solution to treat RP. As detailed in Fernandes’s article, the Second Sight Argus II Clinical trial was conducted from June 2007 to August 2009, with continual follow ups with the patients for up to 3.5 years after the conclusion of the testing [6]. Totaling 32 patients enrolled in the trials at 11 clinical centers, the trial was the largest of its kind for retinal prosthetics to date. Focusing on visual acuity measurements using a high-contrast 4 alternative choice square wave grating test, the trials aimed to investigate the device’s ability to at least partially restore if not fully restore functional vision. From Fernandes’s description of the trials results, with the Argus II, the best patient visual acuity achieved was 20/1260, compared to an ideal 20/20 level [6]. While the result was not ideal, the clinical trial provided significant evidence that the Argus II has the capacity to restore vision in patients with late-stage RP, since visual acuity is a common measure of vision restoration in clinical trials. Furthermore, in further tests conducted in the clinical trials regarding letter reading published in James Weiland’s article “Retinal Prostheses: Current Clinical Results and Future Needs,” 6 subjects were able to successfully identify any letter of the alphabet 63.5% of the time, with 72.5% of subjects able to correctly identify a small set of 8 letters [12]. However, the longevity of the device is in question, as the implant may degrade or come loose due to the inhospitable environment of the eye for the material.

From Weiland’s analysis of the complications experienced by patients with the Argus II in “Retinal Prostheses: Current Clinical Results and Future Needs,” one of the more common adverse events that occurred during clinical trials, with 3 cases out of the 32 subjects, was conjunctival erosion, a condition affecting the mucous membrane on the outer surface of the eye and lining of the eyelids [12]. While all except one device was repaired successfully, the complication affected the extraocular portion of the device, which secures the device in place on the eye. Furthermore, Weiland details how the retinal tack used to fixate the microelectrode array to the epiretinal surface may detach over time, leaving the intraocular portion of the device free to move around [12]. 2 patients required a retack during clinical trials, raising concern whether the Argus II can serve as a permanent treatment for RP. If the device is expected to be a long-term treatment, the material of the Argus II must withstand the harsh environment of the eye and the microelectrode array must be secured properly. Without these characteristics, the Argus II could not be considered a sustainable medical technology. If patients regularly require surgery to fix mechanical issues, then an abundance of resources are spent on maintenance. The need for continuing surgical interventions would suggest that the device is not economically sustainable and does not lead to lasting improvement. Since only 2 patients out of 32 subjects required surgical retacking, the Argus II’s sustainability could be improved, but the success of clinical trials outweighs the concerns of device longevity.

Evaluating these promising results along with the previously mentioned adverse effects discovered during clinical trials, the benefits of the Argus II to restore vision for patients with RP outweighs the health risks posed by the surgery and implant complications, as demonstrated by the FDA approval and CE Mark the device received. Although the Argus II has shown great promise to treat RP in clinical trials, some concerns arose regarding the research methodology of the trials.
Research Methodology Concerns

Since development of RPS is ongoing, the validity of research is crucial to continued improvement. In the article “Retinal Prosthetics in the Medicare Population,” Fontanarosa calls attention to the small sample size of RPS studies. Clinical research is clearly limited by the rarity of willing late-stage RP subjects. Current RPS technology necessitates highly specialized equipment such as the microelectrode array and delicate ocular surgery, so clinical trials require a large investment of resources, additionally limiting the quantity of participants [10]. However, the Argus II study included 32 subjects, significantly more than most other studies.

The Argus II is one of many clinically tested RPS devices. While the Argus II leads the field of RPS in approval and availability, adverse events did occur during its research. The potential for surgical complications or hardware issues makes safety a primary concern in future research. The research methods for RPS device testing are varied and lack a standardization that would otherwise unify the field. With a standardization of evaluation techniques, researchers would have a means of comparing outcomes across devices. Furthermore, researchers could compare classes of RPS, for instance ERP versus subretinal prosthetics, to determine how the placement of the microelectrode array affects specific characteristics of functional vision. The lack of standardization reduces the efficiency of research since data cannot easily be compared and improvement areas not easily identified across device studies. The standardization of RPS testing constitutes one area of necessary future improvement, in addition to technological advancements for the device.

Societal Implications of Retinal Prosthetics

Stemming from the above research methodology concerns, RPS face societal issues pertaining to their effectiveness and longevity. Such issues challenge the sustainability of the technology, especially since RP still lacks a cure, because patients desire a treatment that can restore vision and maintain the restored vision for an extended period of time. The Argus II has shown positive results for vision restoration during clinical trials, reaching a 20/1260 level of visual acuity as mentioned previously from Rodrigo Fernandes’ article “Artificial Vision Through Neuronal Stimulation” [6]. While this result is significant for patients with complete blindness, a visual acuity of this magnitude only provides basic ability to read large printed letters and simple orientation and mobility tasks. For the technology to be considered sustainable, improvements such as a denser multielectrode array are required to increase the effectiveness of the devices for more complex daily function. Ideally, these patients would be able to perform tasks such as cooking their own meals or cleaning their house, tasks that many take for granted, on their own, increasing their sense of independence.

Through the standardization of research methodology, researchers can more accurately estimate the longevity of the device. According to the article “Retinal Prostheses in the Medicare Population” by Joann Fontanarosa, Jonathan Treadwell, David Samson, et al., out of the 32 patients in the Argus II study, 24 of them still had functioning devices at an average follow up of 6.2 years [10]. Therefore, the longevity of RPS cannot fully be determined until further testing and follow up is done with current patients. To this point though, the Argus II and other RPS have shown the ability to provide an effective, lasting treatment for patients with RP. However, they require further research to improve visual acuity for the patient and durability of the product to provide a treatment that can hopefully last the remainder of the patient’s life.

FUTURE RETINAL PROSTHETIC RESEARCH: OBSTACLES AND IMPROVEMENT AREAS

ERP remain the most promising treatment for RP despite some surgical complications and concerns about sustainability of the device. ERP have succeeded in restoring functional vision to patients, but current technology provides low resolution and issues of biocompatibility. In order to improve ERP, the microelectrode array must contain a higher number of electrodes per area, which is the greatest obstacle researchers must overcome. Some researchers have attempted to design a completely implanted retinal prosthetic, meaning no external camera is necessary as detailed in an article by Alan Chow, Vincent Chow, Kirk Packo, et al. titled “The Artificial Silicon Retina Microchip for the Treatment of Vision Loss From Retinitis Pigmentosa” [14]. Such improvements to simplify the device and make it more compatible with the body are the future of ERP. At the forefront of current research regarding the treatment of RP, Dr. José-Alain Sahel, the Chair of the Department of Ophthalmology at University of Pittsburgh Medical Center, elaborates on current research goals to improve RPS.

Increasing Resolution of Artificial Vision Through Improvements on the Microelectrode Array

The goal of ERP is to restore or improve functional vision. The greatest step in achieving that goal requires increasing the resolution of the microelectrode array. The Argus II’s microelectrode array consists of a 6x10 matrix of electrodes. Subjects implanted with the Argus II would only be able to see this grid of light spots, called phosphenes. If a microelectrode array can contain more electrodes, then the subject can see more phosphenes. Therefore, the greater resolution of the microelectrode array, the greater the resolution of the perceived image, and the better the functional vision. Furthermore, in an IEEE Pulse article titled “Visions of a Bionic Eye,” Nigel Lovell emphasizes the importance of “one-to-one connections between electrodes
and neurons” to improve resolution by stimulating individual neural cells [1]. However, the application of this proposition has eluded researchers thus far due to the physical constraints regarding the pitch of the epiretinal stimulation without using current focusing or current steering [1]. However, a one-to-one connection between the individual neural cells and the electrodes would increase the sustainability of RPS because the resolution of the device would significantly increase, improving the effectiveness of the treatment because the patient’s visual acuity will be much clearer. The basic principle of the technology—utilizing electrical stimulation of the remaining retinal neurons to connect the device with the original visual pathway—has proven effective, but needs to be refined for optimum clarity and functionality for the patient. Specifically, the location of the multielectrode array on the epiretinal surface must be optimized to maximize the number of connections with the retinal ganglion cells. Placing a high electrode density array on the macula, the center of the retina that processes sharp, clear vision, significantly improves vision restoration due to the high ganglion cell density in this region, as claimed by Ashish Ahuja in his article “The Argus II Retinal Prosthetics: Factors Affecting Patient Selection for Implantation” [2]. With the macular placement of the multielectrode array, a higher percentage of electrodes can elicit phosphene responses to stimulate the visual system and produce a higher resolution image for the patient. Thus, one key goal of further research and development for the Argus II is to increase the number of electrodes in the microelectrode array to improve the visual acuity and increase the visual field of the patient.

Moving Toward Natural Vision: Fully Intraocular Epiretinal Prosthetics

Another critical advancement researchers are currently pursuing is a fully intraocular epiretinal prosthetic, not requiring any external components such as the Argus II’s specialized glasses, in order to mimic natural vision. To make ERP functional vision more natural, Weiland suggests in the Ophthalmology article “Retinal Prostheses: Current Clinical Results and Future Needs” that an intraocular device or a camera that responds to eye movements would create more natural restored vision [12]. The report “Retinal Prostheses in the Medicare Population” by Fontanarosa describes the reviewed RPS. The only completely intraocular device reviewed was the Artificial Silicon Retina (ASR) by Optobionics. This device consists of a microchip of 5,000 microphotodiodes which convert light from the environment, or incident light, into electrical signals [10]. Microphotodiodes function analogously to solar panels, and thus require no external power source. The research publication of ASR pilot clinical trials titled “The Artificial Silicon Retina Microchip for the Treatment of Vision Loss from Retinitis Pigmentosa” explains the methods and results of the 6-person study. The completely intraocular device functioned electrically during the course of implantation—6 to 18 months. The article states that “visual function improvements occurred in all patients” [14]. However, the research was submitted for publication in 2002 and published in 2004, with only one related thesis presented since [15]. ASR shows promise for fully intraocular RPS, but lacks the strong clinical verification of the Argus II. Future research for ERP should aim toward an intraocular device so that functional vision from the device resembles natural vision as closely as possible. Alternatively, a camera responsive to eye movements would improve the current design of the Argus II, taking the device one step closer to natural vision.

Outlook for Retinal Prosthetics

With the field of RPS rapidly developing, patients who suffer from complete blindness due to RP have to opportunity to regain their sense of sight. Devices such as the Argus II are able to take advantage of the remaining visual pathway to restore vision through electrical stimulation of neurons using a multielectrode array. In an interview with Dr. José-Alain Sahel on March 22, 2017, the future of the Argus II and other RPS was evaluated, with the sustainability of the technology as a focus of the discussion. In its own right, the Argus II is a groundbreaking technology with years of research and clinical trials to support the effectiveness of the technology. However, Dr. Sahel explained that every year the capabilities of RPS improves, as demonstrated by a device in development in Germany that incorporates 1,500 microelectrodes in their array, a significant upgrade from the 60 electrodes in the Argus II [16]. Furthermore, Sahel described the difficulty to determine the longevity of RPS due to the lack of substantial, sustained human clinical trials outside the Argus II study. With a greater subject pool and duration of follow-up post-surgery, researchers can solidify a projected product lifetime for RPS [16]. Greater clinical data and future improvements would increase the sustainability of the Argus II. While the Argus II cannot be considered fully sustainable, RPS overall are a sustainable treatment for RP because they have proven to be effective and thus far have shown to provide lasting restored vision to patients.

RELATIVE VIABILITY OF EPIRETINAL PROSTHETICS FOR VISION RESTORATION

The Argus II exemplifies the current progress of ERP. The ERP class of RPS represents the most successful clinically tested and government approved RPS. Clinical trials of the Argus II included the largest patient sample and showed evidence that ERP restored functional vision in subjects with late-stage retinitis pigmentosa. Other treatments such as gene therapy and nutritional supplements have not proven effective in restoring functional vision. Although ERP clinical trials resulted in some adverse effects, ERP,
especially the Argus II have succeeded whereas these other treatments have not. Increasing the resolution of the ERP microelectrode array would significantly improve restored functional vision. Future research could work toward a completely intraocular ERP. The field of RPS has room for improvement, but nevertheless provides hope for those suffering from degenerative eye diseases.

SOURCES


[16] J. Sahel. Interview regarding retinal prosthetics and other treatments for retinitis pigmentosa. University of Pittsburgh School of Medicine Department of Ophthalmology. 3.22.2017

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