

<b>9.03.15</b>		<b>Retinal Prosthesis</b>	
<b>Original Policy Date:</b>	May 29, 2015	<b>Effective Date:</b>	May 1, 2024
<b>Section:</b>	9.0 Other	<b>Page:</b>	Page 1 of 10

**Policy Statement**

I. Retinal prostheses are considered **investigational**.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

**Policy Guidelines**

**Coding**

See the [Codes table](#) for details.

**Description**

A retinal prosthesis replaces lost photoreceptor function by transmitting external images to an array of electrodes or via light sensors placed in the epiretinal or subretinal space. The artificial retina could restore sight to individuals with blindness secondary to retinal diseases, such as retinitis pigmentosa, hereditary retinal degeneration, and some forms of age-related macular degeneration. Several models of retinal prostheses are in development in the United States, Europe, and Asia. Only the Argus II system has been cleared for use by the U.S. Food and Drug Administration (FDA).

**Related Policies**

- Keratoprosthesis

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

In 2013, the Argus® II Retinal Prosthesis System (Second Sight Medical) was cleared for marketing by the FDA through a humanitarian use device exemption. This exemption is limited to devices that treat or diagnose fewer than 4000 people in the United States each year. The Argus® II system is intended for use in adults, age 25 years or older, with severe-to-profound retinitis pigmentosa who have bare light perception (can perceive light, but not the direction from which it is coming) or no light perception in both eyes, evidence of intact inner layer retina function, and a history of the ability to see forms. Patients must also be willing and able to receive the recommended postimplant clinical

follow-up, device fitting, and visual rehabilitation. Second Sight discontinued the Argus II in 2019. FDA product code: NBF.

## Rationale

### Background

Two approaches are being explored to develop an artificial retina that could restore sight to patients with blindness secondary to retinal diseases, such as retinitis pigmentosa, hereditary retinal degeneration, and some forms of age-related macular degeneration. The first is implantation of electrode arrays in the epiretinal or subretinal space to stimulate retinal ganglion cells. A second approach is the implantation in the subretinal space of light-sensitive multiphotodiode arrays, which stimulate the remaining photoreceptors in the inner retina. Use of a multiphotodiode array does not require external image processing. The latter approach is being evaluated for degenerative retinal diseases such as retinitis pigmentosa, in which outer retinal cells deteriorate, but inner retinal cells remain intact for years.

Research in the United States began with a first-generation, 16-electrode device (e.g., the Argus 16; Second Sight Medical Products), which permitted the distinction between the presence and absence of light. Three government organizations provided support for the development of the Argus II: the Department of Energy, National Eye Institute at the National Institutes of Health, and National Science Foundation. They collaborated to provide grant funding, support for material design, and other basic research for the project.

Devices in development, none of which are approved or cleared by the U.S. Food and Drug Administration (FDA), include the following.

- The Alpha IMS was developed at the University of Tübingen, and has an electronic chip design provided by the Institute for Microelectronics, Stuttgart. The second-generation Alpha IMS device has wireless power and signal transmission and is produced by Retina Implant AG (Germany). The microchip is implanted subretinally and receives input from a multiphotodiode array with 1500 elements that moves with the eye, senses incident light, and applies a constant-voltage signal at the respective 1500 electrodes. The multiphotodiode array transforms visual scenes into corresponding spatial patterns (38° 40 pixels) of light-intensity-dependent electric stimulation pulses with a maximum visual field of 15°.
- The Boston Retinal Implant Project uses an external camera mounted on a pair of glasses and a 100-electrode array. The image obtained by the external camera is translated into an electromagnetic signal transmitted from the external primary data coil mounted on a pair of glasses to the implanted secondary data coil attached to the cornea. Most of the volume of the implant lies outside the eye, with transscleral cables connected to a subretinal electrode array. The Boston Retinal Implant Project is a joint effort of the Massachusetts Institute of Technology, the Massachusetts Eye and Ear Infirmary, the Veterans Affairs Boston Healthcare System, and Cornell University.
- EPIRET3 retinal implant (Philipps-University Marburg, Germany) is a wireless system that consists of a semiconductor camera on the frame of a pair of glasses and a transmitter coil outside the eye, which sends electromagnetic signals to a receiver coil in the anterior vitreous (similar to an intraocular lens), which passes them on to a receiver microchip. A stimulator chip then generates the stimulation pulses and activates a selection of 25 electrodes placed on the epiretinal surface via a connecting micro cable.
- Intelligent Retinal Implant System (Pixium Vision, Paris, France) uses an external camera integrated with a pair of glasses and linked by wire to a pocket computer. Receiver electronics connect via a scleral tunnel to an electrode array on the surface of the retina. Pixium Vision is also developing PRIMA, which uses a subretinal implant.
- Learning Retinal Implant (Intelligent Medical Implants, Zug, Switzerland) uses an external camera on the frame of a pair of glasses and wireless data and power transfer. Receiver

electronics connect via a scleral tunnel to an epiretinal implant. A retinal encoder with 100 to 1000 tunable spatiotemporal filters simulates the filtering operations performed by the ganglion cell and allows individual calibration to improve each patient's visual perception.

- The Microelectrode-STs (suprachoroidal-transretinal stimulation) system (Osaka University, Japan) places its 9-electrode retinal prosthesis in a scleral pocket with a reference electrode in the vitreous cavity. A video camera is used to detect a visual object. Because the electrodes are at a greater distance from the retina, the resolution of the image may be lower than other devices. A proposed advantage of the STs prosthesis over epi- or subretinal prostheses is the safety of the surgical procedure, because the electrodes do not touch the retina.

### Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

### Retinal Prostheses

#### Clinical Context and Therapy Purpose

The purpose of implanting a retinal prosthesis in individuals who have blindness due to retinal diseases is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population(s) of interest is individuals with blindness secondary to retinal diseases, such as retinitis pigmentosa, hereditary retinal degeneration, and some forms of age-related macular degeneration.

#### *Interventions*

The treatment being considered is the use of a retinal prosthesis. The Argus II Retinal Prosthesis System (Argus II) is the second-generation device, which has 60 electrodes. The retinal prosthesis,

with the electrode array, is surgically implanted in and on the eye. The system's external components include a small external video camera, held on eyeglass frames, that captures images then processed by an externally worn microcomputer. These signals are transmitted to an antenna in the prosthesis, an electronics package in the superior temporal quadrant and an electrode array implanted in the back of the eye, which in turn stimulates the optic nerve. It has been suggested that future-generation devices, containing more than 1000 electrodes, will provide more detailed vision.

### ***Comparators***

Standard treatment of retinal diseases; medical therapies in early stage of some conditions and adaptive interventions.

### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, functional outcomes and quality of life. More specific outcomes include: visual function, visual acuity, laboratory-based visual performance measures, and day-to-day function.

Follow-up of at least 6 months would be desirable to assess outcomes.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

### **Review of Evidence**

A 2016 technology assessment prepared for the Agency for Healthcare Research and Quality included a systematic review of the literature on retinal prostheses.<sup>1</sup> Reviewers included studies on the Argus II, the only retinal prosthesis cleared for marketing in the United States, as well as other retinal prostheses. Outcomes of interest were visual function, visual acuity, laboratory-based visual performance measures, day-to-day function, and quality of life. In their qualitative summary of the literature on retinal prostheses, reviewers concluded that the strength of evidence was insufficient for all outcomes.

One single-arm study with 30 patients (NCT00407602) has evaluated the Argus II retinal prosthesis; numerous articles have been published on its findings and on subgroup studies conducted on some or all of the participants. The study was prospective and multicenter, with sites in the United States and Europe. It included patients with retinitis pigmentosa (United States) or outer retinal degeneration (Europe) who had bare light perception or no light perception in both eyes. Articles based on this study are described next.

Humayun et al (2012) reported on interim (minimum 6-month) results on 3 types of visual acuity tasks using a computer and 2 types of real-world utility tests.<sup>2</sup> The computer tasks included square localization (locating a high-contrast white square of light on a black background), direction of motion (indicating the direction of a high-contrast bar moving across the screen), and grating discrimination (discriminating among square-wave gratings of different spatial frequencies presented on a monitor). Patients performed better on all 3 computer tasks with the system on than off. In terms of the 2 real-world utility tests, with the system on, subjects had a 54% success rate in finding a door compared with a 27% success rate with the device off and had a 68% success rate in following a white line on a dark floor compared with a 23% success rate with the device off. Although

all subjects were able to perceive light when the system was stimulated, the Argus II did not affect full-field light perception.

Da Cruz et al (2016) reported on 3- and 5-year results of the visual acuity tests.<sup>3</sup> Patients performed significantly better on the 3 computer tasks with the device on than off. For the simplest task, square localization, 89% (25/28) of patients tested did better with the device on and, at year 5, 81% (17/21) of patients tested did better with the device on. For grating discrimination, the most difficult assessment, 33% (9/27) of patients tested at year 3 did better with the device on and 38% (8/21) of patients tested at year 5 did better with the device on.

Ho et al (2015) reported on safety up to 3 years.<sup>4</sup> At 3 years postimplantation, 23 serious adverse events were reported in 11 patients; the most commonly reported were conjunctival erosion (n=4), hypotony (n=4), conjunctival dehiscence (n=3), and presumed endophthalmitis (n=3). Five-year safety was reported by da Cruz et al (2016).<sup>3</sup> As reported by da Cruz, only 1 additional serious adverse event, a case of a rhegmatogenous retinal detachment, occurred after the 3-year follow-up (»4.5 years).<sup>3</sup> Three devices were explanted, one each at 14 months, 3.5 years, and 4.3 years after implantation. Two patients had experienced recurrent conjunctival erosion and the third experienced chronic hypotony and ptosis.

Several publications have reported on additional functional outcomes in patients participating in the Argus II study. Patients served as their own controls; performance was compared with the device in the on vs off position. Geruschat et al (2016) reported on observer-rated assessments of visual function using the multicomponent Functional Low-Vision Observer Rated Assessment, which evaluates performance of 35 tasks.<sup>5</sup> Tasks were grouped into 4 domains: visual orientation, mobility, daily life, and interaction with others. Twenty-six (87%) of the 30 enrolled patients were included in the analysis at a mean of 36 months (range, 18-44 months) after device implantation. All patients performed significantly better ( $p < 0.05$ ) in each of the 4 domains with the device on versus off, ranging from 19% to 38% improvement. Twenty-four (69%) of 35 tasks had statistically significant improvements in outcomes (i.e., they were easier to perform) with the device turned on versus off.

A 2013 study reported on letter and word reading at 20 months in 21 patients participating in the Argus II study.<sup>6</sup> Correct letter reading ranged from 51.7% to 72.3% with the device on, compared with 15.3% to 17.7% with the device off. The average time to correctly identify letters with the device on ranged from 47.7 to 68.6 seconds. Subjects who successfully completed the letter identification task proceeded to the next task. Six subjects were able consistently to read letters of reduced size. The smallest letter identified was 0.9 cm for 1 subject, but preferred letter size was as much as 22.6 cm. Four subjects were able to correctly identify 2-, 3-, and 4-letter words.

Kotecha et al (2014) reported on further testing of 6 patients from one of the Argus II study sites that had at least 3 years of follow-up; reaching and grasping outcomes were assessed.<sup>7</sup> The test consisted of picking up a white cube from a table covered with black felt and illuminated from above, and was conducted with the electrode array on, array off, and scrambled (i.e., array stimulated with a random, scattered input), in a random order. Also randomized was the location of the object, which could be placed in 1 of 4 positions. To eliminate the use of any residual vision among participants, certain patients had both eyes taped shut during the test. After 4 to 6 weeks, patients were retested to examine repeatability of performance. The percentage of successful grasps was significantly higher with the device on (69%) compared with off (0%); this finding was maintained at the second visit. With the signal scrambled, success rates were 59% at the first visit and 28% at the second visit. There were no significant differences between "on" or "scrambled" conditions for movement onset, time to object contact, or path deviation ratio, which was defined as the "deviation of the movement trajectory from a straight route between the starting and object contact wrist positions."

Dagnelie et al (2017) evaluated performance on several functional tasks in 28 of 30 study participants who had been implanted with the device between 6 months and 3 years earlier.<sup>8</sup> The 3 tasks were

intended to have real-world application. Performance was compared with the retinal prosthesis device on and off. Task 1 was sock sorting; task 2 was sidewalk tracking; and task 3 was walking direction discrimination. On all 3 tasks, subjects performed significantly better with the device on than off ( $p < 0.05$ ). (For the sock sorting task, results were presented in figures, hence precise data were not available.) With a cloth-covered table, subjects sorted approximately 70% of the socks correctly with the device on and 30% correctly with the device off. With a bare table, subjects sorted approximately 50% of socks correctly with the device and 30% with the device off. For the sidewalk task, subjects walked out of bounds a mean of 6.85 times with the device off and a mean of 4.93 times with the device on. For the walking direction discrimination task, 15 (56%) of 27 subjects performed significantly better than chance with the device on and 4 performed significantly better than chance with the device off. Although statistically significant, the clinical significance of the differences in performance on the 3 tasks is uncertain.

### Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No guidelines or statements were identified.

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
<i>Unpublished</i>			
NCT01864486 <sup>a</sup>	Restoring Vision With the Intelligent Retinal Implant System (IRIS V1) in Patients With Retinal Dystrophy (Title in France: Compensation of Vision With the Intelligent Retinal Implant System (IRIS V1) in Patients With Retinal Dystrophy)	20	Oct 2017 (updated 10/17/17)
NCT02303288 <sup>a</sup>	Post-Market Study of the Argus® II Retinal Prosthesis System - France	18	Nov 2018 (updated 06/22/20)

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## References

1. Fontanarosa J, Treadwell JR, Samson DJ, et al. Retinal Prostheses in the Medicare Population (AHRQ Technology Assessment). Rockville, MD: Agency for Healthcare Research and Quality; 2016.
2. Humayun MS, Dorn JD, da Cruz L, et al. Interim results from the international trial of Second Sight's visual prosthesis. *Ophthalmology*. Apr 2012; 119(4): 779-88. PMID 22244176
3. da Cruz L, Dorn JD, Humayun MS, et al. Five-Year Safety and Performance Results from the Argus II Retinal Prosthesis System Clinical Trial. *Ophthalmology*. Oct 2016; 123(10): 2248-54. PMID 27453256
4. Ho AC, Humayun MS, Dorn JD, et al. Long-Term Results from an Epiretinal Prosthesis to Restore Sight to the Blind. *Ophthalmology*. Aug 2015; 122(8): 1547-54. PMID 26162233
5. Geruschat DR, Richards TP, Arditi A, et al. An analysis of observer-rated functional vision in patients implanted with the Argus II Retinal Prosthesis System at three years. *Clin Exp Optom*. May 2016; 99(3): 227-32. PMID 26804484
6. da Cruz L, Coley BF, Dorn J, et al. The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. *Br J Ophthalmol*. May 2013; 97(5): 632-6. PMID 23426738
7. Kotecha A, Zhong J, Stewart D, et al. The Argus II prosthesis facilitates reaching and grasping tasks: a case series. *BMC Ophthalmol*. May 23 2014; 14: 71. PMID 24885164
8. Dagnelie G, Christopher P, Arditi A, et al. Performance of real-world functional vision tasks by blind subjects improves after implantation with the Argus® II retinal prosthesis system. *Clin Exp Ophthalmol*. Mar 2017; 45(2): 152-159. PMID 27495262

## Documentation for Clinical Review

- No records required

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	0100T	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy
	0472T	Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (e.g., retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional
	0473T	Device evaluation and interrogation of intraocular retinal electrode array (e.g., retinal prosthesis), in person, including reprogramming and

Type	Code	Description
		visual training, when performed, with review and report by a qualified health care professional
HCPCS	L8608	Miscellaneous external component, supply or accessory for use with the Argus II Retinal Prosthesis System
	V2799	Vision item or service, miscellaneous

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
05/29/2015	BCBSA Medical Policy adoption
06/01/2016	Policy revision without position change
02/01/2017	Coding update
05/01/2017	Policy revision without position change
05/01/2018	Policy revision without position change
02/01/2019	Coding update
05/01/2019	Policy revision without position change
05/01/2020	Annual review. No change to policy statement. Literature review updated.
05/01/2021	Annual review. No change to policy statement. Literature review updated.
05/01/2022	Annual review. No change to policy statement. Literature review updated.
03/01/2023	Coding update
05/01/2023	Annual review. No change to policy statement. Literature review updated.
05/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.



**Prior Authorization Requirements and Feedback (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

<b>POLICY STATEMENT</b> <b>(No changes)</b>	
<b>BEFORE</b>	<b>AFTER</b>
<b>Retinal Prosthesis 9.03.15</b>  <b>Policy Statement:</b> I. Retinal prostheses are considered <b>investigational</b> .	<b>Retinal Prosthesis 9.03.15</b>  <b>Policy Statement:</b> I. Retinal prostheses are considered <b>investigational</b> .