**Social and Economic Impact of the Commercialization of the Argus II Artificial Retina in the United States**

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# Abstract

Each year, the United States invests about $45 billion in research conducted by federal researchers within federal laboratories. These efforts generate extensive social benefits when results are transferred to the private sector. It is important that we effectively quantify the economic and societal impact of federal technology transfer activities to inform taxpayers and policymakers about the value of public investments in this form of research. The Argus II device, an artificial retina commercialized in the United States by Second Sight in 2013, provides a rich example of how private sector innovation can be enhanced by research collaborations with federal labs and academia. Over the 25-year journey from idea to product, Second Sight carried out research and development collaborations with six Department of Energy national laboratories and seven universities. The case of Argus II also offers valuable insight into (1) how private industry, academia, and government can work together to bring socially beneficial innovations to fruition and (2) the tradeoffs inherent in these public-private collaborations. In this paper, we use a Markov-model methodology from the health economics literature to estimate the realized and potential future social benefits associated with Argus II. We provide an interactive tool that can be used to replicate our findings and modify assumptions using updated patient information as it comes available. We also provide insight into the aspects of federal involvement surrounding the development of Argus II that contributed to its successful commercialization and discuss other spillover benefits from these public-private collaborations.

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# Introduction

Each year, the federal government invests about $45 billion in intramural research – research conducted by federal researchers within federal laboratories (NIST 2016). These research efforts can generate extensive social benefits when results are directly transferred to the private sector through licenses or cooperative research and development agreements (CRADAs) or are indirectly transferred to the private sector through publications and other public domain pathways. It is important that we effectively quantify the economic and societal impact of federal technology transfer activities to inform taxpayers and policymakers about the value of public investments in supporting new discoveries.

The Argus II device, an artificial retina, provides a rich example of how private sector innovation can be enhanced and expanded upon by research collaborations with federal labs and academia. The case of Argus II also offers valuable insight into (1) how private industry, academia, and government can work together to bring socially beneficial innovations to fruition and (2) the tradeoffs inherent in these public-private collaborations. In this paper, we explore these ideas and use a Markov-model methodology from the health economics literature to estimate the realized and potential future social benefits associated with Argus II. We provide an interactive tool that can be used to replicate our findings and modify assumptions using updated patient information as it comes available.

Argus II was commercialized by Second Sight Medical Products, Inc. (henceforth, Second Sight), a privately funded startup. Over the 25-year journey from idea to product, Second Sight carried out research collaborations with six Department of Energy (DOE) federal laboratories and seven universities. The collaborations were funded by the DOE Artificial Retina Project and by the National Eye Institute (NEI) of the National Institutes of Health (NIH). Some of the collaborations contributed directly to the development of Argus II while other work developed component technologies for use in a next-generation retinal prosthesis device. In 2009, the Artificial Retina Project led by Lawrence Livermore National Laboratory (LLNL), won an R&D 100 Award from R&D Magazine in the Life Sciences category.[[3]](#footnote-2)

Argus II was approved to treat retinitis pigmentosa (RP) in the United States by the Food and Drug Administration (FDA) in 2013 and in Europe by CE Mark in 2011. RP is a collection of progressive hereditary eye conditions, often beginning in early childhood and degrading vision over time by decreasing the retina’s ability to respond to light (National Eye Institute 2014; Boyd 2016). Most RP patients’ vision degrades to legal blindness by around age 40 (Fontanarosa et al. 2016). RP is classified as a rare disorder[[4]](#footnote-3) - it is estimated to impact about 1 of every 4,000 people globally (National Eye Institute 2014). Argus II is the first FDA-approved treatment for RP (Fontanarosa et al. 2016).

We measure the benefits of Argus II's commercialization primarily by quantifying improvements in patient quality-of-life using quality-adjusted life years (QALYs). We draw on clinical trial and patient data to calculate the aggregate U.S. impact to date. We forecast future impacts from estimates of future patient populations based on current regulations limiting the use of the device to patients with minimal to no light perception. Still, many additional RP patients stand to gain from the device than are currently approved for treatment. Argus II is also undergoing clinical trials for the treatment of age-related macular degeneration (AMD), which impacts twice as many people as RP. The model and tool developed here can be used to assess the potential impact of Argus II on these patients as well as the impact of follow-on visual aid technology related to Argus II development and the Artificial Retina Project.

We also provide insight into the role of federal funding in the commercialization of Argus II, the degree to which technology transfer occurred, and the other potential spillover benefits from these public-private collaborations. We assess information gathered through interviews with key researchers and executives involved in the development of Argus II complemented by a review of available literature and company and government documents. We compare the two main streams of federal funding from DOE and NIH to glean insights about funding mechanisms and aspects of cooperative agreements between parties that contributed to the commercialization of the device.

# Background

## Demand Environment

Retinitis pigmentosa (RP) is the only indication that Argus II is currently approved to treat. RP is a collection of hereditary eye conditions that impact the retina. RP is progressive, often beginning in early childhood and degrading vision over time by decreasing the retina’s ability to respond to light (National Eye Institute 2014; Boyd 2016). While individuals affected by RP do not frequently lose sight entirely, most individuals’ vision degrades to legal blindness by around age 40 through a combination of effects, including night blindness, steady loss of peripheral vision over time, color blindness, and compromised central vision (Fontanarosa et al. 2016; Boyd 2016).

RP is estimated to impact about 1 of every 4,000 people – or 1.75 million people – globally, including nearly 80,000 people in the United States (National Eye Institute 2014). Of those affected by RP, approximately 25% are legally blind (Grover et al. 1999). Current regulatory approvals in the United States and Europe only allow adult patients whose vision is considered worse than legally blind to be treated with Argus II. Thus, the potential market for Argus II is currently less than 457,500 legally blind RP patients worldwide, with approximately 62,000 potential patients residing in the United States and Europe (National Eye Institute 2014; Second Sight 2015).

Based on available information regarding RP treatment, Argus II does not have any substantial competitors that are approved for use in the United States or Europe. Research that may result in viable treatments for RP is ongoing on many fronts, including implantable devices other than Argus II, gene therapy, and nutritional therapy (Second Sight 2015; FFB 2013). However, most treatments being studied today target slowing down the progression of vision loss. Other treatments that show potential to reverse vision loss are still in pre-clinical trial stages of development (FFB 2013). Although Argus II does not slow the progression of the disease, the technology does restore partial useful vision to the patient, and is the only treatment that is generally available worldwide for late-stage RP (Second Sight 2015). Additionally, Second Sight has a strong intellectual property position with respect to patent licenses for technologies relevant to the RP market (Second Sight 2015).

In addition to RP, Second Sight is investing in research and clinical trials to expand the applicability of Argus II to age-based macular degeneration (AMD). While this does not affect a retrospective impact assessment of Argus II, gaining regulatory approval to include AMD as an indication for Argus II would substantially grow the potential future market for the device. Globally, an estimated 2 million individuals are legally blind due to AMD, with an estimated 552,500 people in the United States (Second Sight 2016). As with the device’s applicability to RP patients, only a subset of these individuals would be eligible for treatment under current regulations restricting Argus II use to adults whose vision is worse than legally blind (Second Sight 2016).

## Supply Environment: The Biomedical Innovation Cycle

The biomedical innovation cycle is characterized by long development cycles, a high degree of uncertainty, and high costs. Commercializing discoveries in the biomedical sector is more difficult than in virtually any other industry (Bradley et al. 2013; Valdivia 2013). Long development cycles are driven by the complexity of biomedical innovation and the high regulatory bar in place to ensure safety and efficacy when a product reaches the marketplace (Markman et al. 2005). High costs are driven by the various stages of medical device innovation from concept development to clinical development including engineering, testing, and ensuring FDA compliance.

Makower et al. (2010) surveyed medical device companies and found the average cost to bring a device from concept to FDA clearance was $31 million to $75 million depending on whether the 510(k) or premarket approval (PMA) pathways were used.[[5]](#footnote-4) In the case of Argus II, the rarity of RP and lack of available treatments allowed Second Sight to obtain the FDA's ‘Humanitarian Device’ designation, which exempts devices from the effectiveness requirements of a traditional PMA pathway. Still, the regulations limit the device’s use to only the worst-sighted RP patients – with minimal to no light perception. An additional commercialization hurdle for Argus II entails obtaining approval for treatment and reimbursement from public insurers. Medicare is the largest provider of insurance for patients that have been implanted with Argus II, covering 32 of 44 patients who received the implant from 2015-2016. However, Medicare operates in 12 semi-autonomous jurisdictions and as of early 2017, jurisdictions covering only 17 states and two territories approve Argus II when medically necessary.

Regardless of approval pathway, the costliest stage of development for medical devices entails carrying out clinical trials. The samples of firms in Makower et al. (2010) are generally representative of high-capital need companies like Second Sight working on innovative, new medical technologies rather than companies making marginal improvements to existing medical device technologies. In the case of Second Sight, federal support from the NEI helped facilitate this critical and costly development stage, contributing to the timely commercialization of the device (see Section 3 for more detail).

## Technology Description

The retina is a thin layer of tissue lining the back-interior wall of the eye. When light strikes the retina, it is translated into nerve signals by photoreceptor cells and delivered to the visual centers of the brain via the optic nerve. RP impairs vision by causing photoreceptor cells to die, over time reducing most individuals’ vision to legal blindness by age 40 with a central field of vision of less than 20 degrees (FFB 2017). However, other cellular layers of the retina survive – including the retinal ganglion cells that exit the eye as the optic nerve. These cells can be electrically stimulated to transmit information to the brain (Humayun et al. 1996).

The Argus II device is a retinal prosthesis that consists of both internal and external components. The implanted components include an electronics case, receiver component, and an electrode array. The electronics case and receiver are secured to the exterior of the eyeball, while the electrode array is implanted on the surface of the retina. External components include glasses with an embedded camera, a transmitter for delivering data to the implant, and a video processing unit (VPU) (Humayun et al. 2012).

Argus II works by bypassing dead photoreceptors to deliver image data directly to the remaining retinal ganglion cells, allowing the user to recover partial useful vision (Second Sight 2015). When the embedded camera captures an image, it is translated into instructions, which are transmitted wirelessly to the electrode array implanted in the patient’s retina. The instructions are delivered in the form of electrical pulses that stimulate the living ganglion cells to send information about the image down the optic nerve to the visual centers of the user’s brain. 

The resulting visual information delivered to the brain allows the user to perceive each electrode as a distinct spot of light, which forms patterns of light and dark that patients learn to interpret. Quality-of-life benefits from the device include improved mobility and sense of orientation; the ability to follow movement of people and objects; and the ability to feel more connected to people and their surroundings (Second Sight 2015).

From the perspective of measurable improvements in vision, results vary across patients, in part because there are many varieties of RP that are triggered by different genetic markers. Thus, patients progress and respond to treatment differently.

Due to a lack of standard assessments of visual acuity for patients with vision below legal blindness, Second Sight developed procedures for assessing visual improvements among their patients, with the input of low vision rehabilitation experts (Vaidya et al. 2014). Here, we focus on the results of the three most quantifiable visual assessment tests within this procedure: square localization, direction of motion, and grating visual acuity. Square localization requires patients to locate a white square on a black screen. Direction of motion requires patients to identify what direction a white bar is moving on a black screen. Last, grating visual acuity tests a patient's ability to distinguish the orientation of black and white lines of various widths (Humayun et al. 2012).

**Table 1** summarizes findings from Year 1, Year 3, and Year 5 clinical trial assessments of Argus II (Humayun et al. 2012; Ho et al. 2015; da Cruz et al. 2016). 30 patients were originally implanted with the device. Most patients experienced improvements in visual function when using Argus II, with improvements increasing most in the first year after implantation and declining somewhat in Year 3 and again in Year 5. After one year, 93.8% of patients experienced significantly better square localization, 62.5% experienced significantly better direction of motion, and 48.2% experienced significantly better grating visual acuity with the device on than off. After five years, 80.9% of patients experienced significantly better square localization, 50.0% experienced significantly better direction of motion, and 38.1% experienced significantly better grating visual acuity with the device on than off.

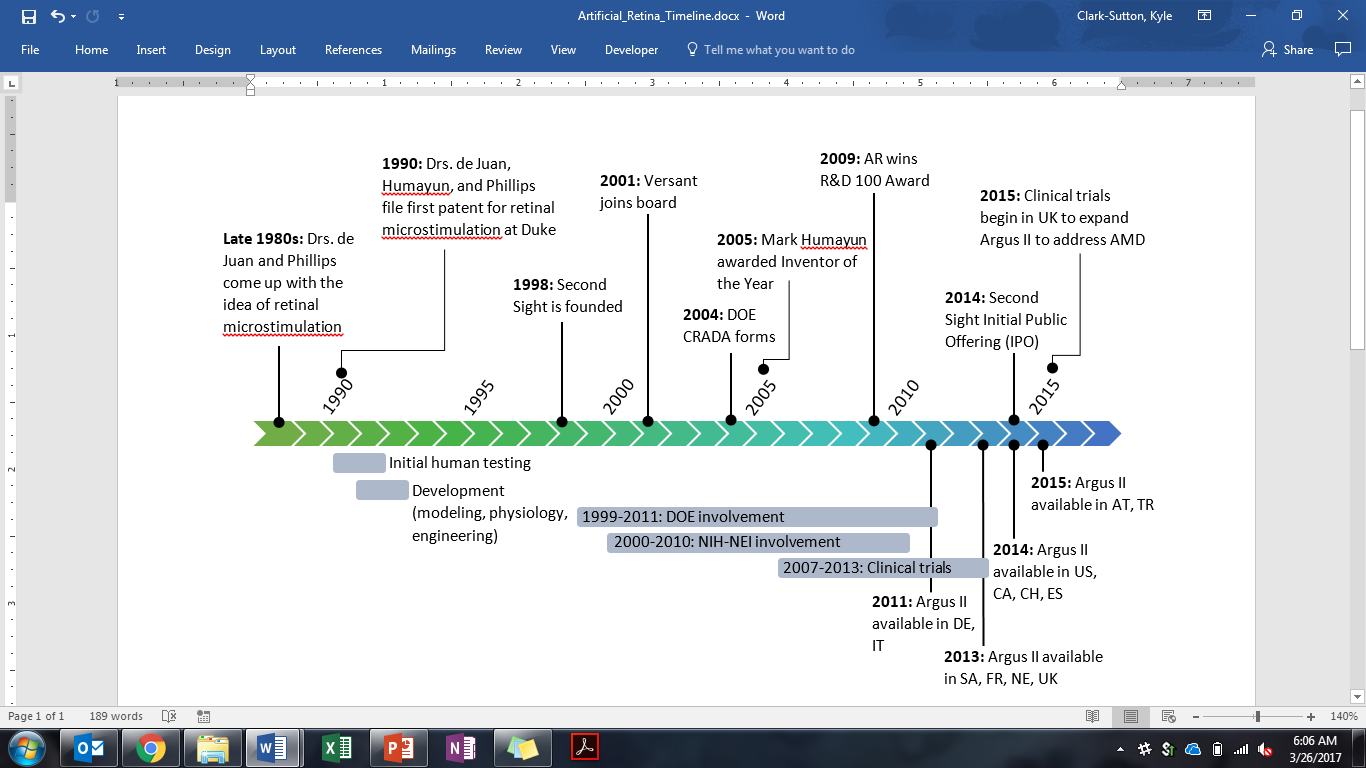
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| **Table 1: Argus II Clinical Trial Visual Function Assessment Results** | | | | | | |
|  | **Year 1 b** | | **Year 3 c** | | **Year 5 d** | |
| **Visual Function Assessment a** | Patients e | Significantly Better On Than Off (%) | Patients f | Significantly Better On Than Off (%) | Patients g | Significantly Better On Than Off (%) |
| Square localization | 16 | 93.8 | 28 | 89.3 | 21 | 80.9 |
| Direction of motion | 16 | 62.5 | 27 | 55.6 | 20 | 50.0 |
| Grating visual acuity | 29 | 48.2 | 27 | 33.3 | 21 | 38.1 |
| 1. Square localization requires patients to locate a white square on a black screen. Direction of motion requires patients to identify what direction a white bar is moving on a black screen. Grating visual acuity tests a patient's ability to distinguish the orientation of black and white lines of various widths (Humayun et al. 2012). 2. Data are from Humayun et al. (2012) 3. Data are from Ho et al. (2015) 4. Data are from da Cruz et al. (2016) 5. Test sample is not complete because the testing protocol was expanded partway through the study (da Cruz et al. 2016). 6. By Year 3, one device had been explanted. 7. By Year 5, two additional devices had been explanted and two had failed. One patient died of natural causes unrelated to the device. Two patients only consented to follow up for 3 or 4 years. Three additional patients were missed to follow up due to health reasons, method deviation, or fatigue (da Cruz et al. 2016). | | | | | | |

## Development of the Artificial Retina

The collaborations that resulted in Argus II and related generations of the device[[6]](#footnote-5) spanned the private sector, two federal funding agencies, at least six universities, and six national laboratories. **Figure 1** summarizes the timeline of Argus II development along with associated federal funding and contributions. **Table 2** lists all the public stakeholders involved in the development of artificial retina and summarizes their role in the research, development, and testing.

The idea for stimulating the retina using electrical pulses started when two neighbors, Gene de Juan, an ophthalmologist, and Howard Phillips, an electrical engineer, were chatting in de Juan's garage. The idea gained traction and in 1990, de Juan, Phillips, and Mark Humayun (then a student of de Juan's) filed the first patent for retinal stimulation. The patent was assigned to Duke University in 1992, where de Juan taught at the time, and de Juan, Humayun and Phillips were listed as inventors. de Juan and Humayun continued to develop retinal microstimulation technology, first at Duke, then at Johns Hopkins University. In 1996, they tested the idea on a volunteer patient, who was later the first to receive the Argus I implant (Humayun et al. 1996).

Robert Greenberg, co-founder of Second Sight, became engaged with the artificial retina research as a student of de Juan and Humayun at Johns Hopkins before moving to California to join the Alfred Mann Foundation, a non-profit medical research group. Through his foundation, Mann founded the first American cochlear implant company, Advanced Bionics.[[7]](#footnote-6) Mann’s colleague and friend Dr. Sam Williams, a talented aerospace engineer and philanthropist, had been an investor in the cochlear implant development and happened to be blind from RP. Williams and Greenberg connected through the foundation and decided to start a company to further develop and commercialize a retinal prosthesis based on the work of de Juan and Humayun (Graham-Rowe 2010).



Second Sight was founded by Mann, Williams, Greenberg, Aaron Mendelsohn, and Gunnar Bjorgin 1998 with private investment (Second Sight 2017b). de Juan and Humayun were brought on as consultants and transferred to the University of Southern California’s Doheny Eye Institute in 2001.

Private investment for Second Sight was bolstered in 1999 by $500,000 of pilot project funding from the DOE to support collaborations with Oak Ridge National Laboratory (DOE 2016). In 2000, the NEI at NIH joined the project, funding a five-year grant to Second Sight to facilitate work with academic collaborators on developing and testing the retinal prostheses (NIH 2017).

In 2004, the DOE, Second Sight, and other research partners (**Table 2**) formed a cooperative research and development agreement (CRADA) to direct research on the artificial retina project going forward. As part of the CRADA, all parties agreed to share intellectual property rights and royalties from discoveries made under the CRADA. In addition, Second Sight retained an exclusive license to any inventions that resulted from CRADA research (USC 2004). The DOE investment grew to $7 million a year until 2011.

In 2005, the NIH provided Second Sight a second five-year grant to continue their academic research collaborations. Another NIH grant was awarded to Second Sight as part of the 2009 economic stimulus package (the American Recovery and Reinvestment Act) to develop testing standards and assessment tools for low vision. The NEI remained as a funding partner until 2010.

DOE and NIH funding over this period was about $75 million and $25 million, respectively. Since 2011, Second Sight has been privately funded. Argus II was approved to treat retinitis pigmentosa (RP) in in Europe by CE Mark in 2011 and was approved by the FDA in the United States in 2013. Clinical trials for the extension of Argus II treatment to patients with AMD began in Europe in 2015.

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| **Table 2. Public funding, research facilities, and other contributing partners** | |
| **Organization** | **Role** |
| ***DOE-Funded Artificial Retina Project*** | |
| *Government* | |
| Department of Energy | Funding and oversight for Artificial Retina project; provided $75 million in funding during the life of the project. |
| Lawrence Livermore National Laboratory | Developed thin-film electrode arrays and advanced packaging to ensure electronics were biocompatible; worked on an ocular surgical tool used in the implant procedure and integration of the components of Argus II |
| Argonne National Laboratory | Leveraged ultrananocrystalline diamond technology to develop hermetically sealed packaging for Argus II to protect it from salt in the eye socket. |
| Brookhaven National Lab | Imaging studies for the Argus I system |
| Los Alamos National Laboratory | Develops advanced imaging techniques to observe and model retinal function and to map the communication between the brain and retina to improve the function of artificial retina devices |
| Oak Ridge National Laboratory | Performed sensitivity tests on the relationship between electrode density and quality of the electrical signals stimulating the living photoreceptors in the eye |
| Sandia National Laboratories | Developed a variety of components for use in the artificial retina devices, including microtools, advanced packaging and advanced circuitry |
| *Universities* | |
| California Institute of Technology | Optimized visual perception through real-time processing of embedded camera output. |
| North Carolina State University | Modeled electromagnetic and thermal characteristics of the device to optimize energy consumption. |
| University of California at Santa Cruz | Performed research and testing on bidirectional telemetry to optimize wireless communication and chip design. |
| Doheny Eye Institutea | Led the Artificial Retina Project, performed preclinical and clinical testing of the electrode array implants. |
| Second Sight Medical Products Inc | Responsible for designing, manufacturing and marketing artificial retina devices developed through this program. |
| ***NIH-Funded Artificial Retina Program*** | |
| *Government* | |
| NIH National Eye Institute | Funding for animal and human testing studies. |
| *Universities* |  |
| University of Southern California | Conducted human clinical testing and developed patch-clamp physiology |
| Doheny Eye Institutea | Conducted surgical and large animal studies |
| Salk Institute | Multi-electrode primate physiology |
| UC Berkeley | Developed electrical stimulation techniques |
| Second Sight Medical Products | Engineering research and development, manufacturing, and regulatory |
| Sources: DOE 2016; NIH 2017; Robert Greenberg, personal correspondence; Matt McMahon, personal correspondence   1. The Doheny Eye Institute was affiliated with the USC until 2011; now affiliated with UCLA | |

# Federal Research Collaborations Surrounding Argus II

The collaborative research programs from the DOE and NIH addressed different aspects of the Argus II development process. The DOE largely funded the development of technology relevant to a third generation 256-electrode retinal prosthesis while the NIH funded the applied development and testing of Argus II. The following subsections provide additional detail about the funding arrangements and project organization between Second Sight, DOE, and NIH.

## Department of Energy

The DOE CRADA was overseen by a steering committee made up of representatives from DOE, the national labs, Second Sight, and participating universities. The steering committee directed funding and collectively determined research priorities.

Individuals interviewed for this study indicated that DOE funding focused primarily on research directed at longer-range plans to develop a third-generation higher spatial resolution device. The next-generation device has a 256 electrode-array compared to the 60-electrode array of Argus II. Second Sight has not pursued commercialization of Argus III to date, but the associated work generated off-target effects for Argus II development as some of the DOE work on electronics, electrodes, stimulation, and modeling was useful for Argus II. For example, the diamond coatings work done by Argonne National Laboratory under the CRADA benefited from the joint-research collaborations and the development of the diamond coating technology directly contributed to Argus II (DOE 2016). This demonstrates a key point: technology and knowledge transfer work both ways – from federal researcher to the private sector and from the private sector to federal researchers.

## National Institutes of Health

The NIH funding for artificial retina development was provided directly to Second Sight. Thus, Second Sight had authority over the research direction and research carried out under this grant was more directly applicable to the commercialization of Argus II. Second Sight allocated the NIH funding towards experiments and human testing to improve the system’s hardware and software. The company used private financing for all clinical trial expenses, such as identifying sites and building data collection infrastructure for the FDA submission.

The NIH funding mechanism used was a Bioengineering Research Partnership Grant[[8]](#footnote-7), which was meant to spur collaboration between industry and academia. One of the primary stipulation of this research funding was that it had to involve university research partners. University research partners included the University of Southern California (USC), the Doheny Institute, the Salk Institute, and the University of California Berkeley (UC Berkeley) USC conducted human clinical testing and refined the patch-clamp physiology for patient use. The Doheny Institute conducted surgical and large animal studies to improve surgical implantation methods. The Salk Institute refined primate multi-electrode physiology techniques to determine the finest spatial patterns that could be produced with electrical stimulation. Refinements to software techniques could be tested with human patients with the implant, while refinements to hardware fed back into design decisions for future implants. UC Berkeley developed electrical stimulation techniques to improve the spatial and temporal resolution of retinal stimulation.

Without the NIH funding, interviewees indicated that collaboration with academic institutions outside of existing channels with USC would have been unlikely. The primary benefits of these collaborations with academics were two-fold. First, the academics were most interested in determining how and why the electrical stimulation worked. This helped Second Sight with the FDA approval because the FDA requests information on "mechanism of action" for brand new devices. Academic collaborations also helped Second Sight move in different directions for how to optimize the electrical stimulation and provided validation for some decisions that were made by the company.

Again, one of the tradeoffs inherent in this arrangement of working with outside researchers was that some of the work was less applied in nature. However, Second Sight had more leeway. Also, the intellectual property agreements were not put in place in advance which led to some conflict about associated spinoff companies that ultimately hurt the productivity of the collaboration with one of the academic institutions.

According to one interviewee, without NIH funding, the engineering work for the device may have proceeded at the same pace, but Second Sight would not have been nearly as fast in making the device work well in patients. For example, Second Sight had to develop a brand-new way of setting the parameters of electrical stimulation to make it work well for everyone. This process was enabled by academic collaborations encouraged by the NIH funding and this aspect of the project would otherwise not have been as well resourced.

# Methods

We examine the impact of Argus II on patients with RP by estimating the potential quality-adjusted life-years (QALYs)[[9]](#footnote-8) to be gained by patients while using the device. We assume the gains in QALYs are the difference between the mean discounted value of the QALYs of a patient who has been implanted with the device over a time horizon of 10 years and those of a patient who spends those years in the baseline state of RP. Because patient outcomes differ for the reasons stated in Section 2, we employ a multi-state transition Markov cohort model to calculate QALYs gained per patient based on their probabilistic transition among vision-related health states (defined below). The probabilities of moving among states are based on the outcomes of clinical trials of patients treated to date.

We first estimate the Markov model based on assumed values and then run multiple robustness checks. The first check is a sensitivity analysis where we estimate the model multiple times while sequentially altering one parameter at a time, using its assumed minimum and then maximum value. The second check is a Probabilistic Sensitivity Analysis (PSA) where we run a Monte Carlo simulation 1000 times while taking random draws of all model parameters from an assumed probability distribution described below. Finally, we relax some of our assumptions regarding device safety and stability to gauge the response of model estimates to changes in assumptions.

Once QALYs gained have been calculated for the simulated cohort of patients, we use information about patients who could potentially be implanted with the Argus device in the future to estimate population-level benefits. This forward-looking estimate is simply an upper bound on potential future benefits to RP patients with minimal to no light perception and does not account for adoption patterns. In contrast, the estimate is based on a lower bound of potential patient populations as it does not account for expansion in the applicability of Argus II to better-sighted RP patients or to individuals with AMD.

## Model Assumptions and Setup

The Markov model we define includes five states of health:

1. Untreated retinitis pigmentosa (RP).[[10]](#footnote-9) This is the baseline condition. Without Argus II, these patients have minimal or no light perception.
2. Square localization (SL) with light perception. This state represents an improvement over the baseline condition and is associated with a higher utility level.
3. Direction of motion (DM) which we assume to represent a higher level of utility compared with SL and hence we will assign it a higher level of utility.
4. Grating visual acuity (GVA) where patients would be able to distinguish the orientation of black and white lines. This state is associated with the highest utility level of all states.
5. Death. This is the absorbing state for those who died during the time horizon we are assuming for the model. However, we assume the patient lives at least one year after implantation.
6. We assume a discount rate of 5% for QALYs.

In previous studies, the DM and SL states were not disaggregated because Brown et al. (2003) assign the same utility value to each of these states (Vaidya et al. 2014; Health Quality Ontario 2016). However, the clinical trial results for Argus II indicate that many more patients achieved SL than DM, indicating the increased visual acuity involved in the DM state (da Cruz et al. 2016). This leads us to treat the two states separately by estimating the utility value associated with the intermediate state (see **Table 3** below).

In addition to the five states of health, the model is based on several assumptions pertaining to setup and data values. Each assumption is explained in detail below:

* The cycle length of our analysis is one year.
* The overall time horizon we consider is 10 years to approximate the useful life of Argus II.
* All patients start out in the RP state.
* In the first year after implantation, a patient can go from RP to SL, DM or GVA. Patients achieve their maximum visual acuity within the first year after implantation.
* Patients can witness a decline in their visual acuity in subsequent years. A patient can regress from any state to the one below it, i.e., from GVA to DM, from DM to SL or from SL to RP.
* Patients may undergo an explantation (removal of the device) only once during the 10-year period and if they do, they revert to the RP state for the remainder of the analysis.
* There is a potential for the device to fail, which causes patients to revert to RP. [[11]](#footnote-10)

## Input Data

The model requires two main types of input data: QALYs (or utility values) and probabilities of experiencing different outcome states, each of which is described below.

### Quality-Adjusted-Life-Years (QALYs)

There are no currently available estimates for the QALYs associated with various stages of RP and only limited information is available on the impact of varying states of visual acuity below legal blindness. A review of available studies on the QALYs associated with varying visual acuities is provided by Wittenborn and Rein (2013). The best available estimates for low levels of visual acuity to date are summarized in Brown et al. (2003) and are provided in **Table 3** below. The first numeric column includes the reported value while the last column displays the limits of the 95% confidence interval (CI). These QALY estimates have been utilized by researchers in Europe and Canada to determine the cost-efficacy of treatment with Argus II relative to baseline RP standard of care for patients in those areas (Vaidya et al. 2014; Health Quality Ontario 2016). We use these same QALY estimates for the sake of continuity and due to a lack of more current information.

**Table 3: QALYs associated with each state in the model**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **Shape parameters of the Beta distribution** | |
| **State** | **Visual Function Assessment a** | **Associated Visual Acuity b** | **QALY c** | **Range** | **Alpha** | **Beta** |
| RP | Baseline – No Argus II | No Light Perception | 0.26 | 0.19–0.33 | 91.62 | 260.77 |
| SL | Square Localization | Light Perception | 0.35 | 0.33–0.4 d | 45.11 | 41.64 |
| DM | Direction of Motion | Hand Motions | 0.44 e | 0.4 - 0.6 d | 118.36 | 153.73 |
| GVA | Grating Visual Acuity | Counting Fingers | 0.52 | 0.36–0.68 | 98.84 | 183.55 |
| SAE | Disutility from SAE | Not Applicable | 0.16 f | 0.12-0.20 | 120.80 | 634.20 |
| 1. Assessment methods are described in da Cruz et al. (2016). 2. Drawn from Brown et al. (2003). 3. Unless otherwise stated, utility values are based on the time trade-off method and are drawn from Brown et al. (2003). 4. Ranges are set within the overall CI found by Brown (1999) while adjusting for the heterogenous potential utility derived from each state. 5. Calculated as the average of SL and GVA. Brown (2003) determines the utility of hand motions to be the same as that of light perception, but patient clinical trial data finds marked differences in patient achievement of these states. 6. Source: Schiffman et al. (2003) | | | | | | | |

### Model Transition Probabilities

The probabilities used in the analysis are mostly based on the outcomes of the clinical trials performed on patients fitted with the device. Even though efficacy testing was performed three times to date: one, three and five years after implantation, two points should be noted. First, not all 30 patients were fitted with the device simultaneously. After the first 15 patients were implanted with the device, there was a 6-month pause followed by the implantation of the rest (da Cruz et al. 2016). The implantation in the latter group of patients was characterized by a refined surgical procedure which enhanced the safety of the device (Vaidya et al. 2014). Consequently, the incidence of severe adverse effects (SAE) was considerably less in the second group than in the first. Since it is reasonable to assume that the improved surgical procedure would be employed henceforth in device implantation, we compute the probabilities of SAE after excluding the incidences that were faced by the first group shortly after the procedure. We also compute the probabilities associated with device explantation and device failure. Furthermore, we allow these probabilities to vary temporally to reflect the actual incidences of SAE and explantation.

Another important point is that nine to ten patients were not tested at the five-year follow-up. The reduced number of patients could potentially bias the results of the test (da Cruz et al. 2016). The results displayed in **Table 1** reveal that a higher percentage of tested patients achieved GVA five years after implantation compared with the three-year test results, which seems unlikely given the progressive degeneration associated with RP. To address this issue, we compute the probabilities of moving from one state to the other by calibrating the probabilities to the one and three year results and do not take the five-year results into consideration.

All probabilities are displayed in **Table 4**. For each probability, a range is defined as 25% above and below the assumed value.[[12]](#footnote-11) The upper and lower limits of the range are used for the one-way sensitivity analysis where we run the model while only changing the values of one parameter at a time. Moreover, we use the values and ranges for each parameter to compute the corresponding shape parameters of the Beta distribution to use for the PSA. **Figure 2** depicts the Markov chain for the first two years as an example. The chain for follow-on years resembles that of Year 2, but with updated probability values.

**Table 4: Model probability values, ranges and shape parameters of the Beta distribution**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Probability of…** | **Value a** | **Range b** | | **Shape parameters of the Beta distribution** | |
|  | **Min Max** | | **alpha** | **beta** |
| achieving GVA in the first year after implantation | 0.4820 | 0.3615 | 0.6025 | 74.11 | 79.65 |
| achieving DM in the first year after implantation | 0.1430 | 0.1073 | 0.1788 | 123.27 | 738.73 |
| achieving SL in the first year after implantation | 0.3130 | 0.2348 | 0.3913 | 98.62 | 216.45 |
| moving from GVA to DM in subsequent years | 0.0873 | 0.0655 | 0.1091 | 131.34 | 1372.80 |
| moving from DM to SL in subsequent years | 0.2169 | 0.1627 | 0.2711 | 112.55 | 406.44 |
| moving from SL to RP in subsequent years | 0.0976 | 0.0732 | 0.1220 | 129.85 | 1200.91 |
| device explantation in the second year | 0.0333 | 0.0250 | 0.0417 | 139.17 | 4035.83 |
| device explantation in the fourth year | 0.0345 | 0.0259 | 0.0431 | 139.00 | 3892.00 |
| device explantation in the fifth year | 0.0357 | 0.0268 | 0.0446 | 138.82 | 3748.18 |
| device failure from the fifth year on | 0.0714 | 0.0536 | 0.0893 | 133.64 | 1737.36 |
| severe adverse events resulting from Argus II implantation in the first year | 0.1333 | 0.1000 | 0.1667 | 124.67 | 810.33 |
| severe adverse events resulting from Argus II implantation in the second or third years | 0.0690 | 0.0517 | 0.0862 | 134.00 | 1809.00 |
| severe adverse events resulting from Argus II implantation from the fourth year on | 0.0357 | 0.0268 | 0.0446 | 138.82 | 3748.18 |
| 1. Probabilities are determined using Argus II clinical trial patient outcome data from Year 1 (Humayun et al. 2012), Year 3 (Ho et al. 2015), and Year 5 (da Cruz et al. 2016). 2. Range is defined as 25% above and below the assumed value for probabilities (Quality Health Ontario 2016). | | | | | |

**



**Figure 2: Markov chain for the first year (Panel A) and second year after implantation (Panel B)**

## Patients Impacted by Argus II

Argus II was approved for use in the United States in 2013, with implantations of the device beginning in 2014. Since that time, 53 patients from the United States have had Argus II implanted. Additionally, Second Sight has stated that more than 150 conditionally qualified patients in the United States are waitlisted for the device (2016). The company estimates that most of the legally blind RP patients in the United States do not currently qualify for Argus II treatment because of the regulatory requirements that patients have bare or no light perception (Second Sight 2017). However, it believes that Argus II could be used to treat better-sighted individuals. The company plans to conduct clinical trials in 2017 for treatment among better-sighted individuals and will pursue regulatory pathways towards increased patient applications should the trials prove successful (Second Sight 2017). Additionally, Second Sight is working to have Argus II approved for treatment of AMD in the future (2017).

We use the estimates of RP prevalence in the United States provided by the NEI (2017) along with results on the visual acuity of RP patients from Grover et al. (1999) and Thobani et al. (2011) to estimate the number of RP patients in the United States with varying levels of visual acuity. The estimates are provided in **Table 5**. We estimate that up to about 3,100 RP patients in the United States may qualify for Argus II treatment under current regulations stipulating that patients have minimal to no light perception. Should treatment extend in the future to RP patients with minimal grating visual acuity or worse, we estimate that up to about 9,975 U.S. patients may qualify. Finally, if Argus II treatment extends to any legally blind RP patients, we estimate that up to about 19,950 U.S. patients may qualify. Finally, should Argus II be approved to treat AMD for legally blind patients, we estimate that up to 552,500 additional patients in the United States may qualify for treatment (Second Sight 2017).

**Table 5: Current and estimated future Argus II patients in the United States**

|  |  |  |
| --- | --- | --- |
| **Type of Patients** | **Patients** | **Source** |
| Patients treated with Argus II in the U.S.: 2014-2016 | 53 | Second Sight 2015, 2016, 2017; Calculations |
| Conditionally qualified patients in the U.S. on Second Sight interest list | 150 | Second Sight 2016 |
| RP patients in the U.S. with no light perception | 400 | NEI 2017; Grover et al. 1999; Calculations |
| RP patients in the U.S. with light perception | 2,700 | NEI 2017; Thobani et al. 2011; Calculations |
| RP patients in the U.S. with visual acuity of counting fingers or worse | 9,975 | NEI 2017; Grover et al. 1999; Calculations |
| Legally blind RP patients in the U.S. | 19,950 | NEI 2017; Grover et al. 1999; Calculations |
| RP patients in the U.S. | 79,725 | NEI 2017; Calculations |
| Legally blind AMD patients in the U.S. | 552,500 | Second Sight 2017 |

# Model Results and Sensitivity Analyses

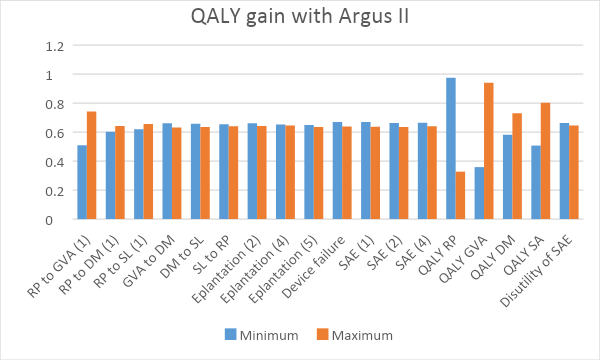
## Estimation Results

Using the deterministic values of the parameters displayed in **Table 3** and **Table 4**, we estimate an average total effect (mean sum of discounted QALYs over the 10-year time horizon) of 1.992 and 2.626 for the baseline and Argus II cases, respectively. Consequently, our findings suggest that the implantation of Argus II leads to an average gain of 0.634 QALYs, representing a 31.8% increase from the baseline state without the device. To check the robustness of the results, we run the sensitivity analyses described earlier in this section. The results of these sensitivity analyses are presented below.

## Sensitivity Analyses

### One-Way Sensitivity Analysis

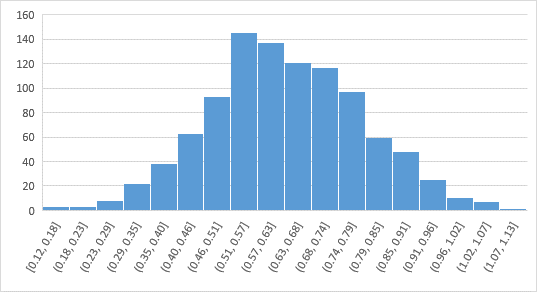
**Figure 3** displays the QALY difference between Argus II and baseline cases while changing one parameter at a time, using the minimum and then maximum values. For many of the parameters, the results do not change much from the deterministic case. However, the QALYs assumed for each state cause a more significant change in the result, especially those of RP and GVA. Also, the probability of going from RP to GVA exhibits an effect on the outcome.





### Probabilistic Sensitivity Analysis (PSA)

We run a Monte Carlo analysis and simulate 1000 iterations where we randomly draw values for all model data using the Beta shape parameters reported in **Table 4**. The mean value of the QALY gain over all simulations is 0.628, which is very close to the value estimated deterministically. **Figure 4** represents the distribution of all QALY gains generated by the Monte Carlo simulations.



**Figure 4: QALY gains distribution resulting from the Monte Carlo simulations**

### Changing Assumptions of Device Safety and Stability

To set an upper bound for the utility gains of the device implantation we assume that the device will be improved further in the future to the point where there are zero probabilities of explantation or device failure. Furthermore, we assume that patients reap the benefits of potential improved vision for the entire 10 years, i.e., the probability of death is zero. As expected, the mean QALY gain rises. Running the deterministic model yields a mean gain of 0.8 QALY and the PSA generates a 0.81 mean QALY gain.

# Social and Economic Impact Results

We use the estimate – generated through the Markov model described above – that RP patients treated with Argus II gain 0.634 QALYs over the first 10 years after treatment to estimate the social and economic impact on current and potential U.S. Argus II patients. First, we estimate the aggregate impact on U.S. RP patients who have had Argus II implanted to date. We add to this an estimate of impacts on Second Sight’s list of potentially qualified interested patients. Next, we estimate the potential impact on U.S. RP patients who may qualify for being treated with the device based on current regulations that Argus II can only be used in patients with minimal to no light perception. To estimate the economic value of patient impacts, we assume an economic value of $100,000 per QALY gained, with $50,000 and $200,000 per QALY gained as lower and upper bounds.[[13]](#footnote-12)

The estimates of patient impacts from Argus II are summarized in **Table 6**. Assuming a value of $100,000 per QALY gained, we estimate the economic value of QALYs gained among treated and waitlisted Argus II patients over a 10-year time horizon to be over $12.8 million. Among RP patients in the United States with minimal to no light perception, we estimate the potential economic value of QALYs gained from Argus II treatment to be nearly $200 million if all patients were treated with the device. As a point of reference, federal investment into the development of Argus II totaled about $100 million.

**Table 6: Calculations of aggregated social and economic value of Argus II implantation**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Type of Patients** | **Patients a** | **Aggregate QALYs**  **Gained b** | **Aggregate Economic**  **Value c**  **(thousands)** | **Economic Value**  **Range d**  **(thousands)** | |
| **Min** | **Max** |
| Patients treated with Argus II in the U.S. from 2014-2016 | 53 | 33.6 | $3,360 | $1,680 | $6,720 |
| Conditionally qualified patients in the U.S. on Second Sight interest list | 150 | 95.1 | $9,510 | $4,755 | $19,020 |
| **Patients treated or on waitlist** | **203** | **128.7** | **$12,870** | **$6,435** | **$25,740** |
| RP patients in the U.S. with no light perception | 400 | 253.6 | $25,360 | $12,680 | $50,720 |
| RP patients in the U.S. with light perception | 2,700 | 1,711.8 | $171,180 | $85,590 | $342,360 |
| **Estimated RP patients with minimal to no light perception in the U.S.** | **3,100** | **1,965.4** | **$196,540** | **$98,270** | **$393,080** |
| 1. See Table 5 and Section 2. for source information 2. Calculated using the mean QALY impact of 0.634 (see Section 5 for more details) 3. Based on the assumed economic value of $100,000 per QALY gained (Neumann, Cohen, and Weinstein 2014) 4. Based on the economic values of $50,000 and $200,000 per QALY gained (Neumann, Cohen, and Weinstein 2014) | | | | | |

# Discussion & Conclusion

## Argus II Impacts

The economic value of QALYs gained for the potential pool of U.S. RP patients who meet current regulatory standards for Argus II treatment – namely those with minimal to no light perception – is nearly $200 million if all patients are treated. This value is twice the level of federal investments in the development of Argus II. It should be noted that the economic value of QALYs gained does not account for differential costs of RP treatment with and without Argus II. Vaidya et al. (2014) and Quality Health Ontario (2016) provide cost-efficacy assessments of Argus II in Europe and Canada. Our goal in this paper was rather to determine aggregate impact of Argus II, which we find to be substantial.

Our estimates of QALY gains among currently qualified Argus II patients are upper bounds, in that they do not account for adoption patterns. However, our estimates of aggregate QALY gains in the United States from Argus II treatment are still likely very conservative. The provided estimates only apply to the potential pool of U.S. patients who meet current regulatory standards for Argus II treatment, which is a small portion of the total number of patients that Second Sight believes may benefit from the device. Should the device be approved for better-sighted individuals and AMD patients, the economic value of QALYs gained among treated patients would likely increase by an order of magnitude or more, given the substantially large number of patients that may be treated. However, it is not accurate to assume that the average QALY gains of 0.634 that we determine through our Markov model would apply to different-sighted patients or patient with different diseases. As data on outcomes for new types of patients and uptake of the device are made available, our model and associated tool can be used to updated the estimates of QALY impacts among treated patients.

## Argus II Lessons for Collaborative Research Ventures

Studying the development and commercialization of Argus II as well as associated public funding streams yielded policy-relevant conclusions in five key areas: (1) funding structure, (2) intellectual property, (3) public role in high-risk research, (4) FDA approval pathway, and (5) broad lessons about technology transfer. These conclusions are important so that policymakers and public-private research collaborators alike better understand factors contributing to effective technology transfer in high-risk, multi-partner R&D efforts to increase the likelihood of success in future initiatives.

### Funding Structure & Inherent Trade-Offs

From a policymaker's perspective, funding structures have different advantages and disadvantages. Thus, using different funding structures has inherent tradeoffs. One of the challenges that the DOE CRADA faced from a commercialization perspective is that funding was controlled by an advisory committee that was less focused on improving the commercial product or accelerating commercialization. As a result, there was a disconnect between the research priorities of Second Sight and lab and university members of the CRADA. One interviewee suggested that collaboration could have been improved by increasing interaction between national lab and Second Sight researchers by "embedding" national lab scientists in Second Sight facilities for short periods of time. Despite the drawbacks of the particular collaboration, it is important to note that research outputs are likely to be aligned with how research priorities are set. The DOE arrangement elevated joint research needs and the steering committee was weighted towards the priorities of public research institutions (DOE, labs, universities) rather than Second Sight. While this collaboration had less of a direct impact on Argus II’s commercialization, there was arguably greater potential for long-run spillover benefit to society, although this is hard to reconcile given the exclusive licensing agreements put in place with Second Sight. The NIH funding on the other hand resulting in much more applied research; Second Sight received the funding directly and was able to set research priorities. Although the NIH funding stipulated collaboration with academics, these collaborations tended to more directly applicable to Argus II than the DOE funded research.

### Agreements about Intellectual Property

Another theme that emerged was the importance of up-front agreements about intellectual property (IP). Specifically, it is important to have agreements in place that protect IP of partners involved and determine the distributions of profits from co-developed IP. Two interviewees noted that establishing clear agreements regarding IP before a partnership commences helps head off a number of problems that might tend to arise in a collaboration with many stakeholders. Another IP agreement that helps to balance protection of intellectual property with an interest in publishing research results is an embargo policy, a common practice in which private sector owners of IP are allowed to review publications or presentation material prior to disclosure to ensure protection of intellectual property. Second Sight exercised such an agreement with USC Doheny Eye Institute.

### Public-Sector Role in Incentivizing High-Risk Investments

The example of the commercialization of Argus II highlights the public role in incentivizing high-risk investments. Public funding acted to boost investor confidence and lend legitimacy to the product, which strengthened Second Sight's value proposition in the private market. Argus II took roughly 15 years to commercialize once Second Sight was founded, and it is hard to imagine this happening with private capital alone. In fact, Dr. Weiland said that, in the absence of federal funding, it would have been hard to fund more speculative or long-term research through universities and national labs because Second Sight was a risky investment in terms of their amount of debt financing.

This is not unique to Argus II. Technology development in the medical sector has long gestational periods, and public funding can be an important source to help innovations come to fruition. For example, since 2009 there has been a shift of venture capital from life sciences, which includes medical devices, to other industry sectors and a shift within life sciences away from early-stage investments to later-stage investments (Fleming 2015).

### FDA Approval Pathway

Second Sight's chosen strategy for FDA approval demonstrates the importance of making the approvals process as frictionless as possible. Second Sight leveraged the Humanitarian Device Exemption, which accelerates approval for treatments of conditions appearing in less than 4,000 individuals a year. This accelerated and less costly approval pathway has allowed them to market Argus II earlier than would have been possible.

### Technology Transfer

Technology transfer is not simply a one-way exchange of federal technology, expertise, and knowledge out of government labs to the private sector. In fact, technology transfer -- specifically collaborative research -- often involves a two-way exchange. The DOE collaboration may be an example where federal labs benefited from exposure to external expertise just as much if not more than the Second Sight benefited from access to federal labs.

There are often off-target effects of federal research funding and technology transfer activities that are hard to trace and predict. This is partially due to the long timelines between when public investment is made and when direct and indirect payoffs occur. The DOE funded collaboration may have spillover benefits in a wide range of areas, but it is too soon to tell. Future spillover benefits may be to other electronic-tissue interfaces (for example, treatments for spinal cord injuries neurological issues). Perhaps the most promising near-term example is ORNL conducted follow on work on related retinal prostheses that could stimulate oxygen production in the eye to treat diabetic retinopathy (DOE 2016).

The cochlear implant provides an interesting example of the difficulty predicting long-run spillover benefits. The first-generation artificial retina was constructed by attaching a grid of flat stimulating electrodes to the implantable electronics from a commercially available cochlear implant (Wired 2010). Cochlear implants benefited from federal funding (NIH 2013), but no one would have foreseen that the cochlear implant would lend key components to an artificial retina years later.

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# Supplement

We develop an online tool that allows a user to run the Markov chain analysis under different parameter value assumptions.[[14]](#footnote-13) These parameters include the probabilities of moving among vision states, death, as well as device failure and explantation. Parameters also include the probabilities of SAEs, utility values associated with varying levels of visual acuity and the discount rate. Given the values that the user enters into the assigned input boxes, the tool runs the Markov model and estimates the mean discounted value of gained QALYs after device implantation. The tool runs the Monte Carlo sensitivity analysis described in the paper. It also produces the corresponding charts and tables provided in this analysis to depict the simulated values of the QALY gains. The tool is available at the URL: <https://mesalem.shinyapps.io/nist_dashboard/>.[[15]](#footnote-14)

1. All authors work at RTI International in Research Triangle Park, North Carolina, United States [↑](#footnote-ref-0)
2. Email: awalsh@rti.org [↑](#footnote-ref-1)
3. See http://www.rdmag.com/award-winners/2009/07/artificial-retina-generates-sight for more detail. [↑](#footnote-ref-2)
4. The FDA designates rare diseases as those affecting fewer than 200,000 people in the United States. [↑](#footnote-ref-3)
5. These figures are not capitalized or adjusted for the rate of failures. [↑](#footnote-ref-4)
6. The predecessor first generation artificial device retina device was known as the Argus I or A-16 for the 16-electrode array. This device was developed with private funds. The third-generation device with a 256-electrode array was largely developed through the DOE artificial retina project, but it has not been commercialized. [↑](#footnote-ref-5)
7. Other innovations attributed to Mann include infusion and insulin pumps, spinal cord stimulators, inhalable insulin, and the application of battery technology developed for satellites to pacemakers (Second Sight 2016b). [↑](#footnote-ref-6)
8. NIH describes bioengineering research grants as encouraging “bioengineering applications that will accelerate the development and adoption of promising tools and technologies that can address important biomedical problems… The goal of the program is to support projects that can realize meaningful solutions within 5 – 10 years.” (https://grants.nih.gov/grants/guide/pa-files/PAR-16-116.html) [↑](#footnote-ref-7)
9. QALYs account for the disutility of living with an illness or other physical impairment. The QALY of a person at full physical and mental capacity is 1, while the QALY associated with death is 0. The QALY of a person who is physically, mentally, or emotionally impaired due to illness or disability will lie somewhere between 0 and 1 depending on the severity of their condition. For states of health deemed worse than death, negative QALY values are possible (Sassi 2006). [↑](#footnote-ref-8)
10. 1 patient in the clinical trials had choroideremia rather than RP. [↑](#footnote-ref-9)
11. Two devices in the clinical trial failed at approximately four years after implantation but were not explanted and remained safely implanted at the five-year follow-up. [↑](#footnote-ref-10)
12. This is the approach employed in the Health Quality Ontario (2016) cost-efficacy study. [↑](#footnote-ref-11)
13. For the past several decades, a single QALY has typically been valued at $50,000. However, Neumann, Cohen, and Weinstein (2014) summarize the many opinions over time that this value is too low. Based on their review of the literature, they suggest treating $50,000 per QALY as a lower bound and considering the additional thresholds of $100,000 per QALY and $200,000 per QALY (Neumann, Cohen, and Weinstein 2014). [↑](#footnote-ref-12)
14. The tool was developed in the R software version 3.3.3 using the Rstudio GUI and the shiny dashboard package. Other packages used in the analysis and tool design are: data.table, markovchain, and shinyBS. [↑](#footnote-ref-13)
15. The tool is currently under construction. [↑](#footnote-ref-14)