Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Retinal Prosthesis

Policy Number: 9.03.15
Origination: 7/2008
Last Review: 2/2019
Next Review: 8/2019

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for retinal prosthesis. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Retinal prostheses are considered **investigational**.

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: • With blindness secondary to retinal diseases	Interventions of interest are: • Retinal prosthesis	Comparators of interest are: • Standard treatment of retinal diseases	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity

A retinal prosthesis is a device that 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 potentially 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. 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.

For individuals who have blindness secondary to retinal diseases who receive a retinal prosthesis, the evidence includes a prospective single-arm study evaluating the device approved by the Food and Drug Administration (FDA) and a systematic review of studies on various devices. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A 2016 systematic review included studies on the FDA-approved retinal prosthesis as well as devices unavailable in the United States; the overall conclusion was that the evidence on retinal prostheses is insufficient on all outcomes of interest. One study with 30 patients has evaluated the single FDA-approved device (Argus II); numerous articles on this study have also been published. Primary outcomes included 3 computer-based visual acuity tests. At 3- and 5-year follow-up visits, patients performed significantly better on the 3 computer tasks with the device on compared with off. Performance on the most difficult task (grating discrimination) was still relatively low with the device on. Substudies have tested performance on more practical tasks. These studies have tended to find significantly better performance with the device on but differences between groups may not be clinically meaningful. The same 30 patients have been evaluated multiple times and as a result of multiple testing, their performance may differ from other individuals with the device. Additional prospective studies and additional evaluations of the ability to perform practical tasks that have a clinically meaningful impact on health outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 U.S. has begun with a first generation, 16-electrode device (e.g., the Argus™ 16, Second Sight Medical Products), which is expected to permit the distinction between the presence and absence of light, and the second generation (e.g., Argus™ II), which has 60 electrodes. The Argus artificial retina consists of a small external video camera, held on eyeglass frames, that captures images that are then processed by an externally worn microcomputer. These signals are transmitted to a coil on the globe, 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 is hoped that further generation devices, containing more than 1,000 electrodes, will provide more detailed vision. 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 the National Science Foundation collaborated to provide grant funding, support for material design and other basic research for the project.

Other devices in development none of which are approved or cleared by the U.S. Food and Drug Administration, include the following.

- The alpha-IMS was developed at the University of Tubingen, Tubingen, Germany with the electronic chip design provided by the Institute for Microelectronics, Stuttgart (IMS) Germany. 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°.

- Boston Retinal Implant (Retinal Implant Research Group, Boston) 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 Retinal Implant Project is a joint effort of MIT, the Massachusetts Eye and Ear Infirmary, the VA Boston Healthcare System, and the NanoScale Science & Technology Facility at Cornell University.

- EPIRET3 retinal implant (Philipps-University Marburg, Marburg, Germany) is a wireless system that consists of a semiconductor camera in glasses frames 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 microcable. A second generation wireless implant is being developed with a greater number of electrodes.

- Intelligent Retinal Implant System (IRIS, Pixium Vision, SA) uses an external camera that is 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 AG) 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.

- Microelectrode-STS (suprachoroidal-transretinal stimulation) system (Osaka University Graduate School of Medicine, Osaka, Japan) places the 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.

Regulatory Status
The Argus II device received commercial approval in Europe in March 2011. In 2013, the U.S. Food and Drug Administration (FDA) approved a humanitarian use device exemption (HDE) for the Argus II retinal prosthesis by Second Sight Medical. HDE approval is limited to those devices that treat or diagnose fewer than 4,000 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 previous history of the ability to see forms. Patients must also be willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation.

Rationale

This evidence review was created in April 2005 and has been updated regularly using searches of the MEDLINE database. The most recent literature update was performed through January 8, 2018.

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.

RETINAL PROSTHESES
A 2016 technology assessment prepared for the Agency for Healthcare Research and Quality included a systematic review of the literature on retinal prostheses.[1] 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 (U.S.) 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.[2] 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 special 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.[3] 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.[4] 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).[3] 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).[3] 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.[5] 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 vs off, ranging from 19% to 38% improvement. Twenty-four (69%) of 35 tasks had statistically significant improvements in outcomes (ie, they were easier to perform) with the device turned on vs off.

A 2013 study reported on letter and word reading at 20 months in 21 patients participating in the Argus II study.[6] 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.[7] 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 (ie, 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.[8] 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.

Summary of Evidence

For individuals who have blindness secondary to retinal diseases who receive a retinal prosthesis, the evidence includes a prospective single-arm study evaluating the device approved by the U.S. Food and Drug Administration and a systematic review of studies on various devices. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A 2016 systematic review included studies on the Food and Drug Administration–approved retinal prosthesis as well as devices unavailable in the United States; the overall conclusion was that the evidence on retinal prostheses is insufficient on all outcomes of interest. One study with 30 patients has evaluated the single Food and Drug Administration–approved device (Argus II); numerous articles on this study have been published. Primary outcomes included 3 computer-based visual acuity tests. At 3- and 5-year follow-up visits, patients performed significantly better on the 3 computer tasks with the device on vs off. Performance on the most difficult task (grating discrimination) was still relatively low with the device on. Subgroup studies have tested performance on more practical tasks. These studies have tended to find significantly better performance with the device on but differences between groups may not be clinically meaningful. The same 30 patients have been evaluated multiple times and, as a result of multiple testing, their performance may differ from other individuals with the device. Additional prospective studies and additional evaluations of the ability to perform practical tasks that have a clinically meaningful impact on health outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

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 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
Ongoing			
NCT01024803[a]	Safety and Efficacy of Subretinal Implants for Partial Restoration of Vision in Blind Patients: A Prospective Multicenter Clinical Study Based on Randomized Intra-individual Implant Activation in Patients With Degenerative Retinal Diseases	39	Apr 2018
NCT02303288[a]	Post-Market Study of the Argus® II Retinal Prosthesis System – France	18	Nov 2018
NCT00407602[a]	Argus® II Retinal Stimulation System Feasibility Protocol	30	Aug 2019
NCT01864486[a]	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	Nov 2019
NCT01860092[a]	New Enrollment Post-Approval Study of the Argus® II Retinal Prosthesis System	53	Dec 2023

NCT: national clinical trial.

[a] 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):779-788. 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):2248-2254. 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):1547-1554. 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):227-232. 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):632-636. 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(R) II retinal prosthesis system. Clin Exp Ophthalmol. Mar 2017;45(2):152-159. PMID 27495262

Billing Coding/Physician Documentation Information

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 intra-ocular retinal electrode array (eg, 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 (New Code 7/1/2017)
0473T	Device evaluation and interrogation of intra-ocular retinal electrode array (eg, retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional (New Code 7/1/2017)
C1841	Retinal prosthesis, includes all internal and external components
C1842	Retinal prosthesis, includes all internal and external components; add-on to C1841(New Code 1/1/2017)
V2799	Vision item or service, miscellaneous
	ICD-10 Codes:
H35.3110-H35.3194	Nonexudative age-related macular degeneration code range
H35.50	Unspecified hereditary retinal dystrophy
H35.52	Pigmentary retinal dystrophy

Additional Policy Key Words

N/A

Policy Implementation/Update Information

7/1/08	New policy; considered investigational.
1/1/09	No policy statement changes.
7/1/09	No policy statement changes.
1/1/10	No policy statement changes. "Subconjunctival" removed from title.
7/1/10	No policy statement changes.
1/1/11	No policy statement changes.
7/1/11	No policy statement changes.
1/1/12	No policy statement changes.
7/1/12	No policy statement changes.
1/1/13	No policy statement changes.
7/1/13	No policy statement changes.
1/1/14	No policy statement changes.
7/1/14	No policy statement changes.
2/1/15	No policy statement changes.
3/1/15	Added HCPCS codes. No policy statement changes.

8/1/15 No policy statement changes.
2/1/16 No policy statement changes.
4/1/16 No policy statement changes.
8/1/16 No policy statement changes.
2/1/17 No policy statement changes.
8/1/17 No policy statement changes.
2/1/18 No policy statement changes.
8/1/18 No policy statement changes.
2/1/19 No policy statement changes.
