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Retinal Prosthesis

Summary

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.

The evidence for retinal prosthesis in individuals who have blindness secondary to retinal diseases includes case series. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Most series are small (ie, 3 to 30 patients), preliminary investigations, and/or do not assess functional outcomes. The largest prospective study (n=30) was conducted using the Argus II system and numerous articles on this study have been published. At a mean follow-up of 36 months, with the device in the on position versus off, there was significant improvement on 69% of tasks assessed by a multicomponent instrument, no change in 26% of tasks, and significantly worse performance on 6% of tasks. Additional prospective studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

FDA 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. FDA product code: NBF

The Alpha – IIMS is approved for use in Europe.
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Intelligent Retinal Implant System (IRIS) is expected to receive CE approval in Europe in 2015

POLICY STATEMENT

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Retinal prostheses are considered **not medically necessary.**

BENEFIT APPLICATION

The BCBS FEP contract stipulates that FDA-approved biologics, drugs and certain devices may not be considered investigational when used for their intended purpose and thus these products may only be assessed based on medical necessity.

RATIONALE

Argus I and Argus II

A prospective multicenter clinical trial evaluating the Argus II Retinal Prosthesis System was conducted and data were submitted to the FDA prior to device approval. The Argus II Study Group has published numerous articles on various findings of this study. In 2012, Humayan et al reported interim (minimum 6-month) results. (1) Thirty subjects with retinal degeneration and bare or no light perception were implanted with the 60-electrode array. Devices were individually programmed, and the subjects received training with the device for activities of daily living. Evaluations were scheduled for day 1, weeks 1, 2, and 4, and months 3, 6, 9, 12, 18, 24, 30, and 36. Eight subjects had reached 24-month follow-up at the time of data analysis. There were 3 types of visual acuity tasks using a computer and 2 types of real-world utility tests. Performance on 3 of the computer tasks (square localization, direction of motion, grating discrimination) was improved with the system on compared with off. With the system on, subjects had a 54% success rate in finding a door compared with 27% success with the device off and had 68% success in following a white line on a dark floor compared with 23% success 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. There were 17 serious adverse events that were considered to be device or surgery related, and 1 device was explanted. Most of the serious adverse events occurred earlier in the study before the device and surgical procedures were modified.

Functional outcomes at 3 years were reported by Geruschat et al in 2016. (1) Functional ability was assessed using the multicomponent Functional Low-Vision Observer Rated Assessment (FLORA) instrument, which uses an observer-rated assessment of 35 tasks performed with the device in the on and off positions. The ability to complete common activities across 4 domains (visual orientation, mobility, daily life, and interaction with others) was assessed. 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 a statistically significant improvement in outcome (ie, they were easier to perform) with the device turned on versus off. Scores associated with 2 (6%) tasks were significantly worse with the device turned on, and the remaining 9 (26%) tasks showed no significant difference with the device on or off.

In 2013, a prospective multicenter trial reported functional outcomes at 20 months post implantation in 21 patients; outcomes were letter and word reading. (3) Correct letter reading ranged from 51.7% to 72.3%
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with the device on, compared with 15.3% to 17.7% with the device off. The average time for correctly identified letters with the device on ranged from 47.7 seconds to 68.6 seconds. Subjects who successfully completed the letter identification task proceeded to the next task. Six subjects were able to consistently 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. Additionally, 6 patients from one of the study sites were further tested in a separate study for reaching and grasping. (4) All had been implanted a minimum of 3 years prior to participation. 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 randomized 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 device off (0%); this finding was maintained at the second visit. With the signal scrambled, success rates were 59% on the first visit and 28% on 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.”

Long-term safety results in 29 of the 30 patients included in the Argus II study were reported by Ho et al in 2015. (5) At 3 years post implantation, 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).

alpha-IMS Subretinal Implant

The ability to recognize complex spatial percepts with subretinal implantation of a 1500-electrode microchip was reported in 3 patients with hereditary retinal dystrophy (retinitis pigmentosa and choroideremia) in 2011. (6) In 2013, short-term outcomes with the next-generation Alpha IMS system were reported from 9 patients with subfoveal placement and from 12 patients with parafoveal placement. (7,8) Preoperatively, 8 of 9 patients with subfoveal implantation had light perception without localization and 1 had complete blindness. During surgery of the first patient, the tip of the implant touched the optic nerve, leading to failure of light perception and exclusion of this patient. Another patient developed postoperative subretinal bleeding and, in several other patients, the observation period was limited by technical instability and removal of the implant. On standardized testing, 8 of 8 patients had light perception, 7 had light localization, 5 had motion detection, 6 had grating acuity up to 3.3 cycles per degree, and 2 had visual acuity of 20/546 with the system turned on. Identification, localization, and discrimination of objects improved over time for these 8 patients with up to 9-month follow-up. Five patients with subfoveal implantation reported useable visual experiences in daily life that included object recognition ranging from table top items to movement of cars. Parafoveal implantation was found to be inferior to subfoveal implantation. (8)

Boston Retinal Implant

No publications or clinical trials in human subjects have been identified.

EPIRET3

Initial results from the EPIRET3 were reported in 6 legally blind subjects with retinitis pigmentosa in 2011. (9) The device was activated on 3 occasions to record visual sensations and then removed at day 28, per the study protocol. During the 1-hour sessions, the current amplitude, pulse duration, pulse frequency, number of pulses per stimulus, and stimulated electrodes were varied. Although the same stimulation
patterns were used, they elicited different sensations in the 6 subjects. Most visual sensations were described as bright colors such as red, green, blue, and yellow, but some subjects also reported seeing dark or black patterns. Some of the subjects reported seeing geometric patterns that corresponded to different stimulation patterns and/or could discriminate the stimulus orientation.

**Intelligent Retinal Implant System (IRIS)**

No published studies were identified. See Table 1 for relevant trials in progress.

**Learning Retina Implant**

An acute trial began in 2003 with 20 patients who underwent electrical stimulation lasting 45 minutes. (10) Nineteen of the subjects described sensations of phosphenes (small spots of light) during stimulation. Chronic studies in human subjects began in 2005, and a multicenter clinical trial is proposed.

**Suprachoroidal-transretinal Stimulation (STS) System**

In 2011, functional testing of the STS system was reported in 2 subjects with retinitis pigmentosa. (11) Visual acuity consisted of light perception; an eye mask was placed over both eyes during the testing. Both subjects performed better than chance for object detection and object discrimination using a video camera. One patient scored better than chance in detecting the direction of motion of an object and grasping objects. The device was removed 5 to 7 weeks after implantation.

**Summary of Evidence**

The evidence for retinal prosthesis in individuals who have blindness secondary to retinal diseases includes case series. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Most series are small (ie, 3 to 30 patients), preliminary investigations, and/or do not assess functional outcomes. The largest prospective study (n=30) was conducted using the Argus II system and numerous articles on this study have been published. At a mean follow-up of 36 months, with the device in the on position versus off, there was significant improvement on 69% of tasks assessed by a multicomponent instrument, no change in 26% of tasks, and significantly worse performance on 6% of tasks. Additional prospective studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**Ongoing and Unpublished Trials**

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

**Table 1. Summary of Key Trials**

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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT00427180</td>
<td>Extended Pilot Study to Evaluate Pattern Recognition With a Chronic Retinal Implant System</td>
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<td>NCT01024803</td>
<td>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</td>
<td>45</td>
<td>Apr 2017</td>
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<table>
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<tr>
<th>Retinal Diseases</th>
<th>Title</th>
<th>NCT</th>
<th>Date</th>
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<td>NCT01864486a</td>
<td>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)</td>
<td>20</td>
<td>Jun 2017</td>
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<td>NCT01860092a</td>
<td>New Enrollment Post-Approval Study of the Argus® II Retinal Prosthesis System</td>
<td>53</td>
<td>Aug 2018</td>
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<tr>
<td>NCT02303288a</td>
<td>Post-Market Study of the Argus® II Retinal Prosthesis System – France</td>
<td>18</td>
<td>Nov 2018</td>
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<tr>
<td>NCT00407602a</td>
<td>Argus® II Retinal Stimulation System Feasibility Protocol</td>
<td>30</td>
<td>Aug 2019</td>
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</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

No practice guidelines related to retinal prostheses were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable

Medicare National Coverage

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

REFERENCES

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## POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy was updated with literature review, adding reference 4, 5, 10 &amp; 11. No changes were made to the policy statement.</td>
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<tr>
<td>September 2016</td>
<td>Update Policy</td>
<td>Policy updated with literature review, references 2 and 5 added. Policy statement unchanged.</td>
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