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Australia and New Zealand Horizon Scanning Network

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AN INITIATIVE OF THE NATIONAL, STATE AND
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AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology

Prioritising Summary

Retinal implants to restore light perception in individuals blinded by retinitis pigmentosa

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*Adelaide
Health Technology
Assessment*

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PRIORITISING SUMMARY

REGISTER ID: 000480

NAME OF TECHNOLOGY: RETINAL IMPLANTS

PURPOSE AND TARGET GROUP: TO RESTORE LIGHT PERCEPTION IN INDIVIDUALS BLINDED BY RETINITIS PIGMENTOSA

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|--|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input checked="" type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|---|-------------|
| <input type="checkbox"/> Yes | ARTG number |
| <input checked="" type="checkbox"/> No | |
| <input type="checkbox"/> Not applicable | |

The United States FDA have given approval for several devices to be used in human clinical trials including SecondSight's (US) ArgusII implant (approved in 2007) and the "artificial silicon retina" developed by Optobionics Corporation, however Optobionics went into liquidation during 2007 (Dowling 2009).

INTERNATIONAL UTILISATION:

| COUNTRY | LEVEL OF USE | | |
|---------------|------------------------------|-------------|-----------------|
| | Trials Underway or Completed | Limited Use | Widely Diffused |
| Australia | ✓ | | |
| Germany | ✓ | | |
| United States | ✓ | | |
| Japan | ✓ | | |

IMPACT SUMMARY:

Several companies produce retinal prosthetics with the aim of restoring light perception in blind individuals. These companies include: Second Sight[®] Medical Products Inc (USA) with the second generation Argus II implant and Epiret GmbH (Germany) with the EPIRET3. Several large research companies have products with no name as yet, including two Australian groups: the Australian Vision Prosthesis Group and the Australian Bionic Eye Foundation. This technology would be made

available through specialist ophthalmology hospitals for individuals blinded by retinitis pigmentosa.

BACKGROUND

The cornea at the front of the eye allows light into the eye and bends it towards the retina. The retina, at the back of the eye converts the light into electrical impulses or signals that the visual cortex of the brain interprets as visual images. The macula, responsible for central vision, is situated in the middle of the retina (Figure 1). The retina contains a layer of light-receiving photoreceptor cells that are connected to the brain by the optic nerve. There are two types of photoreceptor cells in the retina: cone cells and rod cells. Cone cells are densely packed within the macula and are responsible for central vision and colour perception. Rod cells are found outside the macula and are mainly responsible for peripheral and night vision. Macular degeneration occurs when the central part of the retina deteriorates, affecting the cone cells, causing problems with central vision (Wikipedia 2010).

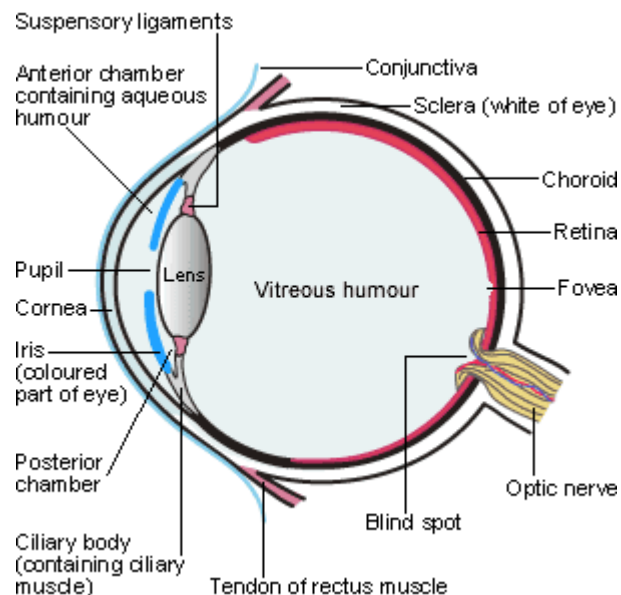


Figure 1 The structure of the eye (Retina Australia Victoria 2010)

Retinitis pigmentosa is a group of inherited (autosomal dominant, autosomal recessive or X-linked) retinal disorders which are characterised by the progressive degeneration of the retinal photoreceptors followed by the degeneration of the retinal pigment epithelium. Light and glare sensitivity (photophobia), night blindness (nyctalopia) and peripheral visual loss, resulting in “tunnel vision”, are usually the first symptoms, presenting in adolescence or early adulthood. The rate of disease progression varies among individuals with many retaining limited central vision, however apoptosis of the cone cells in conjunction with the rod cells may result in complete vision loss in some individuals. Diagnosis of retinitis pigmentosa is usually made by clinical symptoms such as visual field loss, however an electroretinogram (ERG) may be

useful for confirmation of diagnosis and to monitor disease progression. The ERG measures the summation of electrical activity in the retina in response to light stimuli. There is currently no standard treatment or therapy for retinitis pigmentosa, however some measures have been demonstrated to slow the progression of the disease if diagnosis is made early, including nutritional supplements such as vitamin A palmitate. Patients diagnosed with retinitis pigmentosa should be encouraged to seek psychological and genetic counselling for themselves and family members (Shintani et al 2009).

Investigational treatment options for retinitis pigmentosa include gene therapy, stem cell transplantation and neuroprosthetic devices. It has been well documented that electrical, mechanical or magnetic stimulation of the retina or visual cortex may lead to the perception of phosphenes, an entoptic phenomena, described as the perception of light without light stimulation (Dowling 2009; Shintani et al 2009). It is envisaged that these prosthetic devices would *not* restore vision but would restore a measure of light perception which would enable the individual to identify movement and to localise obstacles in their surroundings, increasing their mobility, confidence and safety when moving through their every day environment (Shintani et al 2009; Walter 2009).

Different prostheses have been used in experimental trials, including epiretinal, subretinal and suprachoroidal types. Epiretinal devices comprise an intraocular component with stimulation electrodes (Figure 2) to induce visual stimuli according to their differential patterns activation, and an extra-ocular component to manage data processing and transfer, image acquisition and energy supply. Communication between the components occurs via cables or wireless transmission. In the case of wireless communication, a transmitter unit may be mounted in front of the eye, whereas cabled systems use a variety of pathways, for example, via the sclera to a receiver underneath the conjunctiva, or subcutaneously to a receiver in the earlobe area, not dissimilar to Cochlear implant systems (Walter et al 2009).

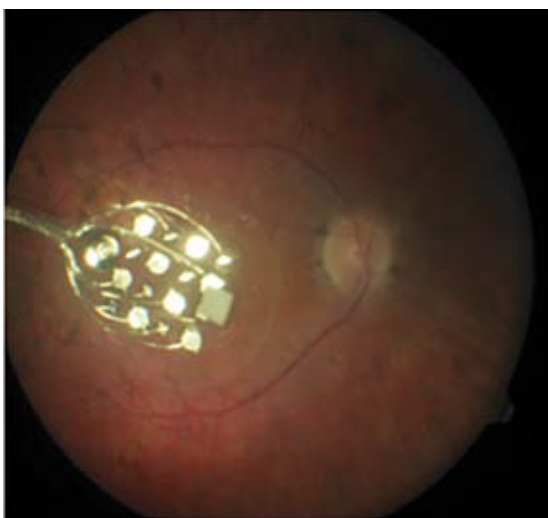


Figure 2 16-electrode array implanted in the on the retinal surface of the eye (Caspi et al 2009).

Subretinal approaches employ the implantation of thousands of microphotodiodes underneath the retina, in conjunction with a number of direct-stimulation electrodes. A cable runs via the sclera to a receiver coil on the scleral surface, while a transmitter coil is mounted to the frame of eyeglasses. Suprachoroidal prostheses have been used with the aim of avoiding risk associated with surgical placement of electrodes onto or underneath the retina. However, it is thought that increased distance of electrodes from the target retinal neurons may limit the spatial resolution of these prostheses (Walter et al 2009).

CLINICAL NEED AND BURDEN OF DISEASE

Incidence or prevalence of retinitis pigmentosa, an overall rare cause of blindness, is not differentiated from other degenerative conditions of the retina reported in AIHW data. A review in the US has reported an estimated one per 3,000 to 5,000 persons are affected world-wide (Shintani et al 2009), and it is estimated that five to seven per cent of newly diagnosed blindness in Western countries is attributable to retinitis pigmentosa (Roessler et al 2009). Blindness is often a progressive condition due to age and one Australian source estimated blindness by cause in 2004 in individuals over 40 years, with retinitis pigmentosa accounting for 1.5 per cent of all cases (Figure 3).

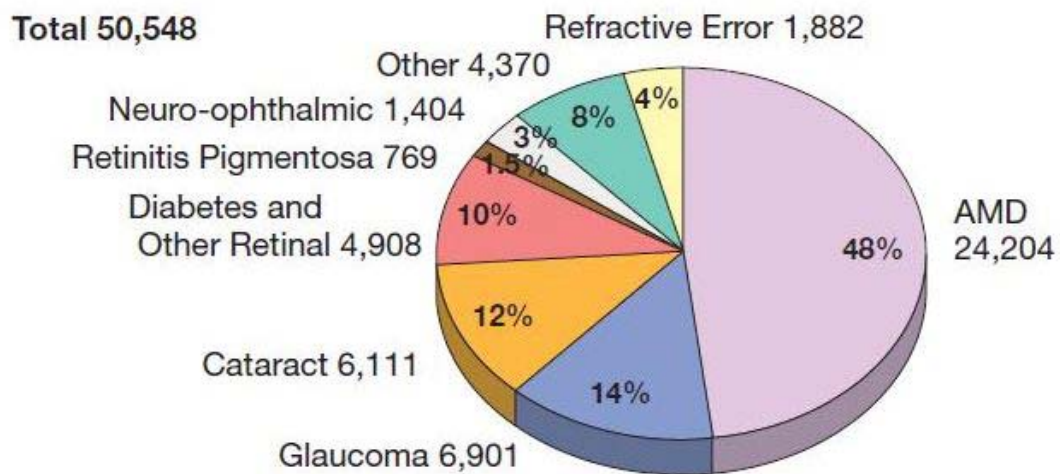


Figure 3 Estimated blindness by cause in Australians aged over-40 years, 2004. AMD = age-related macular degeneration (CERA 2004).

DIFFUSION

In December 2009 Bionic Vision Australia was awarded \$42 million from the Federal Government, to be provided over four years, for the commercial development of an implant at the back of the eye, responding to wireless transmission of vision (BVA 2010).

COMPARATORS

No standard treatment for retinitis pigmentosa exists.

SAFETY AND EFFECTIVENESS ISSUES

The use of retinal implants for artificial photoreception remains in the experimental phase and literature to establish clinical effectiveness and safety is limited. Three small trials are considered in this summary.

A prospective trial in the US conducted visual experiments in three individuals with retinitis pigmentosa after implantation of an epiretinal device.¹ (Yanai et al 2007) (level IV intervention evidence). The prototype low-resolution retinal prosthesis was implanted in the eye with worse light sensitivity for each of the subjects and visual function testing was performed following a single or double masked protocol.² Scores were compared to chance to determine statistical significance.

The first three experiments tested discrimination between different patterns of computer generated electrode activation and required set-choice answers. Electrode discrimination tested percept of relative alignment for two electrodes, sequential activation of paired electrodes simulated a moving spot of light to test percept of planar direction, and the third test was for percept of a row or column simulated by horizontal or vertical activation of electrodes. Experiments four to eight tested visual percept from electrodes stimulated by video camera input and also required set-choice answers. Experiment four tested direction of motion discrimination by passing a white bar across a black background while the subject maintained a stationary head. Head movement was not permitted because head movement could confound the perception of motion. For the remaining experiments, scanning the visual field by movement of the head was encouraged. Experiment five tested object detection by asking subjects if a white object was in the left or right visual field, or absent. The “object absent” choice was to control against spontaneous perceptions not related to stimuli. Experiment six tested patients by asking them to indicate the number of objects in their visual field: zero, one to the left, one object to the right, or two objects. Experiment seven tested form discrimination. Patients were asked to differentiate the orientation of two white bars in an “L” configuration (corner in the upper left or right, or lower left or right). Experiment eight also asked patients to discriminate between forms – three white objects (dessert plate, coffee cup and plastic knife). All experiments were controlled to prevent physical or auditory cues that could assist subjects’ performance. Results are summarised graphically in Figure 4.

¹ For understanding of the different testing protocols, it is important to note that the device had two modes. One mode used direct computer-generated stimuli and the other mode relied on input from a head-mounted video camera.

² How subject masking was possible in this context, or what it entailed, is not clear from the explanation of the methods in the study.

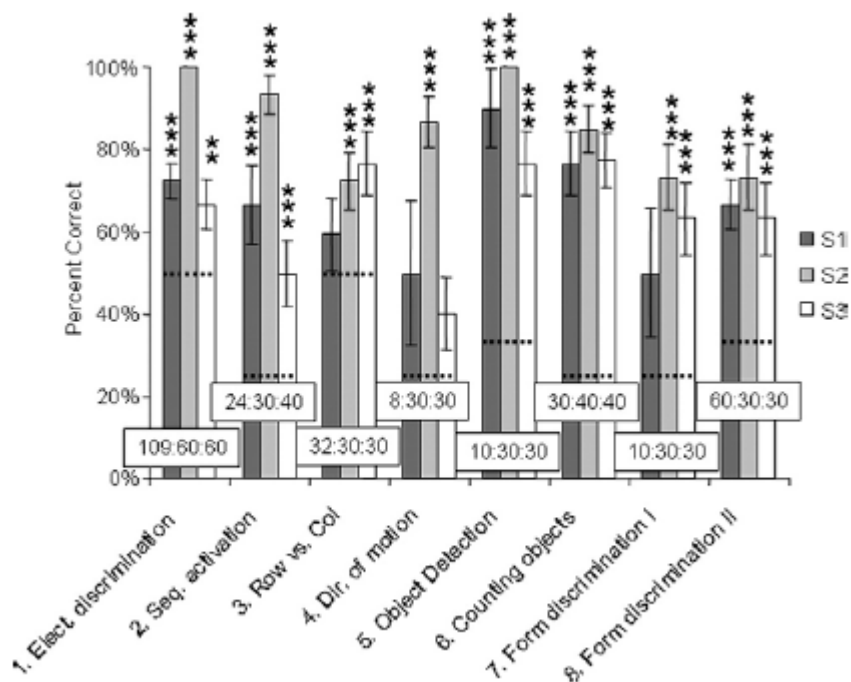


Figure 4 Performance in eight experiments for retinal implant subjects. S1, S2 and S3 indicate subjects 1, 2 and 3. Dashed lines represent chance performance. Error bars are based on binomial error. Number of trials performed for each subject on each experimental task is shown in the box overlying the columns. *** $p < 0.001$; ** $p < 0.01$; $p < 0.05$ (Yanai et al 2007).

A pre-planned comparison was made between single versus multiple pixel³ performance for the four experiments (5 to 8) in which subjects were permitted to scan objects by head movement. Of the 12 comparisons between single and multi-pixel performance (three subjects each undergoing four experiments), two experiments showed significantly better accuracy with more pixels. Significantly quicker reaction times were observed for multiple pixel experiments on two occasions involving two subjects.

Experiments in this study were developed to determine what visual tasks are possible with the aid of a low-resolution epiretinal implant. The authors concluded that percepts map onto expected locations in accordance with the positions of stimulated electrodes, albeit crudely. Performance in the experiments using camera input was better when subjects were allowed to scan their visual field moving their head. Better performance in speed or accuracy was not consistently observed for multiple pixel scenarios, indicating a complex relationship between the number of electrodes and increased visual acuity. Duration of vision loss should be noted as a potential impact on visual performance. One subject often outperformed the other two, possibly because this subject had a much shorter period of complete vision loss compared to the other two subjects (Yanai et al 2007).

³ The 4x4 array of 16 electrodes effectively constitutes 16 pixels as a single pixel corresponds to the visual percept generated by a single electrode.

Six legally blind adults with retinitis pigmentosa were enrolled in a prospective two-centre trial (Roessler et al 2009) (level IV intervention evidence). Investigators in Germany assessed the feasibility for implantation and explantation of a wireless epiretinal device in each subject's worst eye (study eye with the least amount of vision). The methods explained that morphologic and functional data for the study eye were obtained pre-operatively, four weeks after implantation, and six months after explantation. However outcomes in terms of change in visual acuity were poorly reported and no change was evident in the included data. The authors concluded that implantation was successful and well tolerated in all six patients. Post-operative inflammation was moderate, but temporary. Position of the implant remained stable until removal, which was successful in all cases. Adverse events included one case of sterile hypopyon⁴ (initially thought to indicate an infection) which was effectively treated with steroids and prophylactic antibiotics, and one case of a retinal tear that was repaired using silicone oil injection. The authors stated the need for longer follow-up to determine long-term adverse tissue reactions, but follow-up exceeding 28 days was prohibited by German law (Roessler et al 2009).

A US case study described implantation of a wireless epiretinal device in an individual with retinitis pigmentosa and no light perception (Caspi et al 2009) (level IV intervention evidence). Two visual experiments, each involving repeated trials were conducted. The first experiment tested if the 4x4 electrode retinal prosthesis could produce a percept of oriented contours. A single row of electrodes were stimulated directly via computer for one second, followed by one second of single column stimulation. The subject was required to maintain fixation straight ahead. Immediately after the second stimulus, the subject was instructed to draw the perceived pattern on a board at arm's length. The drawn lines were tracked with aid of the head-mounted video camera and a tracking program. For all trials, the subject drew two lines with at a mean (SE) angle of 87.4° (1.8°). Experiment two tested the resolution limit of the retinal prosthesis with orientation of high-contrast square-wave gratings (Figure 5). Electrode stimulation patterns were determined in real time using input from the head-mounted camera. Each grating was displayed on a computer screen for five seconds while the subject scanned the image with head movements. The subject was then asked to choose whether the image was horizontal, vertical, diagonal to the right, or diagonal to the left. With the retinal implant off, the subject identified 39 out 120 orientations correctly, a performance not significantly better than chance ($p > 0.05$). With the implant functioning, the subject identified 69 out of 108 orientations correctly, performing significantly better than chance ($p < 0.0001$). To test if spatial resolution of the implant was determined by how finely the electrodes were spaced, groups of four electrodes were stimulated in a 2x2 arrangement for a total of 4 pixels, effectively reducing resolution by half. Not unexpectedly, the subject's performance dropped to chance levels at a spatial

⁴ Accumulation of white blood cells in the anterior chamber (see Figure 1) of the eye.

frequency twice as low as the original 4x4 array. Finally, scrambling the video image to the electrode map reduced the subject's performance to chance level, in contrast to mapping the retinotopic location of each electrode to the corresponding section of the video image, which resulted in visual acuity well matched to the prosthesis electrode spacing. These findings suggest that the brain interprets a patterned image, not the average brightness resulting from the overall level of stimulation and that the development of prostheses with more electrodes should provide higher spatial resolution for patients.

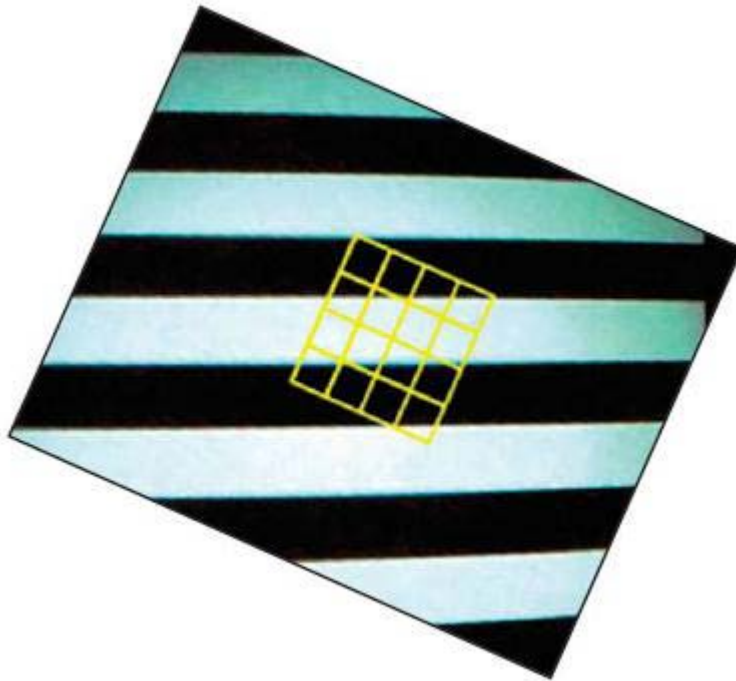


Figure 5 Frame captured from video camera during grating acuity experiment. Yellow lines show the visual field mapped to each of the electrodes (Caspi et al 2010).

COST IMPACT

Second Sight[®] Medical Products Inc (USA) was contacted for estimated costs of the Argus II epiretinal prosthesis and its implantation. Costing in the US was sought because development has progressed further than in Australia where at least four years of work will be required to investigate similar devices in clinical trials before commercialisation is possible (BVA 2010). FDA and CE approval for market of the Argus II device is currently being pursued. Depending on the particular technological pathways chosen by Australian groups, market cost of a device is estimated to range from US\$50,000 to US\$150,000. Typical hospital fees for implantation of a retinal prosthesis would incur an additional estimated cost of US\$15,000. Over time, it is foreseen that the costs could decrease as the required technologies for retinal devices become more mainstreamed (personal communication Second Sight[®]).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

It has been suggested that retinal implants may also have a valid application in the restoration of light perception in persons with age-related macular degeneration (AMD)⁵ (Yanai et al 2007, Dowling et al 2009). If further research emerges to substantiate this, retinal implants have the potential to make a wider impact among sufferers of AMD, which affects a much larger proportion of the population (CERA 2004). The use of retinal implants for AMD could be of particular relevance to Australia with an ageing population.

SUMMARY OF FINDINGS

Evidence of safety and effectiveness for retinal implants considered in this summary was low level. However, comparator treatments do not exist and the cases considered in two experimental trials (Yanai et al 2007, Caspi et al 2010) were shown to experience gains in visual percept from use of the device. The results of Yanai and colleagues indicated that increasing the number of electrodes may not directly translate to improved resolution of percept for patients, whereas Caspi and co-workers undertook experiments that showed a stronger connection between increased electrode number and improved resolution. The studies included very small sample sizes, which may explain discrepancies in the results.

HEALTHPACT ASSESSMENT:

The level of evidence assessed was low. Retinal prostheses to treat retinitis pigmentosa (and possibly age-related macular degeneration) are currently at a developmental stage, especially within an Australian context. No further action by HealthPACT is required at this time.

NUMBER OF INCLUDED STUDIES

| | |
|--------------------------------|---|
| Total number of studies | 3 |
| Level IV intervention evidence | 3 |

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⁵ As in retinitis pigmentosa, AMD is characterised by progressive degeneration of the outer retina with subsequent remodelling of the inner retina.

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SEARCH CRITERIA TO BE USED:

Microelectrodes
Microtechnology/*instrumentation
Photic Stimulation
Photoreceptor Cells, Vertebrate/physiology
Prostheses and Implants
Prosthesis Implantation
Retinal Degeneration
Retinitis Pigmentosa
Electrodes, Implanted
Blindness/*rehabilitation
Electroretinography
Visual Acuity/physiology