Veit Peter Gabel
Editor

Artificial Vision

A Clinical Guide

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Foreword

These are fascinating times for efforts toward restoring vision in individuals who are severely impaired or blind from retinal disease or injury. There is a long history of efforts to create prostheses for the sensory system. Hearing was the first to receive concerted attention. Of course, many hearing impaired individuals benefit from hearing aids which amplify sound and assist millions who are hearing impaired, particularly from presbycusis of hearing loss with age. But for individuals with essentially total absence of hearing, often on a congenital basis from genetic disease, simply amplifying the sound is insufficient, and one must stimulate the cochlea directly with electrodes. Efforts to design a cochlear implant were underway by the 1950s. The auditory system has the advantage that the sensory organ of the ear is readily accessible and that hair cells are laid out in linear one-dimensional order in the cochlea, from low to progressively higher tones. Simply snaking a continuous thread of many electrodes alongside the hair cells allows for stimulating residual cellular function in an orderly and tonally topographic fashion, and this was being done by 1964.

Work on developing a visual prosthesis was being considered in the 1980s. The task for vision is more complex, as stimulating the visual system requires transmitting two-dimensional spatial information, beginning with the retina. The retina is encased within the back of the eye, and access is possible but difficult. I recall that in 1984, during my ophthalmology fellowship at UCSF, vision scientists in the San Francisco Bay area gathered to review lessons learned from the auditory prosthesis and to consider the feasibility of developing a prosthesis for the visual system. Vision requires viewing a scene in two-dimensions, and the density of information is far greater than required for one-dimensional sound. The consensus at the time was a visual prosthesis based on stimulating the retina was too difficult to envision proceeding. Thus, it is gratifying now in 2016, that two visual retinal-based prostheses devices have actually been developed and are available commercially.

The technical challenges for a visual prosthesis are daunting. The majority of blinding conditions involve death of the photoreceptor cells that normally respond directly to light. These photoreceptors are the first stage of the visual process, and they send the visual signals progressively through the retina beginning with the

bipolar cells, and then on to the ganglion cells which send their output through the optic nerve to visual centers in the brain. The death of photoreceptor cells obviously limits vision, as losing all photoreceptor cells consigns one to blindness. Hence, the early quest in the retina was to provide a substitute system to transduce light into electrical impulses and communicate this to the remaining bipolar cells. Such work was underway in the 1990s but proceeded slowly.

Two cellular targets were considered in the retina by different groups. One was the obvious replacement of the missing photoreceptor cells, to stimulate the retinal bipolar cells. Conceptually this could be accomplished by untethered photovoltaic photocells, but ultimately these were found to generate electrical impulses insufficient to activate bipolar cells. The solution required a passive electrode array, energized through a wire harness connected outside the eye. The second target was the ganglion cells which lie at the surface of the retina in orderly fashion in a two-dimensional topography of vision. Stimulating ganglion cells at the far periphery of the retina gives a visual sensation in one's peripheral vision, whereas stimulating ganglion cells in the macula near the center of the retina will generate a visual percept directly ahead in the line of sight.

However, technical challenges are immediately evident from considering the biology of neural visual processing in the retina. The millions of photoreceptor cells each correspond to individual discreet pixels of vision that recapitulate the visual scene. Signal processing through the successive layers of retinal neurons progressively extract visual information, and the initial, discreet pixilated vision of photoreceptors is systematically analyzed by an elaborate neural network in the retina, beginning with the bipolar cells. By the time the visual scene is communicated to ganglion cells at the retinal surface, the information has been recoded into abstract features of intensity, contrast and movement across the visual space from right to left, or top to bottom.

With these neural challenges, it is nothing short of remarkable that two visual prosthesis devices have passed through US and European regulatory approvals and have reached the marketplace and are available for patients. These devices are colloquially termed "retinal implants for artificial vision." Both consist of a two-dimensional array of electrodes to stimulate the remaining retinal cells electrically. One group produced the Tübingen MPDA Project Alpha IMS device that is implanted underneath the retina at the retinal location of the original photoreceptor cells that are lost from disease. This sub-retinal implant has 1500 microelectrodes that contact the retinal bipolar cells, to replace the photoreceptors lost in macular degeneration. Alpha-IMS obtained CE marking in 2013. A second device, the Argus II implant, is a two-dimensional array of 64 electrodes that sits on the surface of the retina, adjacent to the ganglion cells. This was approved for commercial use in Europe in 2012 and in the United States in 2013.

This book explores a range of topics pertinent to moving the field forward. Among these is a consideration of extra-retinal locations to stimulate the visual system, such as at the visual cortex or the optic nerve. The history of stimulating the visual cortex goes back to the 1980's with the first cortical implant based on work of William Dobelle. There has been modest success with this approach, including work by

Richard Norman, and his reflections on this approach are quite useful. This approach uses a matrix of spike electrodes positioned on the brain surface to penetrate into the visual cortex and stimulate cells to generate a complex visual percept. Alternately, stimulating more proximally in the visual pathway is possible by a cuff electrode around the optic nerve which is the ensemble of axons projecting from the retinal ganglion cell to the lateral geniculate nucleus. An optic nerve-based stimulating prosthesis must deal with the unique spatial arrangement of the axons to engage the topography of vision. If successful, one might expect this to yield an abstract visual percept resembling that from stimulating ganglion cells directly at the retinal surface.

For patients a very practical question remains as to what degree of spatial resolution can be obtained by these approaches. Reading vision requires high spatial resolution to achieve the 6/6 acuity that is the hallmark of excellent natural vision enjoyed by the majority of people. There is general agreement that restoring 6/6 acuity is beyond what can be obtained by an electrical visual prosthesis. Other approaches to stimulating the neurons chemically are being developed. In theory this may give tighter spatial localization and higher resolution. But even then, ultimately the spatial resolution at the level of the retina will be limited by retinal disorganization consequent to disease pathology, as collateral cellular damage from disease compromises the visual neural processing network. It has been known for some time that for retinitis pigmentosa, end-stage disease causes disarray even of retinal neurons not directly involved, and the remaining cells sustain damage that ultimately limits the quality of "vision" that could be obtained. Consequently, the topic of assessing the vision of individuals after receiving these prosthetic vision devices is important to consider.

In sum, the technical and biological context to developing retinal and visual neural prostheses is presents a complex challenge. And the topic is critically important to assist individuals with advanced and even end-stage vision loss. One readily finds that the topics are interconnected in complex ways and warrant dedicated study by a variety of disciplines, including scientists, engineers, physicians and sensory psychologists, to envision how best to proceed. That puts us back to the opening statement - that these are fascinating times to work in the arena of restoring sight to vision-limited individuals.

National Eye Institute, NIH
April 14, 2016

Paul A. Sieving, MD, PhD,
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Preface

The socioeconomic impact of blindness is an increasing worldwide problem and every attempt to reduce it is to be welcomed. During the last decades the scientific approaches to restore lost vision in blind patients either by gene and stem cell therapy or by technology development are continuously growing.

Artificial Vision is an exciting and rapidly developing field in both ophthalmology and basic science. The technology has been published in highly specialised scientific journals as well as in the lay press. The latter, however, has often overemphasised single experimental results which can mislead the non-specialist.

My goal as editor was therefore to put together a comprehensive collection of all the leading groups worldwide working on Artificial Vision, by authoring their own work in single chapters. This should give an updated overview on the different approaches currently discussed. The book begins with four introductory contributions on the difficulties in comparing and interpreting functional results in the area of very low vision and the principal prospects and limitations of spatial resolution with artificial tools. This is followed by eight chapters by workers who stimulate the surface or the pigment epithelial side of the retina and five further chapters by experts who work on stimulating the optic nerve, the lateral geniculate body and the superficial layers of the visual cortex.

I do hope this book will be helpful for our colleagues who are working in the wider field of ophthalmology so that they may knowledgeably inform their patients who are often desperate to hear of these exciting medical breakthroughs.

Munich, Bavaria, Germany — Veit Peter Gabel
April, 2nd 2016

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Part I
Introduction or Principles of Functional Assessment

Chapter 1
Assessing Patient Suitability and Outcome Measures in Vision Restoration Trials

Lauren N. Ayton and Joseph Rizzo

Abstract One of the challenging aspects of visual prosthesis clinical trials is the assessment and reporting of efficacy. In this relatively early phase of development, visual prosthesis devices are not able to provide high-resolution visual acuity, and hence standard vision tests such as logMAR acuity charts are not sufficient to measure post-intervention improvements in vision. This has led to the development of a number of functional vision assessments, such as tests of orientation and mobility and activities of daily living, which aim to show the "real-world" benefit of the devices. These challenges face all research groups and companies who are developing vision restoration interventions (including stem cells, gene therapy and optogenetics), and sharing of techniques and knowledge between the groups can only further our quest to provide patient benefit. As such, an International Taskforce was developed in 2014 to generate consensus on the methods of testing and reporting outcomes in vision restoration trials, and has become known as the Harmonization of Outcomes and Vision Endpoints in Vision Restoration Trials (HOVER) Taskforce. This chapter outlines the structure and aims of the Taskforce, and provides an update of the progress to date. In addition, a summary of the patient characteristics that are desirable for a visual prosthesis candidate are provided for the practicing ophthalmologist.

Keywords HOVER Taskforce • Consensus • Outcome measures • Clinical trials

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Key Points

- At the present time, there are no internationally-accepted gold standards for the assessment and reporting of patient outcomes in vision restoration clinical trials.
- An international group, the Harmonization of Outcomes and Vision Endpoints in Vision Restoration Trials (HOVER) Taskforce, is currently working to generate consensus in this area.
- There are a number of clinical characteristics that practicing ophthalmologists should assess for when considering referral of a patient for vision restoration clinical trials or treatments.

Developing an International Consensus on the Measurement and Reporting of Patient Outcomes: The Harmonization of Outcomes and Vision Endpoints in Vision Restoration Trials (HOVER) Taskforce

As is evident from the contributions to this book, the field of vision restoration is rapidly progressing. Treatment options such as stem cells, gene therapy and optogenetics, which were once considered science fiction, are now becoming real options for the future treatment of people with blindness. But of all the vision restoration techniques, visual prosthetic devices (or "bionic eyes") are the most advanced and have yielded the best visual outcomes to date for people with profound vision loss. There have been over ten chronic human clinical trials of these devices, with implants placed in various locations in the brain, the optic nerve and retina. These trials have shown that the devices are generally safe to implant and can, in the better cases, produce improvements in visual function for patients who are otherwise severely vision impaired [1–6]. However, to date these devices have provided vision with relatively low spatial resolution, which confounds attempts to convincingly demonstrate improvements in vision and functional vision.

Assessment of low vision has historically been recognized as demanding, with variability in test results and patient fatigue increasing with lower levels of vision [7]. These factors conspire with other confounding factors, like improved motivation and performance that can occur when patients know an assistive device is being used, given their heightened expectations of benefit. For these and other reasons, it can be challenging to convincingly prove the benefits of vision restoration interventions.

These challenges have long been recognized by the field, both in publications [8–11] and through conference discussions [12]. Guidelines for the measurement of patient outcomes were published by the Food and Drugs Administration (FDA) in 2009, and updated in 2013 [13], and outlined a number of considerations, including methodological standards. This FDA document also detailed the two main areas of

outcome assessment that it considered necessary for the report of visual prosthesis outcomes; visual function (acuity, spatial mapping of phosphenes and form vision assessments) and functional vision (orientation and mobility, activities of daily living and patient reported outcomes).

In more recent years, there has been a call for international cooperation and a higher level of discussion from the researchers themselves, which ultimately led to the formation of the Harmonization of Outcomes and Vision Endpoints in Vision Restoration Trials (HOVER) International Taskforce, founded by Joseph Rizzo (Boston, USA) and Lauren Ayton (Melbourne, Australia) in 2014 [14]. This Taskforce was formed to engage a wide swathe of experts in the fields of vision restoration, low vision, and clinical trial outcomes to work toward developing an international consensus on preferred methods to measure and to report patient outcomes in vision restoration clinical trials, whether of prosthetic devices or any other form of intervention. For several reasons, improving consistency in methodology and reporting will become even more important as the number of vision restoration treatments increases.

To date, over 100 eminent researchers and clinicians have joined the HOVER Taskforce and have been cooperating to develop consensus on areas ranging from visual acuity testing to methods of performing electrical stimulation studies. The Taskforce is overseen by a guidance committee formed of representatives of research groups who have completed clinical trials, experts in each of the fields of stem cells, gene therapy and optogenetics, and a representative of the Food and Drug Administration (FDA) who is an expert on regulatory issues. This guidance committee provides counsel and support to the working groups with the aim of producing a set of consensus documents that will be relevant to all forms of vision restoration technologies. The Taskforce is supported by Detroit Institute of Ophthalmology, with the director, Dr Philip Hessburg, providing executive oversight for the work.

The most important aspect of the HOVER Taskforce is its philosophy of inclusiveness and openness. The committee is aware and sensitive to the fact that there are notable differences among the various approaches to prosthetic intervention. As such, there was no intent to seek detailed specification of methods that would be appropriate for all groups. Rather, this Taskforce was motivated by the goal of improving transparency by developing guidelines to obtain more consistent measures of visual function and more consistent means of reporting results. The guidelines generated by the HOVER Taskforce will reflect the knowledge and experience of a broad, international cohort of researchers, which should provide benefit for all emerging forms of visual restoration trials for decades to come. The Taskforce intends to continuously seek input from its constituency, which will likely lead to modifications to its recommendations as new information and experience is acquired. The Taskforce seeks to distribute the collective wisdom of many experts, not to control but rather to guide future work in this field. Draft guidelines from each of the working groups are being collated and will be published in the near future.

Another aim of the HOVER Taskforce is to provide patients, the low vision community and clinicians with accurate and up-to-date information about the status of

vision restoration research. To this end, we have designed a website to provide this interface between the medical researchers and the patient community, at www.artificialvision.org.

The progress of the HOVER Taskforce has been inspirational, with international experts from all backgrounds working together for a common good. This work will only serve to strengthen the field and advance the development of treatment options for our visually-impaired patients whom we are proud to serve.

Advice to the Practicing Ophthalmologist: How to Test and Advise Patients Interested in Restoration Therapies at Present

With the significant general public interest in vision restoration therapies, it is inevitable that many ophthalmologists will be approached by potential candidates. As evident above, there is still controversy on the most appropriate outcome measures for defining efficacy in vision restoration trials, but it is easier to define a candidate's suitability based on three main aspects:

1. Level of residual vision

   At the present time, vision restoration interventions are only suitable for people with extremely poor levels of vision. Most trials of visual prostheses have included participants with vision of bare light perception or less, with a few including those who are able to identify hand movements. Candidates for a vision prosthesis must have this low vision in both eyes. At present, candidates must also have a history of prior useful form vision, as this is indicative of posterior visual pathway integrity (which may be compromised in cases of congenital blindness).
2. Cause of vision loss

   As detailed in this book, the type of vision loss is a key factor when deciding on which visual prosthesis is the most suitable for a patient. Retinal prostheses, which are the only commercially available prosthesis at this time, are suitable for people with retinal degenerative diseases such as retinitis pigmentosa or choroideremia. In 2015, the first clinical trials were commenced in patients with complete vision loss from geographic atrophy from age-related macular degeneration, but at this time this is not a regulatory- approved indication for the devices. There are no approved cortical prostheses on the market, but clinical trials are anticipated to commence in the coming years. It is believed that a cortical prosthesis could be an option for people who have lost their sight from other diseases, including glaucoma, diabetic retinopathy and trauma.
3. Patient motivation and expectations

   Possibly one of the most important factors to consider when deciding if a patient would be a good candidate for a visual prosthesis is their own expectations and motivations. At the present time, the improvements in vision that such

Fig. 1.1 Currently active visual prosthesis groups, January 2016 (Map by Joe Rizzo & Lauren Ayton Updated 3 January 2016. Produced in collaboration with the Detroit Institute of Ophthalmology, a division of the Department of Ophthalmology, of the Henry Ford Health System)

devices afford is still modest, and so it is vital that patients are aware of the limitations of the technology. In most trials to date, there have been significant variations in patient performance with prostheses, and hence it is not possible to guarantee an improvement in vision to someone who undergoes the treatment. The best candidates for visual prostheses are those who understand these limitations, and who have reasonable and fair expectations.

The best way to be sure of a patient's suitability for a visual prosthesis is to contact the research group or medical device supplier directly. They can then provide practitioners with up-to-date information and advice. A map showing the active visual prosthesis groups in 2015 is shown below (Fig. 1.1), and up to date information can be located online. To date, the three regulatory approved and commercially available retinal prostheses are:

(a) The Argus II retinal implant by Second Sight Medical Products, USA (CE mark and FDA approval); http://www.secondsight.com/
(b) The Alpha IMS retinal implant by Retina Implant AG, Germany (CE mark approval); http://www.retina-implant.de/en
(c) The Iris 150 retinal implant by Pixium Vision, France (CE mark approval); http://www.pixium-vision.com/en

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Chapter 2
Functional Assessment of Artificial Vision

Gary S. Rubin

Abstract "Functional Assessment" refers to tests that capture a person's ability to use vision to perform everyday tasks. These include assessments ranging from basic psychophysical tests of light perception and discrimination to performance-based tests such as reading a newspaper or navigating through an obstacle course. Like all types of clinical tests, functional assessments must use methods that are adequately standardised, but not so rigorously standardised that they lose their relevance to everyday life. Functional assessment can be time-consuming and much effort has gone into making these assessments efficient through the use of intelligent, adaptive testing and scoring algorithms. As for other types of clinical tests, functional assessments must be shown to be reliable, valid, and responsive. The chapter concludes with an overview of currently available functional tests and evaluates their standardisation, reliability and validity, where such data are available.

Keywords Visual function • Reading • Mobility • Navigation • Reliability • Validity • Bayesian adaptive algorithms

Key Points

- Functional assessment must strike a balance between standardisation, to insure that the tests are reproducible across sites, and natural conditions, to insure that the tests reflect performance in real-world conditions.
- Functional assessment typically does not inform us about the mechanisms or aetiology of disease, but it does tell us about the impact of disease and the safety and effectiveness of its treatment
- Forced-choice testing procedures should be used whenever possible to reduce the influence of criterion effects
- Adaptive test procedures significantly reduce test time

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Introduction

In the field of artificial or prosthetic vision, "functional assessment" refers to any of a variety of tests that capture a person's ability to use vision to perform everyday tasks. Functional assessment stands in contrast to structural assessment, such as measurements of retinal thickness made with the OCT. Functional assessment also differs from tests designed to assess eye health such as intraocular pressure. But what about such common tests as visual acuity which are used to predict reading performance, to assess photoreceptor density, and to monitor refractive error? Indeed, many eye tests can have functional, structural, and eye health uses, but in this chapter we will focus our attention on the functional application. Functional assessment is important for the evaluation of treatments applied across the entire range of visual abilities, from patients looking to achieve "super-normal" vision with wavefront LASIK to blind participants hoping for restoration of visual function through gene or stem cell therapies. But as most of the candidates for visual prostheses must have vision worse than counting fingers upon entry into the study, we will limit our discussion to what has been termed "ultra-low vision" (ULV)

Patient reported outcome measures (questionnaires) play an important role in functional assessment, but we will not be discussing them in this chapter. We will also limit our discussion to applications within the field of artificial or prosthetic vision, bypassing much interesting work with sensory substitution such as vibriotactile displays and text-to-speech.

Functional assessment runs the gamut from basic psychophysical tests of light perception and discrimination to performance based tests such as reading a newspaper or navigating through an obstacle course. Functional assessment is used as an outcome measure to assess safety and efficacy of prosthetic devices, and to develop training or rehabilitation plans to improve the use of such devices.

Standardisation

To be useful, especially for multi-centre investigations, functional vision tests need to be carefully standardized. That much is obvious. But it is less obvious that functional tests can be over standardized. Take reading tests. There are many types of tests that are designed to measure reading speed. These include tests based on random words that are matched only for length and word frequency, to sentence based tests that have carefully controlled syntax word length word frequency and syntax [1].

It is argued that the random word reading tests are linked more closely to purely visual factors whereas the controlled sentence tests are strongly influenced by cognitive factors. But which is better related to every day reading? That question has not been addressed for most reading tests, but in our study of the impact of visual impairment on function and quality of life in the elderly [2], we compared a standardized laboratory reading test to reading under natural conditions in the home. The laboratory reading test used short paragraphs of meaningful, continuous text