Confronting Retinitis Pigmentosa: Argus II

Two Student Team

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1. Introduction of Retinitis Pigmentosa

1.1: Overview

Retinitis Pigmentosa, or henceforth referred to as RP, is a range of rare and inherited disorders. There are more than 150 genes that can cause its phenotype, ranging from X-linked, autosomal dominant, and even mitochondrially linked. Symptoms can manifest in childhood and into adulthood (40+), in which the retinas begin to degrade. [1] Generally starting in the rods, a person first loses peripheral vision. The blindness then progresses towards the center of vision, attacking the cones. People can lose colorful sight, or completely lose vision in the most severe cases. 1 in 3,000 to 1 in 4,000 people worldwide have RP.

While RP currently has no definitive cure, Argus II, which has been granted FDA approval in 2013, is a vision prosthesis that has enabled patients with severe symptoms to not only respond to light, but to read out words and letters [2]. As prior treatments for the past century consisted simply of Vitamin A, Argus II presents a significant innovation and benefit to quality of life.

Despite its lack of cure, RP is not life-threatening, and patients can utilize many ways to reduce RP's impact on their quality of life. However, in 20-30% of cases, RP is associated with non-ocular diseases, which can lead to death. [3]

1.2: History of RP

First characterized in 1853 and named in 1857, RP has confounded generations of researchers, who were unable to discover its root cause until the advent of the human genome

enabled researchers to search for a genetic cause. In 1990, T.P. Draya et al. discovered a point mutation in a rhodopsin gene that was linked with RP, and future discoveries involving 150+ genes later cemented hereditary genetics as the primary cause of RP. [3] Symptoms vary depending on how the gene was inherited, and also whether or not the RP is characterized as non-syndromic or syndromic.

1.3: Motivation

Despite RP not being life-threatening, it negatively affects quality of life. With no prior effective treatments, those who lived with RP required assistance to perform basic tasks that involved sight until the arrival of the Argus II. The Argus II marks the first introduction of a FDA approved treatment for late-stage RP. [13] A prosthetic device that one places on their eyes, Argus II utilizes a camera and transmitter system to relay information gathered from one's surroundings to electrically stimulate the retinas of one's eyes. This electrical potential is then relayed through the optic nerve to one's visual cortex, which then allows the patient to perceive his or her surroundings. In order to install the system, eye surgery must be performed, and as a prosthetic, Argus II does not cure the underlying cause of the disease, but allows one with advanced symptoms to alleviate them.

While there are a few shortcomings for Argus II, it is the first effective treatment for a disease discovered 160 years ago, and this fact enables the Argus II to stand out among RP's available treatments.

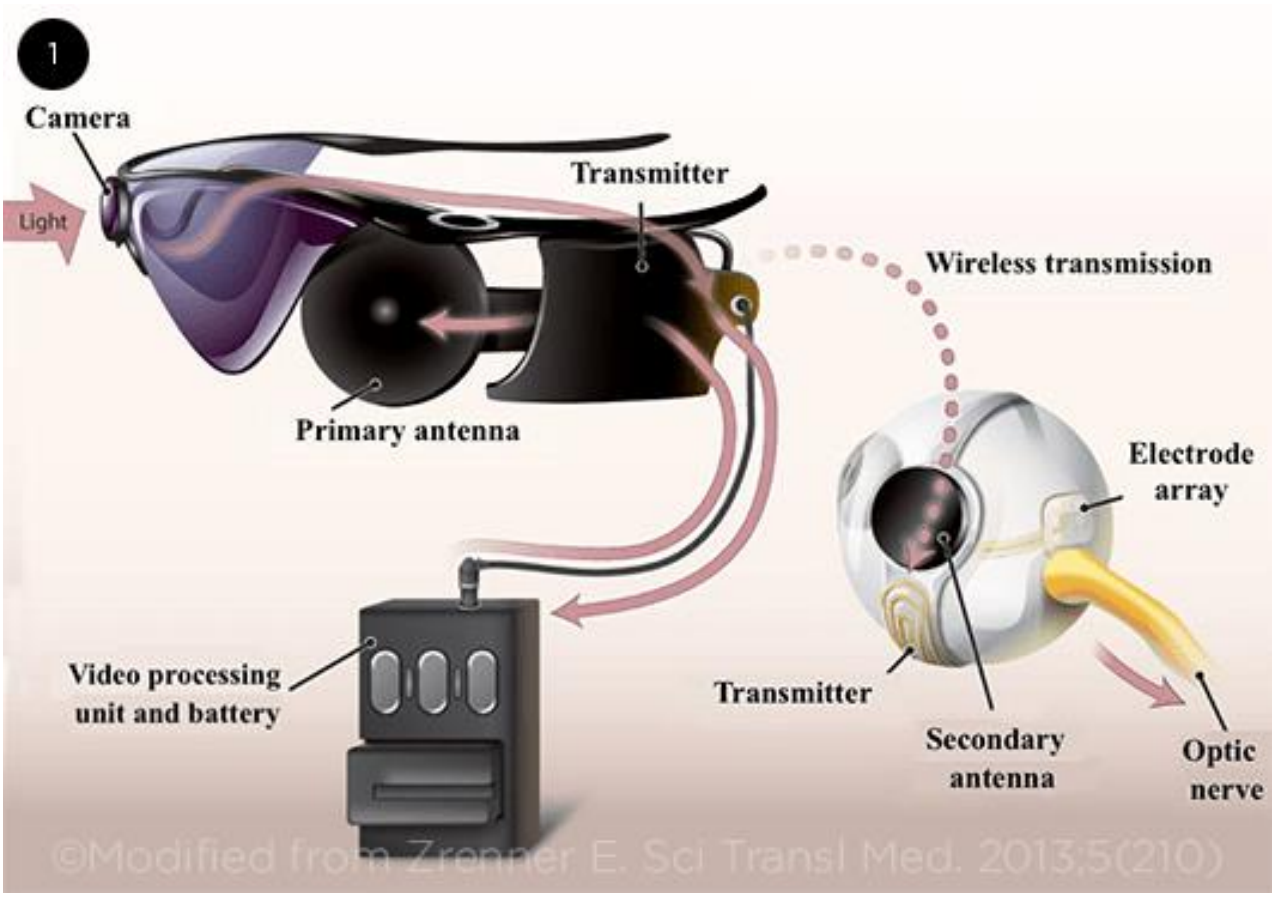

Figure 1: Argus II

2. Prior and Competing Treatments

2.1: Prior Treatments

There have been very few treatments for late stage retinitis pigmentosa. The majority of treatments aim to slow the deterioration of the retinas before it becomes severe. The main three treatments that have been used and are still used include Acetazolamide, vitamin A palmitate, and sunglasses. These three treatments vary in use and effectiveness.

Vitamin A Palmitate is solely used to slow the rate of deterioration of retinal function, and it is not always effective [4]. According to clinical trial data, daily doses of 15,000 IU, or 4.5

mg, on average slowed the rate of deterioration when the treatment was continued for several years [5]. This phase 1 study has not been completed according to the last update in 2017.

As for sunglasses, they are recommended to prevent the harsh UV rays on the already damaged retinas. All sunglasses make eyes less sensitive to light and in the case of retinitis pigmentosa, it prevents speeding up of vision loss [4].

Acetazolamide targets the swelling of the center of the retinas, otherwise known as macular edema [4]. This treatment is used in all stages of RP as the swelling can be present in all stages. Acetazolamide also improves visual acuity when treated with 250 mg/d and 500 mg/d [6]. Regardless of this fact, it is not a cure for RP. The retinas continue to deteriorate, and further dosage of Acetazolamide will be needed or become irrelevant. In late stage RP acetazolamide only reduces the swelling of the retinas and does not help vision acuity. Due to this fact, the Argus II is the only effective treatment in late stage RP.

2.2: Competing Treatments

There are currently no competing treatments for RP. The Argus II is the only device that treats the blindness caused by RP. There are many treatments in clinical trials, gene therapies being a main focus to treat or prevent RP in the future. As it stands today there is no competition for treating the blindness caused by RP, and Second Sight is looking to acquire the only other company - pixium vision - working on a potential competing prosthetic. There is mixed information on this acquisition and the two companies are still negotiating.

3. Argus II: Introduction and Innovation

3.1: Timeline

1853: RP is first characterized

1857: RP is given its name

1990: T.P Draya et al. discover the rhodopsin gene, paving way for gene therapy

2006: Clinical Trial for Argus II begins

2013: Argus II receives its FDA approval on February 13

2014: Second Sight applies for a patent for its Argus II device

2016: Second Sight has its application for a patent accepted

2017: XIRIUS gene therapy trial is submitted to FDA for Phase I/II certification

2018: Argus II is discontinued by Second Sight in favor for Orion

2021: FDA approves Second Sight's Argus 2s retinal prosthesis system on March 5

2034: Argus II patent expires

3.2 Argus II Introduction and Innovation

Introduced in 2013, the Argus II is a prosthetic implant that captures images using a miniature video camera mounted on glasses that send small energy pulses to electrodes implanted on the surface of the retina. It is the only prosthetic that is FDA approved, it brings the patient artificial vision that enables them to experience light perception, contrast sensitivity, and in general visual information once again. [13]

3.3: FDA Clinical Trial Information

Unlike pharmaceuticals, medical devices are subjected to more lax regulations from the FDA. The Argus II system applied for and received a Humanitarian Device Exemption (HDE) from the FDA due to RP being classified as an orphan drug disease. The HDE enabled the Argus II to bypass strenuous stage III clinical trials due to there not being enough test subjects to conduct a wider population study. However, Second Sight needed to submit clinical trial information to the FDA in order to demonstrate Argus II's effectiveness and safety. To meet this requirement, three clinical studies were conducted.

The first of these three studies was conducted between June 6, 2007 and August 11, 2009 by Mark S. Humayan, et al. In this study, the Argus II was tested for safety and efficacy using a number of metrics. For the testing of safety, the study tracked frequency, severity, and relation of adverse events. For the testing of efficacy, the study assessed visual function as a function of performance on orientation and mobility tasks. [15]

The images below help visualize the results of the study, which are discussed below the images.

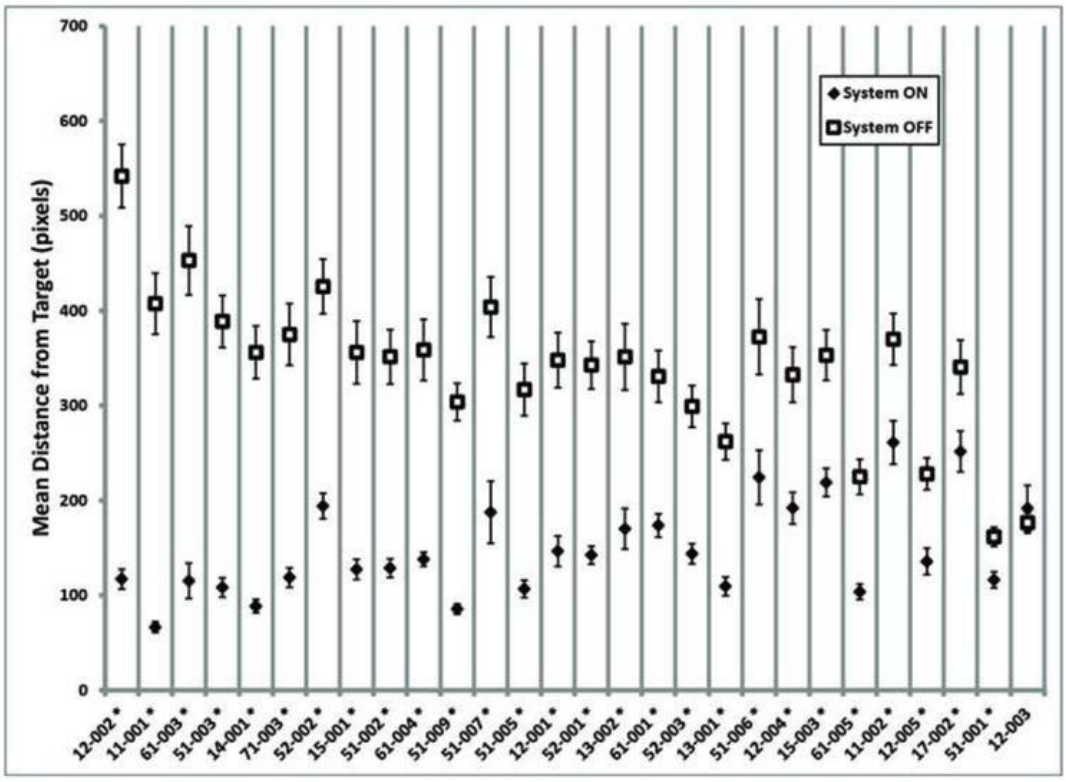

Figure 2: Mean Accuracy on the Square Localization task for each subject. Subject numbers are listed on the x-axis.

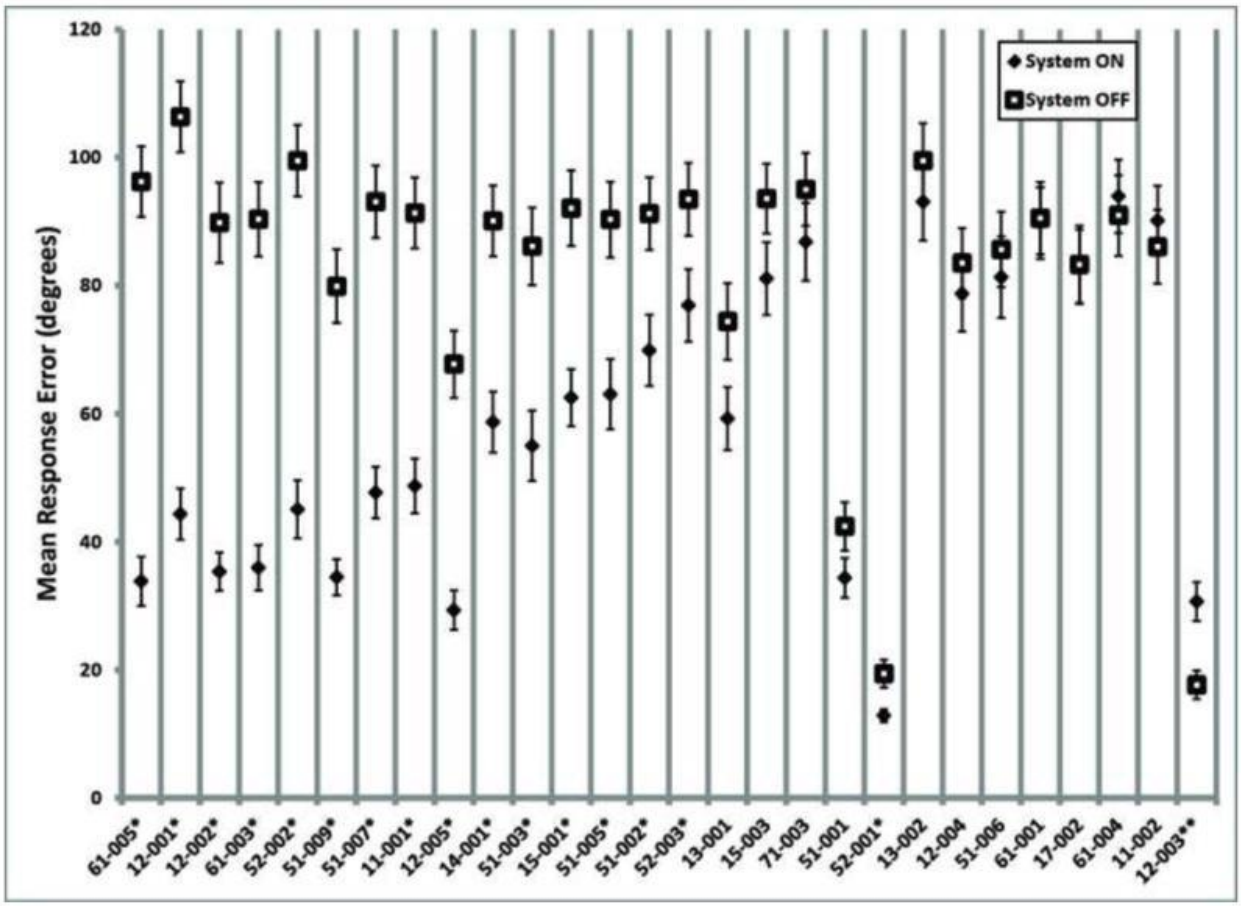

Figure 3: Mean response error for each subject on the Direction of Motion task.

It is clear from the two figures that subjects performed statistically better with the system on versus off in the following tasks: object localization (96% of subjects), motion discrimination (57%), and discrimination of oriented gratings (23%). [15] The best recorded visual acuity to date is 20/1260. Subjects' mean performance on orientation and mobility tasks was significantly better when the system was on versus off. Seventy percent of the patients did not have any serious adverse events (SAEs). The most common SAE reported was either conjunctival erosion or dehiscence over the extraocular implant and was treated successfully in all subjects except in one, who required explantation of the device without further complications.

The second study, conducted in 2012 by Barry et al., focused on 21 patients, and examined fine hand movement and guided movement. [16] Subjects would execute fine hand movement by completing three tracing tests with and without the Argus II machine. The tests were divided into right angle/single turn, mixed angle/single turn, and mixed angle/double turn. The discussion in this paper focuses on the results of the latter test.

Figure 4: An example of what a subject would see during a guided movement test. The green screen appears before the trial begins, the point on the middle image represents the starting location, and the path the subject was the path the subject was to trace.

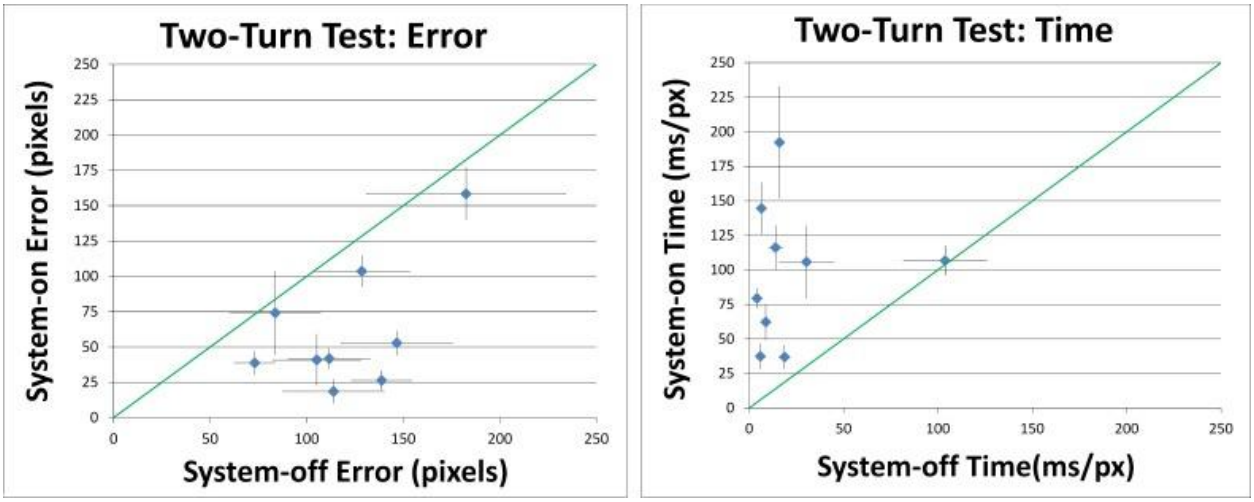

Figure 5: Error scores for patients using guided movement. Note that when the Argus II is on, patients take longer to complete the movement, but accumulate less error.

For right-angle/single-turn sets, average tracing error was reduced by 63% and tracing time increased by 156% when using the prosthesis, relative to residual vision. With mixed-angle/single-turn sets, error was reduced by 53% and time to complete tracing increased by 184%. Prosthesis use decreased error by 38% and increased tracing time by 252% for paths that incorporated two turns.

Based on the significant improvement of tracing performance in patients using the Argus II, it is clear that the use of an epiretinal visual prosthesis can allow RP patients with no more than bare light perception to guide fine hand movement visually. [16] Further, prosthetic input tends to make subjects slower when performing tracing tasks, meaning subjects were making an effort to increase their accuracy due to more accurate input.

The third study, conducted in 2011 by Ahuja et al., focused on 27 subjects, and subjected them to spatial-motor tasks to measure effectiveness of the Argus II. In this experiment, high-contrast stimuli in the form of dots randomly appearing on a screen would appear on a touch monitor, and the subjects were directed to touch the dot. The coordinates of the dot as well as the location the subject touched were recorded. A p-test used to determine statistical significance. [17]

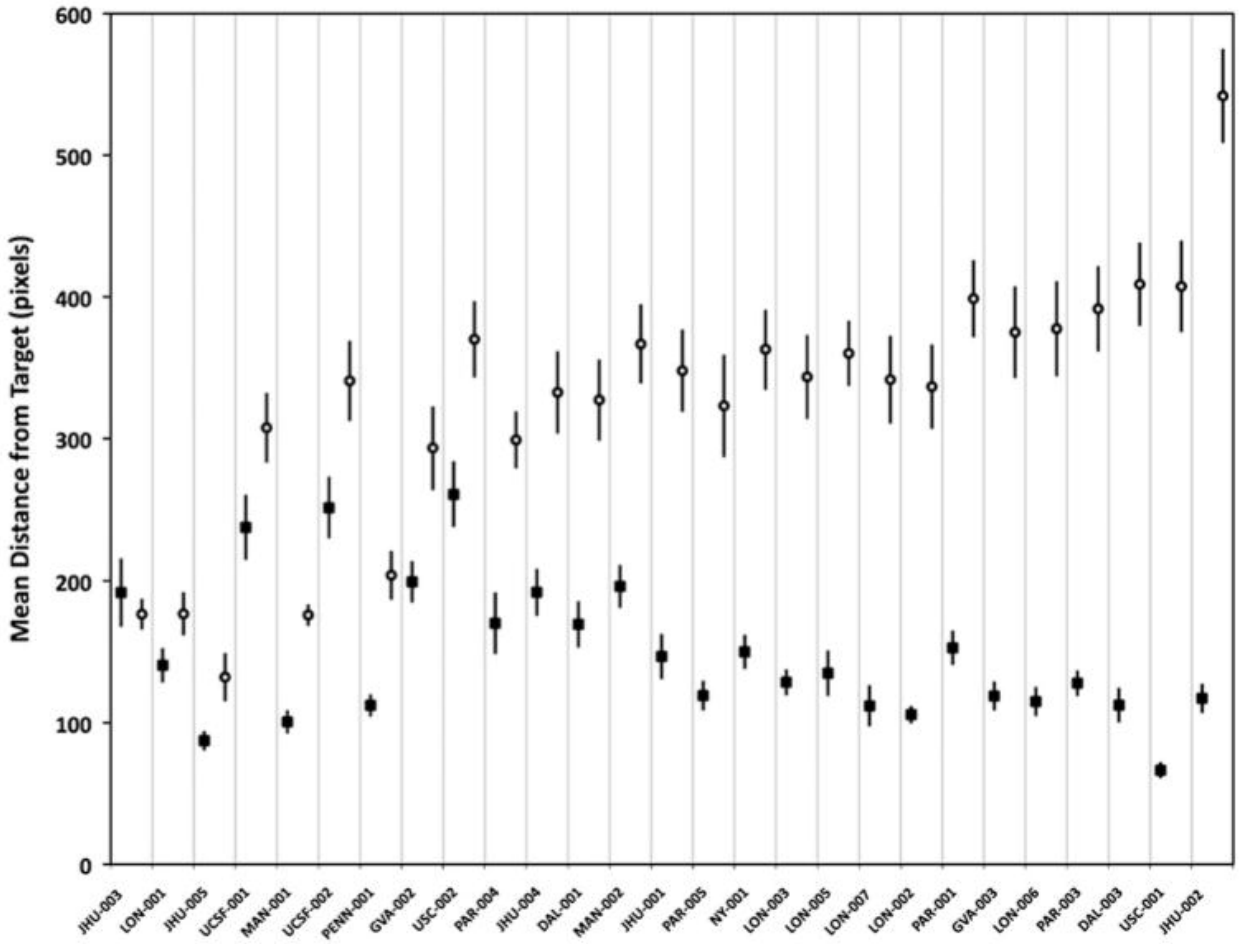

Figure 6: Mean distance from target square centre (pixels) for each subject with system on (black square) and off (white circles). Range of standard error of mean is shown by vertical bars. Subjects are plotted in order of increasing factor of improvement in accuracy (system on vs off).

In the random dot experiment, ninety-six percent (26/27) of subjects showed a significant improvement in accuracy and 93% (25/27) showed a significant improvement in repeatability with the system on compared with off ($p<0.05$, Student t test). A group of five subjects that had both accuracy and repeatability values <250 pixels (7.4 cm) with the system off (ie, using only their residual vision) was significantly more accurate and repeatable than the remainder of the cohort ($p<0.01$). Of this group, four subjects showed a significant improvement in both accuracy and repeatability with the system on. Therefore, the study found that artificial vision from the Argus II augmented information from existing vision in a spatial-motor task, resulting in a large improvement in accuracy in eye-hand coordination.

4. Pricing and Market Outcomes

4.1: Posted Sticker Prices and Actual Patient Costs

The out-of -pocket price for the Argus II implant is approximately $150,000 in the United States [8]. This is just the cost of the implant, the total cost includes the cost of surgery and follow up care. The total cost varies patient to patient, as the follow up care is specialized. The costs associated with the Argus II procedure and follow up is covered by both medicare and medicaid and some private insurance companies. The total cost covered is disputed, according to second sight the costs can be fully covered or partially covered. Second sight has a team of specialists that work with the individual patient and their insurance company to come up with prices. This is similar in other countries.

In European countries, the price for the implant is approximately $100,000 USD [11]. Much like the US this does not include the price of the surgery or follow up care. The costs are covered by national insurances and private insurance, and the process to come up with prices is exactly the same as in the US.

Annual costs after implant, the continued therapies and external hardware upkeep cost, is approximately 15k in the US and 12k in European countries per year. [10] The estimated continuous cost for the current 350 patients is 4.7 million dollars annually.

4.2: Costs to Overall Health Care System

As previously mentioned, the coverage of medicare and medicaid varies patient to patient. In 2018, Healio.com indicated that CMS finalized the outpatient payment rate of the Argus II procedure at $122,500 USD. In 2019, Healio.com indicated that CMS finalized the outpatient payment rate of the Argus II procedure at $152,500 USD. As of 2020 no new

procedures have been made and there is not available data on the total cost to the system. There have been more than 350 procedures performed world-wide, and there is no data on how many of those were in the US between 2018 and 2020. The total cost to the system is approximately 52.5 million dollars at a price of $150,000.

4.3 Stock Price and Market Discussion

Figure 7: Second Sight Stock (traded through acronym EYES)

Second sight started trading stock under the acronym EYES November 19th, 2014. Every quarter since, second sight has reported a loss despite a growing increase of demand for the Argus II prosthetic system. According to MarketBeat the net income over the last 7 years is -14.88 million dollars. Due to the lack of good news, or news in general, the downward trend in EYES has continued to date. EYES originally started trading at $9.00 per share and as of November 7th, 2021 it is trading at $2.81. EYES is following the news that comes out from second sight, with no good news about the Argus II system, prices continue to trend down.

4.4: Cost-Effectiveness and Policy Implications

It is clear that the Argus II system is effective, but that effectiveness comes at a high price. The Implant alone isn't what's so costly to the patient, it is the needed therapies to relearn how to see and the repeated check ups that cost so much. In short, the more you are willing to pay the better your quality of life. To be more direct, "The incremental cost-effectiveness ratio (ICER) was calculated to be €14603 per quality-adjusted life year (QALY) in UK and $207 616 per QALY in Canada" [14]. The Argus II is most effective at a very high cost.

Due to the low number of patients capable of being treated by the Argus II system, this product will not cause any policy changes. It is costly, but there are very few people eligible for this particular prosthetic.

5. Wrap-Up: Discontinuation, Orion, and Gene Therapy

5.1: Discontinuation of Argus II and Introduction of Argus IIs

In May 2019, Second Sight announced it was suspending the production of Argus II units in anticipation of developing its Argus 2s system. Since Argus II refers to the hardware of the system (camera and video processing unit), Argus 2s presents a technological advancement in both the camera and the video processor unit, but clinical trial data from the FDA has yet to be released.

Later, in March 2021, Second Sight discontinued the Argus II product entirely as the Argus 2s system gained full FDA approval. The Argus 2s is meant to be compatible with Second Sight's upcoming Orion system, which is still in clinical trials. However, details on pricing are

uncertain since “A decision on when or if to begin production of the newly approved hardware is pending completion of Second Sight’s planned business combination with Pixium Vision, which currently is in progress” [9]. In tandem with its Orion implant system, The Argus 2s will present another generational innovation to Second Sight’s Argus system.

5.2: Gene Therapy

AGTC, a pharmaceutical start-up specializing in gene therapy solutions for ocular and neurodegenerative diseases, has an XLRP pipeline dedicated to treating X-linked RP. No clinical data exists for the pipeline, however, it is currently in Phase 2 FDA trials. [12] Due to X-linked RP occurring in roughly 10% of RP patients, should it be approved, XLRP would be an orphan drug.

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