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**Important – Publisher’s Note**
The views expressed in Digest are not necessarily those of the Macular Society. To the best of our knowledge the information in Digest was correct at the time of going to press. However, please remember that research into macular degeneration is continually progressing worldwide and it is possible that there have been developments since publication.

In addition, the products and services featured in Digest are not endorsed or recommended by the Macular Society which does not conduct testing or approval. Where appropriate, please take professional advice from an optician, optometrist, doctor or social worker before purchasing.
Welcome to the Macular Society’s 2013 edition of Digest, our annual review of research developments. We hope you like the new look!

In 2012, the Society’s 25th anniversary, there were some very promising research developments. Medical, surgical and biomechanical advances are extending the boundaries of our understanding of macular disease. We really have come a long way since the Society was established in 1987.

Many of us affected by macular disease are reaping the benefits of amazing new technologies; clever new readers, magnifiers, smart phones and tablets are revolutionising daily life. Rehabilitation techniques such as eccentric viewing and steady eye – for which I am a passionate advocate – are becoming more widely recognised as beneficial.

For people with wet age-related macular disease (AMD), new drugs and procedures are promising less frequent hospital visits.

Despite this progress, we still have a great deal of work to do. As we all live longer, AMD is on the increase – from 500,000 today to over 650,000 by 2020. We need to press for greater investment in eye research, more resources for macular clinics and better access to rehabilitation and emotional support.

This edition of Digest is dedicated to the memory of my predecessor, Alan Alderman, who sadly passed away in July 2012. I am determined that we will continue his work and I look forward to leading the Society into our next 25 years.

Richard Elliott
Chairman, Macular Society
2012 was an exciting and encouraging year for macular research. We were privileged to hear from some of the country’s leading ophthalmologists and researchers at our annual conference and ‘Top Doctors’ seminars, held in partnership with the Royal College of Ophthalmologists.

Stem cell therapy hit the headlines in 2012. The technique aims to replace damaged cells in the macula with healthy cells. An American company, ACT, launched phase 2 safety trials with Stargardt’s patients and the London Project to Cure Blindness geared up for a safety trial in a small cohort of acute age-related macular disease (AMD) patients in 2013. With a grant from the Macular Society, Dr Rachel Williams at the University of Liverpool focused on a protocol for growing stem cells on an artificial membrane for transplant into the retina.

Technology also offered great promise during 2012. More sophisticated OCT scanning machines, able to see hitherto invisible layers of the macula, are helping clinicians diagnose, monitor and treat patients. New intraocular telescopic lenses came onto the market for patients with advanced macular degeneration in both eyes and there was research into visual prosthesis, focused on transmitting images from cameras to chips implanted in the brain.

These developments offer new hope to future generations, but it is crucial we remain focused
on improving treatments and support for the half a million people affected by macular disease today.

Prevalence research funded by the Society in 2011 revealed that numbers were higher than previously reported – 70,000 people a year will develop AMD. As our population ages, numbers will increase by a third by 2020. Of these, around half will develop wet AMD (Owens et al 2011).

A survey undertaken by the Society on behalf of Vision 2020 UK highlighted the pressure on macular clinics around the UK. Around half of the clinics reported they were unable to meet the guidelines for treating and monitoring wet AMD. Innovative responses are emerging to meet these demands – from community models to mobile monitoring, online referral and different approaches to assessing and treating patients. However, the fact remains that the NHS is simply not geared to cope with the growing numbers needing access to sight-saving anti-VEGF drugs. We hope that new treatments such as Aflibercept (Eylea, Bayer) and radiation therapies (such as epimacular brachytherapy and stereotactic radiation therapy used in combination with anti-VEGF) will lengthen treatment and monitoring intervals and help reduce the burden on both patients and the NHS. In the meantime we continue to press for more investment in macular services.

Alongside these developments, controversy continued over the use of Avastin, the cheaper unlicensed alternative to Lucentis. The results of a major trial in the US showed the two drugs are ‘about as’ effective, but debate continued over the relative safety of Avastin. The Society’s position remains that we prefer the licensed drug to be used. However, given the costs involved, we understand the reasons for the interest in Avastin. We also accept that for patients who don’t qualify for wet AMD treatment on the NHS, Avastin is a valuable alternative. Before it is used in wet AMD treatment however, a formal appraisal should be undertaken.
by NICE and the Medicines and Healthcare products Regulatory Agency (MHRA). We need to avoid a postcode lottery of treatment with patients being asked to make choices on drugs – especially when the professionals seem unable to agree.

In this context, healthcare commissioners urgently need a more accurate picture of the number of people likely to need wet AMD treatment. So, in 2012 we provided a research grant to Mr Winfried Amoaku, University of Nottingham, to analyse data from the Bridlington Eye Assessment population study. His study will report on disease stage and asymmetry. A further grant was awarded to Ms Sobha Sivaprasad, at Moorfields, to quantify the burden of care for wet AMD patients and carers.

The pressure on eye clinics is also impacting on the patient pathway, with fewer dry AMD patients seeing an ophthalmologist for diagnosis, monitoring and referral to low vision services. To explore this and other issues facing patients, a third grant was awarded to Professor Clare Bradley at Royal Holloway to study the experiences of an AMD patient – everything from diagnosis to information, treatment and access to rehabilitation and emotional support.

The field of genetics is also moving apace. In 2012, we were pleased to team up with Fight for Sight to co-fund research by Professor Andrew Webster at Moorfields. This project will use whole exome DNA sequencing to look at the genomic variants contributing to macular cone dysfunction in patients with occult maculopathy.

We are passionate about the need to raise awareness of Charles Bonnet Syndrome – the perfectly normal visual hallucinations experienced by as many as 60% of people with advanced macular disease. So, we undertook a large survey of 4,000 Macular Society members looking at the impact of visual hallucinations.

The role of nutrition and supplements remains a hot
topic. With no treatment for dry AMD, people are keen to keep their eyes healthy. In 2012, we launched a research collaboration with Aston University to compile evidence on the different nutrients, antioxidants and supplements thought to contribute to good macular health.

The Society’s eccentric viewing programme went from strength to strength in 2012. A literature review commissioned by Cardiff University demonstrated the value of eccentric fixation and steady eye techniques for people with central vision loss. Along with the independent evaluation of our own volunteer training programme being undertaken by the University of Manchester, this literature review will help us promote the technique to health and social care commissioners.

Finally, we have a new name and look. We talked to a large number of members, patients and professionals to understand perceptions about the Society. We learnt that our services and investment in research are highly valued but that not enough people know about us. We also learnt that the vast majority of patients and members are uncomfortable with the word ‘disease’. So we decided to simply change our name to the ‘Macular Society’ and have refreshed the look of our publications to appeal to a larger audience. Our priority is to get our leaflets and patient information out through eye clinics, optometrists and GPs. Our new professional member scheme will also provide a range of free resources and help us work together more effectively to support patients.

The Macular Society’s research programme is made possible thanks to the generosity of our members and donors. We are an independent charity and receive no funding from government or pharmaceutical companies. This year, we are delighted to have been in a position to offer larger research grants. Thank you for your support and we look forward to the next 25 years!

Helen Jackman
Awards for Excellence 2012

Chairman’s Award for Volunteering
- Geoff and Mavis Ramsden, Basingstoke Group Leaders
- Betty Richards, Fareham Group Leader

Chairman’s Award for Fundraiser of the Year
- Jean Boyd – skydiving fundraiser
- The 2011 Kilimanjaro Team – Steve and Alison Brazier, Andrew Cant, Chris Collings, Allannah Gaffney, Penny Pardon, Amar Shah, Tim Woodley

Support & Community Rehabilitation Professional of the Year
- Judith Grant and Lynn Reitz, Tameside
- Rebecca Marsden, Solihull Hospital

Optician or Optometrist of the Year
- Andrew Miller, Focus Birmingham
- Pat Wild, Isle of Man

Clinician or Clinical Service of the Year
- Blackburn East Lancashire Macular Team
- Moorfields Macular Team
- Richard Gale and team, York Hospital

Special Judges’ Award for Services to People with Macular Conditions
Andrew Lotery, Southampton

The Macular Society’s annual awards scheme continues to increase in popularity. Now in its fifth year, we will launch our 2013 Awards for Excellence on 2 April (please use enclosed poster from this date). Here are just some of our 2012 award winners, whose stories may inspire you to make a nomination.

Eileen Browning, a patient, nominated the Blackburn East Lancashire Macular Team: “I would particularly like to mention nurses Tracy and Gillian who, despite all the pressures of a very busy department, are always smiling and take the time to put you at ease, on one occasion they even held my hand whilst...”
I was having the injections as I was so nervous. In my opinion, the NHS needs more people like this who embody the essence of the caring profession.”

**Focusing on rehabilitation**

Andrew Miller, Lead Optometrist at Focus Birmingham, was joint winner of our Optometrist of the Year category. Focus Birmingham is a charity that supports local people affected by visual impairment. Mr Miller leads a centre providing Low Vision Assessments, an Adult and Children’s Emotional Support Service, IT training and support and a Resource Centre demonstrating and supplying daily living aids. He said: “Developing and delivering a low vision service is very rewarding. In my job, I support and help people who are struggling with the challenges of being visually impaired. I am constantly motivated by the courage and determination shown by my service users.”

**Reaching new heights**

It’s not just excellent treatment and care that professionals are recognised for. Amar Shah and Allannah Gaffney, from Bristol, both work as optometrists and recently climbed Kilimanjaro to raise money for the Society. They said: “It was an amazing once in a lifetime experience that was both mentally and physically exhausting! We decided to do the climb as we come across the effects of macular disease regularly and know how valuable the support of the Macular Society is.”
Macular Society Appeal for Research 2013

Help today, hope for the future

Over the last few years so many new and exciting avenues of research have shown promising results which could one day lead to a cure for patients with macular conditions.

In response the Society increased the amount of money available for research for 2013, more than doubling the fund to £340,000. We received more applications than ever and 11 passed the first phase of peer review. But we won’t have enough to fund all we would like to.

To keep the momentum going and fund more of these vital projects we urgently need to raise more funds for research. We have set an ambitious target this year of £300,000. We hope you will consider helping by giving generously to this year’s research appeal.

To donate now call 01264 350551 or visit our website www.macularsociety.org

Since the Society was set up over 25 years ago we have promoted research into macular conditions exclusively.

This research is hugely important to our members. Thanks to their donations and legacies over the last 11 years we have invested over £1.6 million in this crucial area. To make most impact with our money we typically fund small or early stage research projects which go to on to lever in additional funding.

Visit our website to learn more about our research grants.
Macular Society launches professional membership scheme

Cathy Yelf, Head of Communications and External Relations, Macular Society

Free membership for all who work in eye care.

The Macular Society has always been keen to work closely with eye care professionals and is now offering all eye care professionals free membership of the Society.

New members will receive a welcome pack with samples of our patient information and other materials. They will get our member magazines and this annual scientific journal. Free supplies of all materials can be ordered by email, telephone and from our website. We are also launching a smart phone app for easy ordering.

Other benefits include a quarterly newsletter on developments in the macular field and early bird offers and bursaries to educational events.

We are increasing the range of patient information available to include more than a dozen leaflets on specific aspects of macular disease and central vision loss, a DVD and Amsler grid card.

Our materials are produced with the help of appropriate experts and viewed before publication by a professional panel.

Eye care professionals will find a Freepost membership response envelope inside this edition of Digest and an order form for materials.

We are grateful to eye care professionals for their dedication and commitment to people with macular conditions and we look forward to working closely with more professionals in the sector in 2013 and beyond.
Genetic predictors of blood antioxidant levels and the risk of AMD – progress update

Professor Astrid Fletcher, Principal Investigator of the European Eye Study

People vary in their diets and much research is dedicated to identifying risk factors associated with different patterns and components of diet. In addition to variations in diet, genetic factors may also differ between people, for example in the metabolism and transport of dietary components in the body. With support from the Macular Society, we have been investigating genetic influences on the antioxidant vitamins C and E, and the carotenoids (lutein and zeaxanthin) thought to play an important role in protecting the eye. These antioxidants cannot be synthesised by the body and must be obtained from dietary sources.

We analysed data from the European Eye Study which took place in seven different countries from north to south Europe. We looked at a number of variants in two genes which influence the transport of vitamin C – the sodium-dependent vitamin C transporter proteins SVCT1 (encoded by the gene SLC23A1) and SVCT2 (encoded by SLC23A2). We looked at differences in vitamin C levels and also whether these variants were associated with age-related macular degeneration (AMD).

We did not find differences in plasma vitamin C levels in any of the variants in SLC23A2 or any association with these variants.
and AMD. In contrast, we found that two variants (rs33972313 and rs10063949) in SLC23A1 were significantly associated with neovascular AMD.

Rs33972313 was associated with a two-fold increased risk and rs10063949 with a lower risk. For rs33972313 we also found that plasma vitamin C levels were significantly lower in those with the rare genotype, around a 15% difference.

We then investigated these variants in four UK and European studies to see if the association with AMD was also found. No other studies found such a strong relationship with these variants and AMD as we observed in EUREYE. The meta-analysis of all studies taken together did not provide robust evidence to support the findings from EUREYE.

We also investigated genes influencing other antioxidants. The SCARB1 gene has previously been shown to mediate the uptake of vitamin E and lutein. In the EUREYE study, we found that a variant in SCARB1 (rs5888) was associated with lower vitamin E and lycopene levels but not with lutein or zeaxanthin. Interestingly, rs5888 showed an increased risk of early AMD and of late AMD, but only for geographic atrophy and not for neovascular AMD. These results for early AMD and geographic atrophy have not previously been reported in the literature. Only one study has looked at the rs5888 variant in AMD and found no association for neovascular AMD.

It is possible that the associations we found relate to lycopene. In our analyses higher levels of lycopene were associated with lower risks of early AMD. As lycopene has not previously been implicated in AMD further research is required to replicate these findings.

Investigating the genetic basis of Stargardt’s disease with high-throughput DNA sequencing

Andrew Webster, Moorfields Eye Hospital and Institute of Ophthalmology, UCL, and Kaoru Fujinami, National Institute of Sensory Organs, Tokyo, Japan

The investigation of the inherited disorders that affect the macula gives insights into biological pathways that are vital to the health of this important part of the retina, which mediates detailed vision. Stargardt’s disease is the most common, by far, of the macular dystrophies. In fact, the proportion of individuals affected by this disorder comprise almost one third of those presenting with inherited disease to the eye clinic.

Despite the fact that the gene causing the disorder, known as ABCA4 was discovered as long ago as 1997, it is still not possible by using conventional genetic technology to account for all the genetic changes in patients and families with the disorder. At Moorfields and the Institute of Ophthalmology, we are one year into a project exploring this issue by utilising the large number of patients presenting to us, and by using a grant from the Macular Society to exploit the advantages of new DNA sequencing technology.

So far, we have recruited over 380 probands affected with recessive inherited macular dystrophy compatible with Stargardt’s disease. Conventional DNA analysis, using a procedure that tests for over 500 known variants in the gene, has been carried out so far on 278 of these. This generates the molecular diagnosis for many, confirming the precise diagnosis. One expects to find two mutations (one is inherited from the father and one from the
mother) but none were found in approximately a quarter of families. This cohort forms the basis of this project.

One pertinent question is whether the patients with no mutations are clinically different to those with one or two. In those entering the study, it has been possible to obtain detailed information about the structure of their retina. This is done with photography to examine the retinal pigment layer of the retina (autofluorescence imaging) and to look at the layers of cells in the neurosensory layer of the retina (optical coherence tomography). When comparing these images, it is apparent that the patients with no mutations include patients with a specific appearance and pattern of degeneration, seen less commonly in those with two mutations. This strongly suggests that one or more other rare genes may be involved in recessive macular dystrophy. This would in part explain the low detection rate when examining the ABCA4 gene specifically.

During the remainder of the study, we intend to perform exome sequencing on these specific patients. This analysis looks at the coding region of all genes in the human genome. Changes from the standard sequence are filtered and compared against databases from the general population. This leaves still many hundreds of DNA variants. An algorithm identifies variants that are seen in more than one individual of the cohort. These few are examined further for a likely role in the retina. It remains to be seen whether one or more novel genes will be found.

Secondly, a small number of those with a typical Stargardt’s appearance but no mutations will be examined using genome sequencing. In this approach, all nucleotides are sequenced, and the selected area of interest filtered not biochemically, but in silico. It may be possible to find important mutations that reside in areas of the gene not previously explored. Both approaches will give insights into the pathophysiology of macular dysfunction and contribute to greater sensitivity in the molecular diagnosis of such patients.
Vascular endothelial growth factor (VEGF) is a protein molecule which is important for blood vessel growth in the body. In macular degeneration, the inappropriate production of VEGF leads to abnormal vessel growth and leakiness of these new vessels. This is then manifest clinically as wet macular degeneration. Unfortunately, without treatment, this causes severe central sight loss. VEGF blocking drugs such as Lucentis and Avastin have been shown to improve the eyesight in approximately a third of patients with wet age-related macular degeneration (AMD). Unfortunately, some patients are resistant to treatment and sight can deteriorate despite treatment.

There is evidence that responsiveness to the VEGF blocking drugs may be due to variations in genes that patients have inherited. Indeed our group was the first to show such ‘pharmacogenetic’ correlations in AMD.

However the specific genes that cause this variation are currently unknown. To date, only a small number of backward looking (retrospective) studies have been done to test for association between genetic variations and macular degeneration.

There are problems with these sorts of studies in terms of their scientific validity. Therefore we have collected blood samples from patients undergoing
anti-VEGF treatment as part of the IVAN study to study how differences in their DNA could account for their response to this treatment. This is a large scale forward looking (prospective) clinical trial of Lucentis and Avastin in 600 patients in the United Kingdom. The one year results of the clinical trial were published in May this year and this has allowed us to proceed with the genetic analysis.

We have tested for replication of genes previously associated with responsiveness to anti-VEGF treatment and, in addition, we have tested an additional 500 genes implicated in the development of new blood vessel growth (angiogenesis).

Our results have implicated some novel genes as being associated with responsiveness to treatment. This work is currently being written up for publication. We hope our results will encourage other scientists to investigate these biological pathways. Eventually this may lead onto more effective treatments.

Andrew Lotery was awarded the Macular Society’s Special Judges’ Award for Services to People with Macular Conditions in 2012.

This is in recognition of his exceptionally good practice in the care of people with macular disease, and his work surrounding juvenile macular dystrophies. Professor Lotery and his team were described as “outstanding” and “caring” by those who nominated them.

“I’m very proud to be selected for this award,” said Professor Lotery. “I’m conscious that I wouldn’t have won it without the support of the great team of doctors, nurses and scientists whom I have the privilege to work with in Southampton.

“Developing better treatments for patients is my number one passion. Training and interacting with the next generation of clinician scientists and scientists is very rewarding.”
Refinement of TLR3 association with atrophic age-related macular degeneration

Professor Usha Chakravarthy, Dr Gareth McKay, Dr Giuliana Silvestri, Queens University Belfast and Professor Jayakrishna Ambati, University of Kentucky USA

Age-related macular degeneration (AMD) remains an important cause of sight loss despite the introduction of new treatments that can prevent worsening in patients with the wet form (wet AMD). A large proportion of the burden of sight loss is due to the atrophic type of AMD. Geographic atrophy (GA) is the term used to describe the loss of nerve cells of the retina, the supporting cells of the pigment epithelium and the blood vessels of the choroid. When these tissues atrophy,
areas of the macula become denuded and if the area involves the fovea, the central region, then sight loss can be severe.

Even when wet AMD is successfully treated, long term follow up has shown that many of these eyes will lose eyesight due to the onset of GA. Thus GA is considered to be the default pathway. There is therefore a compelling need for clinicians and scientists to explore the mechanisms that cause GA and to see what might be done in terms of development of new therapies that can slow down or prevent the onset of GA in AMD.

Genetic predisposition in AMD has evoked much interest in the past decade and genes that control the immune system were shown to influence susceptibility to wet AMD. More recently, the gene TLR3 (which stands for Toll Like Receptor) was shown by some researchers to influence susceptibility to GA, while other researchers found no such effect.

We too hypothesized that this gene could influence the development of GA because it is involved in immunity to bacterial infections. In particular, we felt that there were reasons why a certain region of this gene might have been altered by recombination (this is the mechanism by which genes are reshuffled and give us our unique characteristics) and therefore variable associations with disease might be present and constitute the reason why some researchers showed positive results while others showed negative results.

We developed a programme of study funded by the Macular Society to look very carefully at the entire TLR3 gene structure and its expression in tissues of the eye using eye-bank material from different donors.

Specifically, we wished to locate regions of the gene based on our expression studies which showed variability of gene expression and variability of the gene structure so that we could then test for association with persons with GA or wet AMD.

Our research showed that a particular combination of
Refinement of TLR3 association with atrophic AMD

TLR3 gene variants resulted in increased expression of the TLR3 gene in the retinal tissues. Based on this information and the detection of variability of gene structure in this region of the gene, we located a single nucleotide polymorphism (known as a SNP) that was present. We then tested for this SNP to detect the variation in the gene in samples from patients with wet AMD or GA. We found that a particular variant of this SNP was more frequently present in patients with GA.

We asked our colleagues in the USA to similarly examine their bank of samples of patients with GA and persons with any AMD. They reported that this SNP was more common in their GA patients and became statistically significantly different particularly in the female gender.

We believe that this work is of value as it gives for the first time a reason why AMD may be slightly more common in females and also identifies TLR3 as an important gene to study further to develop better therapeutics.
Sub-retinal transplantation of retinal pigment epithelial (RPE) cell grafts in the treatment of non-exudative age-related macular degeneration (AMD) has demonstrated some promising results. However, the surgical procedures for this are very delicate and require optimisation to ensure clinical success. The absence of signs of rejection in patients has provided us with proof of principle that replacing the diseased RPE with healthier RPE or RPE-like cells under the macula could restore some vision.

We have previously highlighted the importance of transplanting cells as a correctly oriented single layer, supported by a suitable non-degradable membrane that has the closest resemblance to the native Bruch’s membrane in its nature and properties. The Bruch’s membrane in AMD patients has usually undergone changes such as increased...
thickness, making it less efficient in allowing nutrient and waste exchanges between the RPE cells and the underlying choroid. The waste, accumulated in the form of fatty deposits, partly contributes to the separation between the retina and the Bruch’s membrane. We have managed to manufacture an artificial substrate to the same thickness and mechanical strength as healthy Bruch’s membrane. This will minimise anatomical damage to the macula following implantation. We have designed this substrate to be porous to allow metabolic exchange between the RPE and choroid.

We believe there is an advantage in using the patient’s own cells, however, in patients whose RPE cells have already been depleted and diseased, using their own RPE cells is not always the best option. Iris pigmented epithelial (IPE) cells have been shown to have several of the same functions as RPE and may be an alternative source of autologous cells. Furthermore, IPE cells are easier to obtain using a procedure routinely used in clinical practice.

Dr Eliesmaziah Alias, a postdoctoral researcher working on the laboratory aspects of the project, has successfully established the protocol for harvesting and culture of primary bovine and porcine RPE and IPE (Figure 1). She has optimised the behaviour of primary RPE and IPE cultured on our membranes with the objective of developing the right cell-substrate combination for transplantation. She has also demonstrated that the primary IPE cells can be grown as an intact differentiated cell monolayer with similar functionalities to the RPE in vitro.

We have set up our own clinical experimental laboratory, including a vitreector and new operating microscope. Mr Theodor Stappler, consultant vitreoretinal surgeon at St Paul’s Eye Unit and part of the project team, is assisting with the development of optimised surgical procedures.
to achieve transplantation of our cell-substrate implants. He is keen to point out the benefits of a transplantation treatment and commented: “Current medical treatments for AMD only mitigate the disease’s effects. It is only through a surgical approach that the root cause could be removed and replaced with healthier tissue.” We are also working closely with our colleagues with expertise in laser processing in the School of Engineering to produce a suitable surgical tool to enable the safe delivery of the cell-substrate construct into the subretinal space in the eye. A prototype has been manufactured and is in the process of evaluation in the clinical laboratory on enucleated eyes. This is a critical phase of our overall plan to translate this work to the clinic.
Advanced Cell Technology, Inc. (ACT) has treated 13 patients so far in its three ongoing trials for dry age-related macular degeneration (dry AMD) and Stargardt’s disease using human embryonic stem cell (hESC)-derived retinal pigment epithelial (RPE) cells. The first two trials were initiated in July 2011. The three clinical trials involve four of the top-ranked eye hospitals in the US, and two of the leading eye hospitals in the UK.

The RPE layer plays a central role in the health and function of the photoreceptor layer. In treating various forms of macular degeneration, such as dry AMD and Stargardt’s disease, the goal of ACT’s RPE cell therapy is for repair and replacement of those areas in the eye where the RPE layer has degraded with new cells, and in doing so, recapitulate the correct working environment around the photoreceptor layer.

Across the various clinical trial sites, with regular patient follow-up, no adverse safety issues relating to the transplanted cells have been observed. At up to 16 months following treatment, no hyperproliferation, tumorigenicity, ectopic tissue formation, or apparent rejection were observed in any of the 13 patients at any time. Detailed clinical and diagnostic laboratory assessments were performed at multiple post-transplantation evaluations. In addition to monitoring the safety of the transplanted cells, the clinicians have also been carefully assessing patients – on regular follow-up visits – for evidence of anatomical and functional integration of the RPE cells.
“Using high resolution imaging technology, we have been observing evidence indicating that the transplanted RPE cells are getting to the right place in the sub-retinal space, are engrafting and apparently resurfacing areas of the retina with a new RPE layer,” said Robert Lanza, MD, ACT’s chief scientific officer.

“With multiple follow-ups happening across multiple trial sites with these patients, we also continue to see an encouraging trend with respect to subjective and objective observations relating to visual acuity, colour perceptions and contrast in vision. In the case of the first dry AMD and Stargardt’s disease patients, the visual acuity gains we saw more than a year ago continue to persist.”
Scientists funded by the Medical Research Council have shown for the first time that transplanting light-sensitive photoreceptors into the eyes of visually impaired mice can restore their vision.

Scientists from UCL Institute of Ophthalmology injected cells from young healthy mice directly into the retinas of adult mice that lacked functional rod-photoreceptors. There are two types of photoreceptor in the eye – rods and cones. The cells transplanted were immature (or progenitor) rod-photoreceptor cells. Rod cells are especially important for seeing in the dark as they are extremely sensitive to even low levels of light.

After four to six weeks, the transplanted cells appeared to be functioning almost as well as normal rod-photoreceptor cells and had formed the connections needed to transmit visual information to the brain.

The researchers also tested the vision of the treated mice in a dimly lit maze. Mice with newly transplanted rod cells were able to use a visual cue to quickly find a hidden platform in the maze whereas untreated mice were able to find the hidden platform only by chance after extensive exploration of the maze.

Professor Robin Ali, who led the research, said: “We’ve shown for the first time that transplanted photoreceptor cells can integrate successfully with the existing retinal circuitry and truly improve vision. We’re hopeful that we will soon be able to replicate this success with photoreceptors derived from embryonic stem cells and to eventually develop human trials.”

The London Project to Cure Blindness: an update

Professor Pete Coffey, Lead researcher, The London Project to Cure Blindness, Institute of Ophthalmology, University College London

Professor Coffey recently gave a presentation at our annual conference in London (22 September 2012). Here is an edited extract of his talk, which describes the various processes The London Project to Cure Blindness team has gone through over the past five years.

“We The London Project had to work out and understand how to produce an eye cell from a stem cell. We’re not putting a stem cell into an eye, we’re putting the eye cell that dies through the disease into the eye. And, specifically for age-related macular degeneration (AMD), we’re putting the cell that dies in that disease that supports the seeing part of the eye, so it’s the layer of cells right at the back of the eye. And what we managed within the first year of the project was to do that. We turned the stem cell into the eye cell that is affected in AMD.

“We then had to go through at least four components to bring it into the clinic. One of them is a ‘pre-clinical’ package. You have a cell. You can turn into the eye cell that’s affected.

“Can you then show that it has any beneficial effect in any animal model which has a similarity to the disease the patient has? We showed that replacing it in an animal, in which that same cell is diseased, does actually maintain the vision in that animal.”
“We then had to manufacture the cells to a clinical grade standard, bringing in engineers and manufacturers.

“In May 2012 we started clinical manufacture for the trial due to start 2013. Clinical manufacturing will finish in February 2013 so post-February we will be ready to use it in the clinic. We then have to go into a discussion with the UK regulators, who determine whether we can use that in a patient.

“We had to design our own surgical tool for microsurgery and go through another regulatory route to get that tool approved. We now have approval in the form of a CE mark for it.

“So everything is nicely coming together. We said it would take five years and I think we did it.”

Need an excuse to bring cakes into work?
Fancy a get-together and a chat with friends?

Then why not hold a Tea for MD event and raise money for the Macular Society at the same time? Parties, barbeques, cream teas – Tea for MD events come in all shapes and sizes!

Last year, your amazing efforts across the UK raised more than £12,000 enabling us to support more people than ever – and we need your help to top that this year.

For more information or a party planning pack, visit www.macularsociety.org or contact Felicity on 01264 321 964 or felicity.h@macularsociety.org.
The Bionic Eye

Mr Lyndon da Cruz, Moorfields Eye Hospital

The bionic eye or artificial retina has been a mainstay of science fiction and action heroes and villains for some decades now. However, the fact is, as of April 2011 when the Argus II retinal prosthesis received the regulatory CE mark, the bionic eye has become a reality and is permitted for use independent of a research trial in patients with profound visual loss for the condition retinitis pigmentosa (RP). It has therefore joined the list of pacemakers, artificial hips, the cochlear implant and many other artificial devices that restore function and improve the quality of life of many people.

This milestone is particularly important for the visually impaired community, as it is at present the only available treatment that can restore, in part, the vision of people who are totally blind.

There are many different types of bionic eyes and also some other prosthetic visual systems that plug in to higher levels of the brain such as the optic nerve and visual cortex. Despite this, there is only one device that has regulatory permission for use in Europe – the Argus II retinal prosthesis system. Another device – also an artificial retina, from Retina Implant AG – has begun a multicentre trial but remains a research device. There are other devices from Germany, Australia, the United States, Japan and China that are also being developed but are not in clinical use as yet.

Artificial retinas work by stimulating the remaining retinal nerves with electrical currents. Usually in RP, the rods and cones that catch light and turn it into electric currents are missing due to the disease. Other nerves in
The retina are still there but receive no signals when light enters the eye. The artificial retina therefore has to capture the light from the object that is being viewed and turn it into a set of electrical signals that matches the shape of what is being viewed.

There are two ways that this has been achieved. Firstly, using a video camera to catch the signal and secondly, a photocell – a device that catches light and turns it into electricity on its surface. The electrical signal that is created stimulates the remaining retina and the visual signal is then transmitted up the optic nerve in the normal way.

Patients who have the bionic eye implanted have varying levels of vision restored. The best outcomes have shown patients who can read large letters and words on a screen while others are only able to navigate large objects or make out light and dark crisply. Many say that the best outcome is to be oriented so that they know where they are in a room and where the other people are in the room. Others give particular examples of their ability to see fireworks, their children running around (though not recognise their faces) or the movement on the television or a fireplace. Although these are relatively simple recoveries, they report that it importantly puts them back into a seeing world and allows them to return to simple but important visual functions.

Due to the way the artificial retina works, there is the need for some residual retina and a functioning optic nerve. These two requirements are critical and define the group of patients that can be treated.

At present, the quality of vision that is generated by the artificial retina is not sufficient to replace macular function in patients with age-related macular degeneration or other macular diseases. This is because the macular vision is very detailed and at present the artificial
retinas that are being developed cannot match this fine level of vision.

This is why the device is restricted to use in patients who are totally blind from RP. Although theoretically an artificial retina may be developed for macular function, the level of vision required is too sophisticated and detailed for the current level of devices.

Research is now ongoing in the UK into both types of bionic eye mentioned above. The Argus II studies will investigate how to better understand the differing levels of vision recovered and to see if even better outcomes can be achieved by earlier implantation.

The Retina Implant AG device will continue in its clinical trial to determine safety, reliability and function. In terms of availability, the Argus II prosthesis is currently being assessed by NICE for potential funding through the NHS. The device is currently being implanted in Italy and Germany through the state health systems and has recently been recommended by the US Food and Drug Administration (FDA) specialist panel to be made available across the USA for RP patients with profound vision loss. The trial of the Argus II implant that led to the regulatory permission in Europe and soon in the USA was in large part carried out in the NHS at Moorfields Eye Hospital and the Manchester Eye Hospital.

It is particularly rewarding that NHS research has contributed to a historical moment for the treatment of blindness and that the bionic eye, long of science fiction, is now a reality.
I now believe (having entered my more mature years) that science is a funny business; you go into research thinking you have the answer to everything and leave it wondering if you have found out anything at all worthwhile. Do remember that although spectacular breakthroughs are heralded with massive publicity in fact such events are rare, so giving the public a false impression of the usual road to scientific “truths”.

Most scientific endeavours are painstakingly slow and erratic, like the progress of ill-equipped travellers through a storm. In my world exciting basic research findings often show promise for a future therapeutic hope but somewhere along the essential route to and then through patient-based clinical trials the vast majority of treatments and concepts founder, remain unclear or produce conflicting results. The research and investigation process (that medical scientists call “translation”) can take so long that questions so important at the outset of clinical investigation become historical and irrelevant at the conclusion. Such problems have been experienced in many research fields including those of nutrition and supplementation.

We have known for many years that poor diet is one of many risk factors for age-related macular degeneration (AMD) because our food (particularly fruit and vegetables) provide antioxidants that help protect the body from harm. Impressive basic research shows that crucial protection is afforded to the retina and macula by a wide range of antioxidants, some of which are depleted in people with AMD or...
at risk of AMD. As a result it seems logical that eating foods rich in antioxidants or taking antioxidant-rich supplements has to be a good thing. It may be logical but initial clinical studies produced horribly conflicting results.

Food intake and nutritional experiments are notoriously difficult to control and in addition many of the early supplement studies were too small and only looked at the effects of one antioxidant.

The Age-Related Eye Disease Study (AREDS) trial

This was a huge investigation conducted in the 1990s and sponsored by the American government following 3,600 people for many years on a cocktail of antioxidant vitamins and zinc.

The large trial released its findings from 2001 onwards and importantly showed that the cocktail of antioxidants which is now called the AREDS formula could “play a key role in helping people at high risk for developing advanced AMD keep their remaining sight”.

As a result for years the public and AMD patients in particular have been bombarded with literature and adverts extolling the virtues of supplements for the “treatment, cure and prevention” of AMD.

Most of this publicity is driven by marketing and not by the careful analysis of further research findings. In addition although the AREDS formula is available as an “over the counter” supplement, many of the supplements being sold contain different constituents from AREDS and as a result they are not the same thing.

Is it any good?

However, what of the AREDS formula, is it any good? Well for a start it is “not a cure for AMD” and that is pointed out by all responsible authorities including the original investigators. For careful evaluation of clinical trial data academics rely heavily
on the findings of a worldwide independent network that involves over 100 countries called the Cochrane Collaboration that provides high quality assessment and information on what is safe to conclude from trials.

Jennifer Evans for the Cochrane Collaboration reported in 2009 from her evaluation of the AREDS trial and eight other large trials that “more well-conducted trials were needed” but “supplementation with antioxidants and zinc may be of modest benefit in people with AMD”.

If you do not have AMD what is the benefit of AREDS?

Evans and Lawrenson reported in 2012 for Cochrane that analysis of relevant trials show that taking antioxidants plus zinc “is unlikely to prevent the onset of AMD”.

It would seem that there is a modest benefit for people with AMD of taking supplements as a treatment but prevention is less likely for those without the disease and supplements of any kind are not a cure.

Potential side effects

The AREDS formula has very high concentrations of antioxidants so there is potential for side effects and it should not be used without care. As the preparation contains beta carotene smokers should not use it because of heightened risk of cancer, vitamin E has vascular effects and excess zinc can produce fatigue and other problems.

After all the hype is this the end for supplements?

In my opinion it is certainly not the end.

There is a role for the AREDS formula but in the right people with appropriate informed advice.

In some ways it is surprising and encouraging that the AREDS antioxidants work at all given that most doctors and scientists believe that the most important
macular antioxidants were not included in the original formula.

Two important omissions were the macular yellow pigment called lutein and also omega-3 fatty acids but they are now important components of new formulations prepared for an ongoing American trial called AREDS2, which will start to report findings later this year.

I do not think the debate is about whether we need to boost our antioxidants, it is which ones are needed most and how do we deliver them to the macula where the key antioxidants can do the most good?

Our trials and the evaluation of those trials show we still have a long way to go.

The ups and downs of the supplement debate should not detract us from the need for a good healthy diet rich in fruit and vegetables to provide the essential antioxidants we need to combat macular damage and the onset of AMD.

If we have spent a lifetime with not enough antioxidants reaching our retina then supplements may be necessary.
Scientists find link between herpes and AMD

News release, George State University

A team of researchers has found that a type of herpesvirus infection of the eye is associated with neovascular age-related macular degeneration (nvAMD).

The scientists found that human cytomegalovirus, a type of herpesvirus, causes the production of vascular endothelial growth factor, or VEGF, a signal protein that regulates the formation of new blood vessels. With the formation of new blood vessels, retinal tissue destruction occurs, leading to the development of wet AMD and eventually, vision loss.

Richard D. Dix, professor at the Georgia State Viral Immunology Center’s Ocular Virology and Immunology Laboratory, said: “Prior to this work, co-factors for the development of AMD included genetics, a high fat diet and smoking. Now, we are adding an infections agent as another co-factor.”

Human cytomegalovirus is a common herpesvirus. About 80% of the population is estimated to have antibodies for the virus, and it is often acquired during childhood.

“If a person has a normal, healthy immune system, the virus becomes latent in the cells of bone marrow and blood,” Dix said. “But in the elderly, the immune system’s function is reduced, the virus proliferates, and the production of VEGF increases.

Identifying human cytomegalovirus as a co-factor in the development of AMD opens up new paths for the treatment of AMD. One route
could include reducing the viral load – the amount of the human cytomegalovirus in the blood stream – by treatment with an antiviral drug known as ganciclovir.”

Additional research paths include looking at the genetics involved in the upregulation of VEGF by human cytomegalovirus. “If we can knock down a certain gene or genes of the virus that stimulates VEGF production, we might be able to decrease its production and minimise AMD,” Dix said.

The research was supported by National Institute of Health grants and Fight for Sight.


Affiliated research institutions include:

Duke University Eye Center,

Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine,

Viral Immunology Center at Georgia State,

Department of Ophthalmology at the Emory University School of Medicine.
Wet or neovascular age-related macular degeneration (wet AMD) is a condition which causes severe loss of sight in older people. In 2006, a new treatment with a drug called Lucentis (Ranibizumab) was found to prevent sight loss in over 90% of recipients when given as injections into the affected eye for periods of up to two years. Lucentis is extremely expensive (about £750 per injection for the drug alone)*, with patients requiring re-treatment almost every month.

Another drug called Avastin (Bevacizumab), which is licensed for colorectal cancer therapy, is similar to Lucentis in its properties and has also been used to treat patients with wet AMD. This drug is much less expensive (about £50-£100 per dispensed dose) because the large amount needed to treat cancer (at a similar cost to the cost of a single dose of Lucentis) can be divided up into many small doses for injection into the eye. The hospital staff costs of reviewing and treating patients is the same for both drugs.

In the UK, the randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN) study is comparing the success of treatment with either Lucentis or Avastin for wet AMD. The study is also testing the frequency of re-treatment by comparing injections given as needed with monthly injections over a two year period. The success of treatment is being assessed by measuring eyesight using a letter chart, other tests of near reading ability, safety and the quality of life of the participants.

* The price has recently come down slightly by varying amounts.
To be eligible for the study, a participant had to have wet AMD newly diagnosed in an eye and be over 50 years old.

The IVAN study enrolled and treated 610 participants, with an average age of 78 years, between March 2007 and October 2010. By the end of the first year of follow-up, 24 had died and 60 had withdrawn. The effect of treatment on participants’ eyesight was very similar, irrespective of the drugs or treatment regimen. The thickness of the retina, which increases with disease activity, did not differ by drug but was slightly less with monthly treatment.

The IVAN study collected information on angina, heart attacks, strokes and other illnesses caused by a blockage of blood vessels because we suspected that these illnesses might be associated with the drugs. These events (collectively known as arteriothrombotic events) occurred slightly more frequently in those who received Lucentis compared to those who received Avastin. Other serious systemic adverse events were slightly more frequent in persons who received Avastin compared to Lucentis. A similar American study (the CATT study) found that both arteriothrombotic events and other serious adverse events were more common with Avastin compared to Lucentis. Combining the information from the two studies showed that there was no difference between the drugs with respect to arteriothrombotic events. However for other serious systemic adverse events, because both trials found that these were slightly more frequent among participants who received Avastin, the combined analysis showed the increased risk more clearly.

In summary, after one year of follow-up, the IVAN study showed that Lucentis and Avastin are equally effective in the treatment of wet AMD, but there is concern that Avastin may increase the risk of a serious systemic adverse event. The outcome data after two years of follow up in the IVAN trial will become available early this year. This information will allow a more detailed analysis of the effectiveness of the two treatments and their safety profiles.
A team of University of California, Berkeley, scientists in collaboration with researchers at the University of Munich and University of Washington, in Seattle, has discovered a chemical that temporarily restores some vision to blind mice, and is working on an improved compound that may some day allow people with degenerative blindness to see again.

The approach could eventually help those with retinitis pigmentosa as well as age-related macular degeneration. In both diseases, the light sensitive cells in the retina – the rods and cones – die, leaving the eye without functional photoreceptors.

The chemical, called AAQ, acts by making the remaining, normally ‘blind’ cells in the retina sensitive to light. AAQ is a photoswitch that binds to protein ion channels on the surface of retinal cells. When switched on by light, AAQ alters the flow of ions through the channels and activates these neurons much the way rods and cones are activated by light.

“This is similar to the way local anaesthetics work: they embed themselves in ion channels and stick around for a long time, so that you stay numb for a long time,” said lead researcher Richard Kramer, UC Berkeley professor of molecular and cell biology. “Our molecule is different in that it’s light sensitive, so you can turn it on and off and turn on or off neural activity.”

Because the chemical eventually wears off, it may offer a safer alternative to other experimental
approaches for restoring sight, such as gene or stem cell therapies, which permanently change the retina. It is also less invasive than implanting light-sensitive electronic chips in the eye.

“The advantage of this approach is that it is a simple chemical, which means that you can change the dosage, you can use it in combination with other therapies, or you can discontinue the therapy if you don’t like the results. As improved chemicals become available, you could offer them to patients. You can’t do that when you surgically implant a chip or after you genetically modify somebody,” Kramer said.


Microneedles to target therapeutics to the back of the eye

News release

Researchers from the Georgia Institute of Technology and Emory University have demonstrated that microneedles less than a millimetre in length can deliver drug molecules and particles to the eye in an animal model. The injection targeted the suprachoroidal space of the eye, which provides a natural passageway for drugs injected across the white part (sclera) of the eye to flow along the eye’s inner surface and subsequently into the back of the eye.

The minimally-invasive technique could represent a significant improvement over conventional methods that inject drugs into the centre of the eye – or use eyedrops, which have limited effectiveness in treating many diseases.
Microneedles to target therapeutics to back of eye

Samirkumar Patel, the paper’s first author and a postdoctoral researcher at Georgia Tech, is also director of research for Clearside Biomedical – a startup company formed to commercialise the technology. He said the study also showed that the suprachoroidal space could accommodate a variety of drugs and microparticles. That could open the door for the use of timed-release drugs that could reduce the need for frequent injections to treat chronic eye diseases.

The suprachoroidal space is located between two important structures in the eye: the sclera and the choroid. Fluids injected into that space travel circumferentially around the eye, which flows drug solution directly over the choroid and adjacent retina – which are the targets for many drug compounds. The new study showed that injections of fluids containing molecules and particles into that space not only reach the targeted structures, but also remain there for extended time periods. And equally important, the molecules and particles do not significantly reach the lens or front part of the eye, where side effects from drugs can occur.

“The study showed that if we inject non-degradable particles into the suprachoroidal space and wait as long as two months, the particles remain,” said Mark Prausnitz, a Regents professor in Georgia Tech’s School of Chemical and Biomolecular Engineering. “That means there is no natural mechanism to remove the particles from the eye. Knowing this, we can design biodegradable particles with drugs encapsulated in them that can slowly release those drugs over a period of time that we could control.”

The full study was reported in the July issue of the journal Investigative Ophthalmology & Visual Science. The research was supported by the National Eye Institute, which is part of the National Institute of Health, and by the organisation Research to Prevent Blindness.
Acucela ACU-4429 update

An update from Acucela regarding the development of a therapy to treat dry age-related macular degeneration (AMD).

Acucela is leveraging promising science and its proprietary visual cycle modulation (VCM) technology to develop novel therapies for treating blinding eye diseases.

Acucela’s VCM technology works by reducing the activity of the eye’s rod visual system and relieving or ‘lightening’ the metabolic load on the retina. Modulating the visual cycle has been shown to protect the retina from light damage, improve retinal vasculature and reduce the accumulation of retinal-related toxic by-products, including A2E, which is implicated in dry AMD.

There is currently no approved treatment for the dry form of AMD. Acucela’s lead VCM programme, ACU-4429, is a non-retinoid oral therapy currently being evaluated in a Phase IIa trial in patients with dry AMD. In May 2012, Acucela presented the first patient data from the ACU-4429 programme during The Association for Research in Vision and Ophthalmology (ARVO) 2012 Annual Meeting.

In this 90-day, dose-escalation safety study, 56 subjects with geographic atrophy (advanced dry AMD) received either ACU-4429 or placebo once per day. Approximately four hours after subjects were given either ACU-4429 or placebo, and following pupil dilation and dark adaptation, electroretinogram (ERG) measurements were recorded at multiple time points after three minutes of exposure to a bright, bleaching light.
Overall, these interim data demonstrated that patients receiving ACU-4429 had a dose-dependent response and that rod visual system activity was modulated as measured by ERG for doses up to 10mg.

In March 2010, ACU-4429 was granted Fast Track status by the US Food and Drug Administration (FDA) for the treatment of dry AMD, and positive Phase I was published in RETINA: the Journal of Retinal and Vitreous Disease.

The Phase IIa trial is continuing, and the company will make an announcement about the progress of the trial early this year.

For more information about ACU-4429 and VCM, visit www.acucela.com

Clinical trial of self-administered eye drops for wet AMD

News release

Ohr Pharmaceutical has announced the initiation of a Phase II clinical trial to evaluate the efficacy and safety of Squalamine Eye Drops for the treatment of the wet form of age-related macular degeneration (wet AMD).
The randomised, double blind, placebo controlled study will enrol patients at 21 ophthalmology treatment centres across the US. Interim results are expected in the fourth quarter of 2013.

“An eye drop to treat wet AMD and ophthalmic neovascular disorders would be transformational for the large patient populations currently taking chronic treatments of Lucentis or Eylea, both of which are injected directly into the eye,” stated Dr Irach B. Taraporewala, CEO of Ohr.

“I am very excited to be participating in the clinical study of this potentially groundbreaking product,” commented Dr Lawrence Singerman, of Retina Associates of Cleveland, and a member of Ohr’s Scientific Advisory Board. “The addition of a self-administered eye drop to treat wet AMD as an alternative or adjunctive therapy to our current treatment modalities would be a tremendous step forward for patients who suffer from this debilitating condition.”

Study OHR-002 is a randomised, double blind, placebo controlled Phase II study to evaluate the efficacy and safety of Squalamine Eye Drops for the treatment of wet AMD.

The study will enrol 120 treatment naive wet AMD patients at 21 clinical sites in the US, who will be treated with Squalamine Eye Drops twice daily for a nine-month period. The primary and secondary endpoints include visual acuity parameters, need for rescue intravitreal injections, and safety. The protocol includes an interim analysis upon the completion of the treatment period in 50% of the patients (approximately 60).

More information on the clinical trial can be found at http://clinicaltrials.gov/
CATT results show Avastin and Lucentis are equivalent in treating AMD

News release

At two years, Avastin (bevacizumab) and Lucentis (ranibizumab injection), two widely-used drugs to treat age-related macular degeneration (AMD), improve vision when administered monthly or on an as needed basis, although greater improvements in vision were seen with monthly. Of the two drugs, Avastin is most frequently used to treat AMD. However, prior to the Comparison of AMD Treatments Trials (CATT), a two-year clinical trial, the two drugs had never been compared head-to-head.

Avastin and Lucentis block growth of abnormal blood vessels and leakage of fluid from the vessels. Lucentis was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of AMD. Avastin is very similar to Lucentis but is not approved by the FDA for this purpose. Avastin is approved for other indications.

Most clinicians use these drugs on an as needed basis when there is evidence of active disease, such as fluid leakage. However, in the original clinical trials for AMD, Lucentis was administered monthly. It was unknown if as needed dosing would produce the same long-term visual improvements achieved with monthly administration.
Thus, CATT was designed to compare Avastin and Lucentis with monthly and as needed treatment schedules. At enrolment, patients were assigned to four treatment groups defined by drug (Avastin or Lucentis) and dosing regimen (monthly or as needed). After year one, patients initially assigned to monthly treatment were randomly reassigned to monthly or as needed treatment without changing their drug assignment.

At two years, visual acuity with monthly treatment was slightly better than with as needed dosing, regardless of the drug. As measured on an eye chart, monthly treatment resulted in a mean improvement of about half a line better than as needed dosing. Switching to as needed treatment after one year of monthly treatment yielded outcomes nearly equal to those obtained with as needed treatment for the full two years. Changes in retinal anatomy differed by drug and frequency of treatment, but did not have an impact on vision through two years.

“Both drugs were highly effective regardless of the approach to dosing. There was slightly less vision gain with as needed treatment. Patients seeking the small extra advantage of monthly treatment need to be mindful of the additional burden, risks, and costs of monthly injections. Since as needed dosing required 10 fewer eye injections over the course of two years and yielded similar visual results, many patients may choose this option,” said Daniel F. Martin, MD, study chair for CATT and chairman of the Cole Eye Institute at the Cleveland Clinic.

Adverse events indicate development or worsening of a medical condition. They may or may not be causally associated with the clinical trial treatment, but they are always monitored and reported in any clinical trial. The median age of patients in CATT was over 80 years, and a high rate of hospitalisations would be anticipated as a result of chronic or acute medical conditions more common to older populations.
Serious adverse events (SAEs) occurred at a 40% rate for patients receiving Avastin and a 32% rate for patients receiving Lucentis. Although Avastin had a higher rate of SAEs, they were distributed across many different conditions, most of which were not associated with Avastin when evaluated in cancer clinical trials, in which the drug was administered at 500 times the dose used for AMD. Fewer doses were associated with a higher rate of SAEs, which is not a typical dose-response relationship. The number of deaths, heart attacks, and strokes were low and similar for both drugs during the study. CATT was not capable of determining whether there is an association between a particular adverse event and treatment.

Additional data from other clinical trials may provide information on long-term safety profiles of these drugs when used to treat AMD.

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**TANDEM trial update**

**Alex Foss**, FRCOphth MRCP, Queen’s Medical Centre, Department of Ophthalmology, Nottingham

It has been one year since my previous article on the TANDEM trial and it has been a busy year for those who have been involved in the Avastin-Lucentis debate. In that time, the second year results from the CATT trial in the USA and the first year results from the UK’s IVAN trial have reported that Avastin and Lucentis are equally effective in terms of vision, which is a major relief. The TANDEM trial involves comparing different doses and dose regimens for Avastin and was premised on the assumption that Avastin and Lucentis were equally effective. The circumstantial evidence seemed compelling, but it was greatly reassuring to see this confirmed by large and properly conducted trials.

The other event that rocked observers of this debate was the
decision by Novartis to request a judicial review of the policies of SHIP (Southampton, Isle of Wight, Portsmouth and Hampshire Trusts) for allowing Avastin to being used. And over this time, the roll out of these drugs to other conditions such as diabetic maculopathy remains held up due to issues of affordability.

However, the TANDEM trial is not affected by such issues, having the necessary approvals from all the appropriate regulatory bodies.

The trial is now open and has recruited patients at four sites – Nottingham, Leicester, Lincoln and Mansfield – with 165 patients recruited so far and is progressing smoothly. The trial has secured funding to run for four years and we are actively looking to recruit other sites with the aim of recruiting a total of 2,000 patients.

The aims and objectives of the trial remain unchanged despite the changing landscape. The two major barriers to healthcare delivery still remain the cost and the frequency and the demonstration that two-monthly Avastin is effective would overcome both. Safety is always a dominant concern and calculations suggest that half dose Avastin, given two-monthly, would still be fully effective and should carry a superior safety profile. Doing all this in the context of a formal trial should improve the standard of care given as discussed in my previous article.

The TANDEM trial remains an experiment in developing a model for health care delivery with the aim of improving the standard of care while also providing the information required for intelligent future planning. The fact that these benefits may all be achieved along with a net saving to the overall NHS budget all act to make this particularly exciting.
ThromboGenics, an integrated biopharmaceutical company focused on developing and commercialising innovative ophthalmic medicines, has announced that JETREA® (ocriplasmin) has been selected to receive a Single Technology Appraisal (STA) from the UK’s National Institute for Health and Clinical Excellence (NICE).

The outcome of the STA, in the form of NICE guidance, is expected later in 2013, following the launch of JETREA® in the UK.

The JETREA® European Marketing Authorisation Application is currently under review by the European Medicines Agency. A decision on European approval is expected this year. JETREA® was recently approved by the US Food and Drugs Administration for the treatment of symptomatic Vitreomacular Adhesion (VMA).

In March 2012, ThromboGenics signed a strategic partnership with Alcon (Novartis) for the commercialisation of ocriplasmin outside the US.

Dr Patrik De Haes, CEO at ThromboGenics, said: “We are delighted that the UK Department of Health has asked NICE to appraise JETREA® for the treatment of vitreomacular traction. We strongly believe that JETREA® has the potential to dramatically change the treatment paradigm in the UK for this progressive sight threatening condition.”
New treatment for wet AMD

Eylea® (aflibercept solution for injection, known in the scientific literature as VEGF Trap-Eye) has been licensed for the treatment of wet AMD and was launched in the UK in December 2012 by Bayer Healthcare. This new medicine means that now there is an alternative treatment available which works as well as current treatment but requires fewer hospital visits, reducing the burden for patients, relatives and the NHS.

It is designed to interfere with two chemicals, vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF), that cause the growth of abnormal and fragile blood vessels beneath the macula. By interfering with these chemicals Eylea® prevents more abnormal blood vessels from growing and causing further damage to sight.

Two clinical studies of Eylea®, VIEW 1 and VIEW 2, have been published. In these studies, Eylea® dosed every eight weeks, following three initial monthly injections, was shown to be clinically equivalent to Lucentis (ranibizumab injection) dosed every four weeks, as measured by the primary endpoint of maintenance of best-corrected visual acuity (less than 15 letters of vision loss on an eye chart as measured on an ETDRS scale) over 52 weeks. Eylea® is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in Eylea®. The most common adverse reactions (frequency of 5% or more) reported in wet AMD patients receiving Eylea® were conjunctival haemorrhage, eye pain, cataract, vitreous floaters, vitreous detachment, and increased intraocular pressure.

Stereotactic radiotherapy for the treatment of neovascular AMD

Mr Tim Jackson PhD FRCOphth HEFCE, Senior Clinical Lecturer, Honorary Consultant Ophthalmic Surgeon, King’s College London

Stereotactic radiotherapy (Oraya Therapy™) is a new X-ray based treatment for neovascular age-related macular degeneration (nvAMD). It was developed to maintain or improve vision while reducing the number of anti-VEGF injections required.

Radiotherapy is an established treatment for diseases characterised by rapidly proliferating cell change. Its anti-angiogenic, anti-inflammatory, and anti-fibrotic effects mean that radiation has the potential to halt nvAMD progression.

A non-invasive procedure, intended as a one-time, outpatient treatment, stereotactic radiotherapy uses highly targeted, low-voltage X-rays to inhibit and prevent the growth of abnormal blood vessels under the macula (choroidal neovascularisation) which characterises nvAMD. The beams are directed through the inferior portion of the eye while the patient sits in a chair, with the head positioned on a chin rest. The procedure takes about 20 minutes.

One-year results from a sham-controlled, double-masked study involving 230 patients show that a one-time treatment with stereotactic radiation significantly reduces the number of anti-VEGF injections, using either a 16 or 24 Gray dose.¹

Patients who received stereotactic radiation required approximately 35% fewer...
injections than the sham group, while maintaining, or in some cases improving, visual acuity. No radiation-related adverse events were reported (including analysis of 25% of the study group who reached two-year follow-up), but delayed radiation retinopathy can occur so safety follow up is continuing.

A responder analysis showed the greatest benefit (55% reduction in injections and significantly better acuity than sham) was achieved in patients with actively leaking lesions fully within the central 4mm treatment zone.

Anti-VEGF drug treatment (ranibizumab) revolutionised the management of nvAMD, quickly becoming the standard of care. However, for many patients the effects are transient, often requiring on-going injections to maintain vision. Moreover, with the currently recommended ‘as needed’ approach for
anti-VEGF treatment, patients tend to lose vision after the initial gains.\textsuperscript{2,3,4}

Although monthly injections have been shown to maintain vision,\textsuperscript{2} such an approach is neither economically or practically viable. Alternative treatment options that reduce the burden of injections but maintain vision are keenly sought by doctors and patients alike.

Stereotactic radiotherapy is currently available privately through Optegra eye hospitals (www.Optegra.com), but the hope is that it will be available through the NHS in the future.


Scientists at the Washington University School of Medicine, USA, are altering the eye cells of mice with retinitis pigmentosa in an effort to restore their vision. If successful, it is hoped that this treatment may also help people with macular degeneration.

Joseph Corbo, MD, PhD, senior author of the study and assistant professor of pathology and immunology, said: “We think it may be significantly easier to preserve vision by modifying existing cells in the eye than it would be to introduce new stem cells. A diseased retina is not a hospitable environment for transplanting stem cells.”

The retina has two types of light-sensing cells or photoreceptors. The rods provide night vision, and the cones sense light in the daytime and detect fine visual details. In retinitis pigmentosa, the rods die first, leaving patients unable to see at night. Daytime vision often remains intact for some time until the cones also die.

Corbo and others have identified several genes that are active in rods or in cones but not in both types of photoreceptors. He wondered whether turning off a key gene that is activated only in rods could protect the cells from the loss of vision characteristic of retinitis pigmentosa.

The new study focuses on a protein known as Nrl, which influences development of photoreceptors.
Cells that make Nrl become rods, while cells that lack the protein become cones. Turning off the Nrl gene in developing mice leads to a retina packed with cone cells.

To see if this rod-to-cone change was possible in adult mice, Corbo created a mouse model of retinitis pigmentosa with an Nrl gene that could be switched on and off by scientists.

He said: “In adult mice, switching off Nrl partially converts the rod cells into cone cells. Several months later, when the mutant mice normally had very little vision left, we tested the function of their retina.”

The test showed a healthier level of electrical activity in the retinas of mice that lacked Nrl, suggesting that the mice could still see. Corbo is now looking for other critical development factors that can help scientists more fully transform adult rods into cones. He notes that if complete conversion of rods to cones were possible, this therapy could also be helpful for conditions where cone cells die first, such as macular degeneration.

The paper was published online: Reprogramming of adult rod photoreceptors prevents retinal degeneration, Montana CL, Kolesnikov AV, Shen SQ, Myers CA, Kefalov VJ, Corbo JC, Proceedings of the National Academy of Sciences, online January 14, 2013.
Scientists at Trinity College Dublin have discovered that a part of the immune system called the inflammasome is involved in regulating the development of age-related macular degeneration (AMD). They have discovered that controlling an inflammatory component IL-18 in cases of AMD could prevent the development of the disease.

The key diagnostic feature of AMD is the presence of ‘drusen’, which are recognised during an eye exam as yellowish/white deposits in the central region of the retina called the macula.

Dry AMD is characterised by the presence of excessive amounts of drusen and there are currently no forms of therapy other than recommended lifestyle changes such as giving up smoking, which is a recognised risk factor.

However, a significant number of cases of the ‘dry’ form of AMD can progress to the ‘wet’ form, where blood vessels underneath the retina begin to grow, leading to central blindness.

The leading co-authors of the Nature Medicine paper, Trinity College scientists Dr Sarah Doyle and Dr Matthew Campbell, have together discovered that drusen accumulating in the macula can lead to the production of two inflammatory components termed IL-1beta and IL-18. These findings were based on studies involving drusen isolated from donor AMD eyes in tandem with pre-clinical studies on models of the disease.

“Traditionally, inflammation in the retina or indeed the eye in general is not beneficial and is a pathological hallmark of many eye diseases, including AMD."
However, we have identified that one inflammatory component termed IL-18 acts as a so-called anti-angiogenic factor, preventing the progression of wet AMD,” said Dr Campbell.

“The progression from ‘dry’ to ‘wet’ AMD appears to be mediated by the inflammatory component IL-18. Our results directly suggest that controlling or indeed augmenting the levels of IL-18 in the retinas of patients with dry AMD could prevent the development of the wet form of disease, which leads us to an exciting new prospect for a novel therapy for AMD,” said Dr Doyle.

The research paper, ‘NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components’, is published in Nature Medicine, and is supported by Science Foundation Ireland, the American Health Assistance Foundation (AHAF), the Health Research Board (HRB) and Fighting Blindness Ireland.
causes retinal cells to die in patients with geographic atrophy. In a healthy eye, a ‘Dicer’ enzyme degrades the Alu RNA particles.

“We discovered that in patients with geographic atrophy, there is a dramatic reduction of the Dicer enzyme in the retina,” said Dr Ambati, professor and vice chair of the Department of Ophthalmology and Visual Sciences and the Dr. E. Vernon and Eloise C. Smith Endowed Chair in Macular Degeneration Research at the UK College of Medicine. “When the levels of Dicer decline, the control system is short-circuited and too much Alu RNA accumulates. This leads to death of the retina.”

Alu elements make up a surprisingly large portion – about 11% by weight – of the human genome, comprising more than one million sequences. However, their function has been unknown, so they have been called ‘junk’ DNA or part of the ‘dark’ genome.

The discovery of Alu’s toxicity and its control by Dicer should prove of great interest to other researchers in the biological sciences, Dr Ambati said.

Dr Ambati’s team developed two potential therapies aimed at preventing geographic atrophy and demonstrated the efficacy of both approaches using laboratory models.

The first involves increasing Dicer levels in the retina by ‘over-expressing’ the enzyme. The second involves blocking Alu RNA using an ‘anti-sense’ drug that binds and degrades this toxic substance. UK has filed patent applications for both technologies, and Ambati’s group is preparing to start clinical trials by the end of this year.

The article was published online in the journal *Nature: DICER1 Deficit Induces Alu RNA Toxicity in Age-Related Macular Degeneration, Nature* – 6 February 2012 (DOI: 10.1038/nature09830).
An estimated 2 million people in the UK repeatedly see things that are not there – experiences referred to as visual hallucinations. The hallucinations range from simple patterns and colours to grotesque disembodied faces, bizarre figures in elaborate costume, nonsense text and letter strings and extended landscape scenes. Given the number of people affected, surprisingly little is known about the symptom or how to treat it; but this is about to change. The Macular Society is part of a collaborative group awarded £1.9 million by the National Institute for Health Research (NIHR) to fill gaps in our understanding.

The association of eye disease, in particular macular disease, and visual hallucinations is referred to as the Charles Bonnet Syndrome (CBS). It is one of the most important causes of visual hallucinations, alongside Parkinson’s disease and Alzheimer’s disease.

At present, treatment advice for visual hallucinations is different, and often contradictory, in each of these conditions, in part because different medical specialties treat each condition. Ophthalmologists look after people with CBS, neurologists look after people with visual hallucinations in Parkinson’s disease and Old Age Psychiatrists look after people with visual hallucinations in Alzheimer’s disease. Each specialty has its own perspective but none has an overview of the problem as a whole.
The NIHR research programme will bring together experts from each clinical specialty. Research teams based in Universities and NHS trusts in Newcastle, Cambridge, Liverpool and London, together with the Macular Society, Parkinson’s UK, Alzheimer’s Society and Thomas Pocklington Trust will be working together to answer a number of different but related questions.

One area of research will establish how many people with eye disease, dementia, Parkinson’s disease or combinations of these conditions have visual hallucinations. People with visual hallucinations in each clinical group will be followed over time to find out what happens to their hallucinations, how the hallucinations impact on their quality of life and the economic impact of the symptom.

Another area of research will explore treatment options and address a key unanswered question of whether a single type of treatment will work for visual hallucinations in eye disease, dementia and Parkinson’s disease or whether different types of treatment are required for each. One of the treatments to be studied will be the eye movement strategy developed as part of a Macular Society grant to the Institute of Psychiatry.

The Macular Society will play a key role in all aspects of the research. It will sit on the steering committee to ensure the research questions being asked are relevant to people with macular problems and that the way the research is being conducted and presented is suitable for people with visual problems. It is also hoped that members with past or present experience of visual hallucinations will help advise the programme from personal experience and participate in the studies themselves.

By championing awareness of Charles Bonnet Syndrome, the Macular Society has helped place the problem centre stage in a research agenda of national and international importance.
Living with macular degeneration

Burden of AMD treated with anti-VEGF therapy on patients and caregivers

Miss Sobha Sivaprasad, Consultant Ophthalmologist Moorfields Eye Hospital and King’s College Hospital, London

Since 2007, the prognosis of wet age-related macular degeneration has changed dramatically due to the introduction of anti-vascular endothelial growth factor treatment (anti-VEGF). These drugs are given as regular injections into the eye and tend to stabilise or improve vision in most cases. However, these patients need to be monitored at monthly intervals and treated if necessary. These hospital appointments usually span from 1 – 3 hours. Most patients are accompanied by relatives or friends when they come for their appointments.

It is therefore important to understand the potential burden of these treatments and impact of the treatment and visual outcome on the quality of life of both the patients and their caregivers. Studies published on this issue are usually related to the economic impact on healthcare resources. The magnitude of patient and caregiver-related burden is unknown.

In this study, we intend to explore the disease and treatment-related burden of both the patient and the caregiver by studying 200 patients and their caregivers from three NHS trusts.

Patients will be stratified by age and duration of follow-up. The data collected from the patient will include demographic
variables, co-morbidity data, daily living scores, vision-related quality of life, treatment satisfaction and the details on visual outcome. The data from caregivers will include demographic data, general health, satisfaction of health service and the caregiver burden. Validated questionnaires will be used, if available.

Data will also be collected from case notes and databases on the visual acuity at recruitment, change in vision since the start of anti-VEGF therapy, duration and number of treatments and number of clinic visits to date.

The anticipated outcomes will be an estimate of the caregiver burden, the burden of the disease and treatment on the patients, the correlation of the caregiver burden with the patient’s vision, vision-related quality of life and visual outcome and burden. The factors that determine the burden in caregivers and patients will also be explored.

As there are no validated questionnaires available for caregivers for patients with visual impairment, this project will also define and test a caregiver questionnaire.

Our free telephone counselling service is available to anyone who needs professional support.

Many people find it hard to come to terms with macular disease and some experience significant psychological and emotional problems, which can impact on their quality of life.  

We are here to talk and support.

Contact our team of qualified counsellors through the Macular Society’s helpline **0300 3030 111** or email counselling@macularsociety.org.
Macular disease can have a detrimental impact on the ability to read, with profound consequences for quality of life. We have developed an app for the iPad (called the MD evReader) that is designed to enhance the effectiveness of the eccentric viewing and steady eye techniques when reading.

Eccentric viewing involves shifting the point of gaze away from the fovea (the central area of vision, responsible for our ability to see fine details), to make use of the relatively preserved peripheral vision. Eccentric viewing is a simple technique that people with macular disease may adopt naturally, or can be trained to use, that can benefit tasks such as reading.

One of the problems with eccentric viewing is that it relies on the ability to maintain an unnatural (eccentric) viewing position and to suppress the natural tendency to make eye movements called saccades.

Saccades are the fast movement of the eyes made to direct the fovea onto an object of interest. They are an important part of our normal visual behaviour (we make two to three every second) and are part of a system that has evolved specifically to shift our focus of gaze onto the focus of attention. Reading is an example of a task that is dependent on a stereotypical pattern of saccades (made from left to right) and fixations made onto individual words, thus enabling cognitive processing. Saccades and fixations onto a word are, however, counterproductive for people with macular disease but are difficult to voluntarily suppress.
The steady eye technique is designed to reduce the reliance on eye movements during reading by encouraging the individual to keep their eyes and head still and to move the page. The technique takes practice but is thought to improve reading performance.

The MD evReader has been designed to facilitate reading by scrolling each line of text (from an eBook, for example) across the screen from right to left (‘ticker-tape’ format) thus eliminating the need to make saccades. Reading is performed while holding an eccentric viewing position on a visible marker, that can be positioned anywhere on the screen to match the individual’s preferred eccentric viewing location.

The speed of scrolling is controlled by a finger movement made on a ‘track pad’ located at the bottom of the iPad touch screen. The direction of scrolling can be reversed enabling text to be re-inspected as would occur during normal reading. The user can select their preferred font size and colour and the iPad can be connected to a digital TV screen enabling very large font sizes to be used. An initial pilot study has shown that eight out of 12 people with macular disease thought reading with the app was better than with static lines of text (two said no different and two said it was worse). Reading in this way may take practice but the app may prove useful in eccentric viewing training programmes.

Our aim is to release a version of the app in the future via iTunes and to perform a formal evaluation of reading performance. The development costs for the app are not excessive and this illustrates the potential uses of technological devices, such as the iPad, for developing bespoke visual aids tailored towards the needs of specific users.

At this time, the main limitations for the app are the digital rights restrictions used by publishers, which limit the platforms that eBooks can be used on. This means that at present it can be used only with books that are out of copyright.
Many members of the Macular Society will have heard about the eccentric viewing and steady eye techniques that are believed to help a person with macular degeneration use their residual vision more effectively. Some will have participated in the Macular Society’s Re:vision programme which offers free one-to-one coaching in both eccentric viewing and steady eye skills through a network of volunteer trainers (many of whom have central vision loss themselves).

Recently, the Macular Society has joined with partner organisations to recruit additional trainers and to make sure that training is available in as many areas of the UK as possible. The aim is to promote eccentric viewing training to the extent that it is available routinely through health or social care providers to anyone with macular problems throughout the country. Objective published evidence of the effectiveness of the training would be very helpful in supporting this expansion. The eccentric viewing Evaluation Study was therefore commissioned by the Macular Society to measure the results produced by the training, and is being carried out by an independent team of researchers: Prof Chris Dickinson (University of Manchester), Dr Ahalya Subramanian (City University) and Dr Robert Harper (Manchester Royal Eye Hospital).

Typically, the Re:vision training involves three one-to-one sessions between trainer and
learner, usually in the learner’s home or a local community centre, each lasting about an hour, and with about two weeks in between. Eccentric viewing involves the learner identifying which is the best way to position their eyes in order to see most clearly. Steady eye strategy involves moving the print rather than the eyes when reading, and can be of benefit when used either on its own or combined with a magnifier and/or eccentric viewing.

With practice, these skills can be developed and many people report finding it easier to read, to walk about, to recognise faces and do other tasks once they have been trained. The techniques do not work for everyone but for many people they appear to make a very significant difference to their ability to use vision effectively. Learners also benefit from a wealth of other advice (for example about lighting) and psychological support.

The eccentric viewing Evaluation Study involves a telephone interview with the learner, in which they are asked a standard set of questions about their well-being and mood, how much difficulty they have in managing everyday activities, and how much reading they do. The trainer also records the learner reading some simple sentences. The reading test and the interview are then repeated after the training is completed to see if any changes have occurred.

The research team are hoping that all the trainers and learners involved in the Re:vision programme over the next year will agree to also be involved in the eccentric viewing Evaluation Study, and they hope to recruit around 150 learners. Participation is voluntary, but it is really important to recruit as many learners as possible, in order to get as much evidence as possible about how the training works for a wide range of different individuals.

Please help the Macular Society through participation in the evaluation whether you are a trainer or a learner or can encourage someone else who is!
A systematic review of literature evaluating eccentric viewing and steady eye training

Allannah Gaffney, Tom Margrain, Alison Binns, Cardiff University, Catey Bunce, Moorfields Eye Hospital

Background

Central vision loss hinders many activities of daily living, including reading, mobility, visual search and face recognition. Eccentric viewing is an adaptive strategy used to compensate for central vision loss, in which relatively healthy paracentral areas of retina are used to fixate objects. During eccentric viewing training, individuals are either taught to optimise their use of a self-selected ‘preferred retinal locus’ or to use a ‘trained retinal locus’.

Eccentric viewing training is often administered in conjunction with training in more accurate eye movements, or a steady eye strategy, in which the eyes are held steady and the text is moved from right to left.

Given the number of people worldwide who could potentially benefit from eccentric viewing training 1-2, there is a need for a strong evidence base regarding the ability of different training strategies to achieve positive outcomes in people with central vision loss.

The aim of this project was to systematically review literature evaluating the effectiveness of eccentric viewing and steady eye strategy training in people with central vision loss.
Methods

Literature was identified by searching the following databases: Web of Science, EMBASE, Medline, Cochrane CENTRAL, PsychINFO, and CRD. The search terms were divided into two categories: target population and intervention, and the selected studies were required to match at least one search term from each category.

Additional literature was identified by hand searching of relevant reviews and by contacting experts in the field.

Results

Of the 2,536 articles identified by the literature search, 32 met the inclusion criteria for the review (Figure 1). However, only two of these studies presented the results of a well-designed randomised controlled trial.\(^3\)\(^-\)\(^4\) Instead, the majority of studies used a relatively weak ‘before and after’ comparison design. In addition, few studies incorporated a control group and there was a lack of longitudinal data to show how well the effects of training are maintained over time.

![Figure 1. Breakdown of included studies by study design. B&A = before and after study, RCT = randomised controlled trial.](image-url)
The literature provided very good evidence that eccentric viewing in conjunction with steady eye strategy/eye movement training improves near visual acuity and reading speed in participants with central vision loss.\(^3\)\(^-\)\(^6\) However, few studies examined the effect of training on distance visual acuity.

There is very good evidence from the literature that eccentric viewing and steady eye strategy/eye movement training improves the ability of participants with central vision loss to perform activities of daily living.\(^3\)\(^-\)\(^4\) However, few studies examined the effect of training on quality of life.

There is insufficient evidence to conclude that a particular model of eccentric viewing training is superior to another, as only three studies compared the effectiveness of different models.\(^6\)\(^-\)\(^8\) In addition, there is no evidence regarding the relationship between participant characteristics, such as age and severity of visual loss, and the outcomes of training.

Currently, there is also no evidence regarding the cost-effectiveness of eccentric viewing training. This poses a significant problem to the development of an economic case for its use in the rehabilitation of individuals with central vision loss.

**Summary**

Although there is evidence that eccentric viewing and steady eye strategy training improves outcomes in people with central vision loss, particularly with respect to near visual acuity, reading and performance of activities of daily living, there is a need for further robust research studies. This will advance our understanding of how eccentric viewing and steady eye strategy training can best help individuals with central vision loss and to explore the cost-effectiveness of different training strategies.
References


The arrival of drugs that can successfully treat wet age-related macular degeneration (AMD), for example Lucentis, has transformed the quality of life of many patients. However, these treatments are not without their negative aspects, such as the need for frequent hospital visits and the prospect of multiple injections into the eye.

The aim of the LAT study was to explore patient experiences of being assessed for and receiving treatment for wet AMD with Lucentis. We interviewed 22 participants (13 women and nine men; average age 77 years) who were being assessed or treated for wet AMD; 18 were interviewed twice. The first interview took place either just before or just after their first injection; the second interview was several months later. In the first interviews, an in-depth narrative interviewing method was used with a measure of self-reported visual function (NEI-VFQ). With the second interview a treatment satisfaction questionnaire (the MacTSQ) was completed alongside the narrative interview.

Results from the NEI-VFQ indicated relatively high levels of functional vision, but poor general health.
Satisfaction with treatment: findings from the MacTSQ

The MacTSQ results indicated high levels of satisfaction with the treatment received.

However, data from the narrative interviews revealed that these findings concealed a range of issues that had considerable negative impact upon patient experiences. The eight themes that emerged from the analysis of interviews are detailed below.

Experiences of living with AMD treatment: findings from the narrative interviews

1. Changes in perspectives towards treatment over time

Participants reported feeling less anxious about the treatment in their second interviews than in their first and all were satisfied with the treatment outcome to date, though they reported frustration with aspects of the service delivery.

2. Accessing treatment

Treatment was accessed via a range of routes. Some reported delays in accessing treatment due to the referral to the eye clinic being via their GP rather than through the rapid access referral system.

3. Communication and information

Participants reported widely varied needs for information about their condition and the treatment. A lack of information about treatment contributed to feelings of anxiety and apprehension. An individualised approach to informing patients is required.

4. Feelings about the injections

Participants reported a range of feelings about receiving an injection into the eye. These ranged from very fearful, through varying levels of anxiety and apprehension, to some who reported that the injection had not concerned them. Feelings of anxiety greatly reduced following the initial injection.
5. Experiences of and feelings about the injection procedure

The actual experience of the injection was far less unpleasant than participants expected. It is an unpleasant experience but one which they could cope with.

6. Side effects

While no clinically serious side effects were reported, our participants described a number of non-serious side effects. These were unpleasant and, when unexpected, could cause anxiety. No one suggested that these would make them consider stopping treatment. Very often, all that was required was some reassurance from clinic staff by way of a phone call.

7. Treatment outcomes

Participants who experienced improvement in visual function were delighted.

8. Service delivery and clinic environment

Participants identified a range of service delivery issues. In particular, the amount of time spent waiting within clinics was frustrating and contributed to anxiety.

Conclusion

Overall, participants reported positive experiences of receiving treatment with Lucentis. Whilst the notion of an injection into the eye invoked anxiety, much of this dissipated following the initial injection.

Further work is required into how to better inform patients about the treatment, focusing upon developing individualised approaches to communication. Whilst very satisfied with treatment outcome, some areas of service delivery require attention in order to improve the patient experience.
Four years ago

It has been four years since the landmark NICE approval of Lucentis intravitreal injection for wet age-related macular degeneration (AMD). Since then, we have been very fortunate to be able to prevent blindness for many patients. The Royal College of Ophthalmologists recommended that patients with wet AMD should be treated with Lucentis within two weeks.

Four years ago, there was little awareness of the clinical urgency of the condition in the community. Patients were often sent by optometrists back to their GPs with a generic note suggesting hospital referral. It normally takes up to six to eight weeks to be seen in a hospital clinic. On several occasions, we had to break devastating bad news to patients that we were unable to salvage their vision as they were not referred in time for treatment.

It was clear that the existing system did not provide us with the right tool to support an integrated care pathway. In May 2010, we set up a basic secure webform on our Trust website accepting referrals for fast track wet AMD screening directly from optometrists in London:

www.imperial.nhs.uk/gps/referralletters/index.htm

With a small grant from the Imperial College Healthcare Charity, we conducted a local
awareness campaign, encouraging local optometrists to refer patients directly for fast-track AMD screening either online or by fax. Our audit showed that we were able to screen patients within eight days in 50% of the cases and within three weeks in 95% of the cases.

With these preliminary results, we were able to apply for funding to develop a nationwide electronic wet AMD referral solution accessible to community optometrists. We were fortunate to have generous funding from the Macular Society and we have since been working closely in partnership with Health Intelligence, a diabetic retinopathy screening provider and clinical data hosting company, in developing a secure IT platform to handle electronic referrals.

The situation now
Despite improved awareness of the condition, patients are still having problems getting access to treatment in time. The situation is getting worse with our present financial crisis. According to a recent survey conducted by the Macular Society, eye clinics all over the UK are struggling to meet the demand for AMD services with few resources at their disposal.

Our previous audit identified that only 23% of the patients referred based on objective criteria indicating for fast-track screening had true wet AMD. Our research coordinator Serge Miodragovic conducted interviews with a number of local optometrists, demonstrating a general support for an electronic referral system amongst optometrists. However, a number of them expressed the need for a manned phone referral service in case of technical failure with fax machines or internet connection.

Current solution
We are due to launch our pilot wet AMD referral scheme PASTA (Phone for Appointment to Screen and Test AMD) at the end of this year, initially at Western
Eye Hospital, with further plans to roll out in other trusts once we have refined the software to a more stable version.

**The PASTA scheme consists of the following four steps:**

**P (Phone or Online)**
The optometrist will refer patients suspected of wet AMD by dialling a dedicated centralised hotline or accessing a secure online referral page.

**A (Appointment)**
The centralised IT system will book a screening clinic appointment at a treatment centre selected by the patient. Patients presenting signs and symptoms suggesting wet AMD will be issued with an urgent screening appointment on the spot before leaving the optometrist’s practice.

**S (Screen)**
We will set up Virtual Screening Clinics within hospitals, manned by qualified technicians who are trained to perform visual acuity assessment, fundus photography and optical coherence tomography (OCT) scanning under ophthalmologists’ supervision.

**TA (Treat AMD)**
The screening results will be reviewed by on-duty Medical Retina Fellows or Medical Retina Consultants, who will decide whether to see and treat the patient the same day. On average, only one in five patients referred requires urgent attention.

We believe that this pilot scheme will reduce the referral to treatment time delay to one week. This increase in productivity can only be brought about by integrating the existing resources from both the NHS and the private sector efficiently.
Age-related macular degeneration (AMD) is the most common cause of irreversible visual loss in the western world. It is known that the population in the UK and the rest of the world is shifting significantly upwards with longevity of life. With the increasing demographic shift towards an ageing population, the prevalence of AMD is expected to double in the coming decades unless preventative strategies are developed and implemented. There are also potential new treatments for the previously untreatable dry forms of AMD on the horizon.

There are several publications on AMD prevalence in the UK. However, most are not population based, but rather based on data from registration of visual impairment which includes only late AMD, and which is often incomplete. The few UK population studies that exist are either very old, small, or have given different results because of varied study designs, different criteria or age inclusions.

A recent review by Chris Owen and his team indicates that AMD has a much higher incidence of the late stages of AMD in the UK than previously thought, and that this would increase as the population continues to age.

There is inadequate data on the early stages of AMD, or patients who have advanced
disease in one eye only. Whilst patients with bilateral vision impairment are registered as such, patients with asymmetric AMD, i.e. advanced disease in one eye and near normal vision in the other eye, may go unnoticed otherwise.

There is an urgent need to provide accurate population estimates of the prevalence of different stages of AMD in the UK population. This is important as it will allow adequate health care planning and provision.

The Bridlington Eye Assessment Project (BEAP) was set up by Professor S. Vernon to screen for eye disease in the elderly population of 65 years and over using clinical examination by trained optometrists and digital imaging technology. Retinal photographs, including the macula, from every participant were acquired and stored. The database has been analysed for glaucoma previously. However, data regarding AMD has not been analysed to date.

Our project aims to analyse the valuable population database in order to determine the prevalence of different stages and asymmetry of AMD in this UK population. Specifically, we aim to determine the prevalence of different stages of AMD in the elderly UK population and their correlation with measured visual acuity. We also aim to elucidate the proportion of patients with macular degeneration who are yet to develop symptoms or visual impairment because of disease asymmetry.
The Macular Society recently surveyed members to explore their opinions regarding the use of unlicensed Avastin for the treatment of wet AMD. The survey was completed by 237 people, the majority of whom were members of the Macular Society, and many of whom had previously received treatment for wet AMD.

The vast majority (96.5%) of the individuals who completed the survey were aware of the debate regarding the use of Lucentis and Avastin for the treatment of wet AMD. In addition, over three-quarters of the respondents (81.9%) felt sufficiently well-informed to make a decision regarding the drug used to treat their own eyes. These results indicate that, in general, the members of the Macular Society have a good understanding of the debate regarding Avastin and Lucentis. However, as completion of the Avastin survey was optional, it is possible that those individuals who chose to participate were motivated to do so because they were already aware of the debate surrounding Lucentis and Avastin. This ‘selection bias’ may have caused the results to ‘exaggerate’ the extent to which this issue is understood by the membership as a whole.

Over half of the respondents (53%) considered Lucentis to be the only drug that is appropriate for the treatment of wet AMD on the basis that it is licensed and
approved for use in eyes. Consequently, a similar proportion of participants felt that the NHS should not be using unlicensed Avastin to reduce expenditure.

Only a third of the respondents felt that the safety and effectiveness of Avastin were appropriate justifications for the use of this unlicensed drug to treat wet AMD. This was consistent with the key explanations given by those participants that had refused to undergo treatment with Avastin in the past, more specifically concerns regarding its safety and the fact that it was not licensed for use in eyes.

A quarter of the respondents were unsure if the safety of Avastin was sufficient justification for its use in eyes by the NHS.

The Macular Society would like NICE to appraise Avastin before it comes into widespread use in eyes, in order to ensure that there is a coherent policy that will allow ophthalmologists to make transparent decisions that are in the best interests of their patients. The Avastin survey did not specifically ask participants whether they were in agreement with this stance. However, a recurring outcome of the survey was that the respondents were uncomfortable with the use of unlicensed medications when a licensed alternative was available.

For example, approximately 44% of people that had previously declined treatment with Avastin reported doing so because it was not licensed for use in eyes and over half of the respondents stated that the NHS should not be using unlicensed Avastin as a strategy for reducing its expenditure. This implies that the members would support an appraisal of the use of Avastin in eyes.
As readers of Digest will probably know, a Rehabilitation Officer for Visually Impaired People (ROVI) is the professional who is most often involved in the independence training that people experiencing sight loss are entitled to.

A ROVI’s work would include the initial assessment; subsequent orientation and mobility; daily living skills; and low vision training.

ROVIs are most often employed by local authority adult social service departments. Yet despite the acknowledged benefits of such services, there has for some time now been concern about the dwindling number of this workforce. Last year, the Social Care Association undertook a survey to find out how many ROVIs there were in the UK, where they were working and the kind of teams they were working in.

Results

The survey estimates that there are some 600 or so ROVIs in the UK. Some 400 of these work under contract for local authorities in England, 30 in Scotland, 40 in Wales and 25 in Northern Ireland. That averages out at around three for each local authority, but in some there are more and some less (and not necessarily full-time). In a number of local authorities, a lone worker is serving a total population of more than 150,000. This figure only takes on real meaning if you imagine...
that this lone worker will assess and work with the 100 or so people whose Certificates of Visual Impairment (CVI or BP1 in Scotland) come across their desk each year – a figure that doesn’t start to consider those who need help but do not have a CVI and those who need services year after year because of changing circumstances.

Most workers are either in traditional sensory teams (i.e. along with people who provide services for those losing hearing and/or sight) or in reablement teams (along with Occupational Therapists or Home Care Managers).

Vision 2020 UK Future of Rehabilitation Group

This group, comprising representatives from various charities and local government from around the UK, was formed last year to address the growing number of issues facing rehabilitation. One of these issues is the lack of voice that social care workers have, with no widely recognised governing body to speak on their behalf.

Overcoming myths about service provision

How often do people working in this field hear that access to a rehabilitation service is restricted by the eligibility criteria? This should not be the case. Indeed, one of the most fundamental objectives of the Future of Rehabilitation Group is to set rehabilitation in its proper context in the eye care pathway so that managers can understand this.

Firstly, an explanation. Eligibility criteria (known in the trade as Fair Access to Care Services or FACS) is the mechanism that each separate local authority in England uses to decide how they ration the services that social services provide to its population. In most areas, services are rationed to those with the most complex needs.

However, what is not widely appreciated is that certain services which local authorities provide should not be subject to these eligibility criteria. These services are those that swing into action to prevent the
Eye health management

The current and future role of a ROVI

need for more services further down the line (for example home care when someone is discharged from hospital). These are known as ‘reablement’ services. The Department of Health has stated that they are not to be charged for at present and are not subject to eligibility criteria. Visual Impairment Rehabilitation is one of these services and part of the core services that a local authority should offer someone experiencing the need to adapt their skills.

Keeping track of the situation

Readers of Digest would do well to find out what services are like in their area. What department do the CVIs go to? Are they filtered and contacted by a worker who is qualified to understand all the information on it and all its potential implications? Do they receive an assessment?

A CVI is a trigger for an assessment and it is a legal duty to offer one. How many ROVIs does the area have?

If you have concerns then RNIB’s Cuts Watch (www.rnib.org.uk/getinvolved) is a good place to start, or you can contact me simon.labbett@bradford.gov.uk to find out more about the sight loss pathway.
Glossary

Digest is aimed at both eye care professionals and our interested members. We know from feedback that some of our members would appreciate more clarity on certain words and phrases, so we have listed here a selection of those that appear in this edition.

**ABCA4**
ABCA4 is a gene, which provides instructions for making a protein that is found in the retina, the specialised light-sensitive tissue that lines the back of the eye. The most common form of Stargardt’s disease is the recessive form caused by mutations in the ABCA4 gene.

**AREDS**
The Age-Related Eye Disease Study carried out by the US National Eye Institute. In 2000, it reported that a diet high in antioxidants and zinc can slow the progress of advanced dry AMD. A second AREDS study is now underway.
Autofluorescence
The natural emission of light by some biological structures.

Autologous
Derived or transferred from the same individual’s body. For example, autologous blood donation or an autologous bone marrow transplant.

Bruch’s membrane
The inner-most layer of the choroid. The retinal pigment epithelium transports metabolic waste from the photoreceptors across Bruch’s membrane to the choroid. With age, the Bruch’s membrane becomes thicker, which slows this transportation.

Choriocapillaris
The layer of the choroid next to the Bruch’s membrane. It consists of a network of capillaries, which supplies nutrients to the retina.

Choroid
The choroid is the layer of blood vessels and connective tissue between the sclera (the white of the eye) and the retina.

Eccentric viewing
The eccentric viewing technique involves identifying and using the healthiest parts of your macula/retina at the back of the eye. If you have lost your central vision, this will be a non-central or ‘eccentric’ area. By working with a low vision therapist or eccentric viewing trainer, you can identify the best point of vision to help you make the most of remaining vision.

Genome
Every organism has a genome that includes all the biological information needed to build and maintain a living example of it. This information is encoded in its DNA, which is divided into units called genes, which contain instructions for which chemicals (or proteins) they need to produce.

In silico
In silico is an expression that means either performed on a computer or through computer simulation.

In vitro
In vitro is Latin for ‘within the glass’. This is experimentation.
in a test tube or a petri dish in a controlled environment.

**In vivo**
In vivo is Latin for ‘within the living’. This is experimentation using a whole, living organism, rather than a partial or dead organism. For example, clinical trials are a form of in vivo research.

**Neovascular AMD (nvAMD)**
Neovascular AMD is the formal medical term for ‘wet’ age-related macular degeneration (AMD), in which abnormal blood vessels in the eye leak and scar the macula.

**Pathophysiology**
Pathophysiology explains the processes within the body that result in the signs and symptoms of a disease. It doesn’t deal directly with the treatment of the disease.

**Pharmacogenetics**
Pharmacogenetics is the study of how the actions of, and reactions to, drugs vary with the patient’s genes.

**Proband**
Proband is a term most often used in medical genetics. It refers to the particular subject (person or animal) being studied. Most commonly, the proband is the first affected family member to seek medical attention for a genetic disorder.

**Retina**
The retina is the thin membrane at the back of the eye that contains light sensitive cells. The macula is in the centre of the retina.

**Retinal Pigment Epithelium (RPE)**
The pigmented cell layer of the retina. It nourishes the retinal visual cells and shields the retina from any excess incoming light.

**Retinitis pigmentosa**
Retinitis pigmentosa is an inherited degenerative eye disease caused by abnormalities of the photoreceptors or the retinal pigment epithelium of the retina, leading to progressive sight loss. Some people with the condition may experience difficulties with light to dark or
dark to light adaptation, or night blindness. Most experience ‘tunnel vision’ through the degeneration of their peripheral vision, while sometimes central vision is lost.

**Rods and cones**

Rods and cones are the two types of photoreceptor cells in the retina. Photoreceptors convert light into signals, that are then passed down the optic nerve (which connects the eye to the brain) to the visual cortex area of the brain to form a representation of the visual world – sight. Rods provide us with our peripheral vision, providing ‘awareness’ and movement vision and do not provide colour vision. There are around 120 million rods in each eye. Cones are located in the macula, with around 7 million cones in each eye. They provide our ‘central vision’, as well as detail, reading and colour vision.

**Stargardt (or Stargardt’s) disease**

Stargardt’s disease is an inherited juvenile form of macular disease – a macular dystrophy. It usually appears in young people aged between 10 and 20. The cells of the macula are affected, leading to distorted central vision and sometimes colour perception.

**Steady eye strategy**

Steady eye strategy is a technique specifically for reading. Usually when we read, we hold the page still and move our eyes from left to right across it. This scanning movement (called the saccadic reflex) becomes automatic as we learn to read. If you lose your central vision, this way of reading no longer works; the damaged part of the macula constantly blocks out the words. Steady eye strategy is when you keep your head and eyes still and move the page from right to left in a scrolling movement across the best part of your vision.

**VEGF**

VEGF is the Vascular Endothelial Growth Factor, a protein responsible for the development of new blood vessels. In wet macular disease, these blood vessels are abnormal. Anti-VEGF drugs are used to stop their development.
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