Important – Publisher’s Note
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.

Products and services featured in Digest are not recommended or endorsed by the Macular Society which does not conduct testing or approval. Please take professional advice from an optician, optometrist, doctor or social worker before purchasing.
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Welcome to Digest 2016, the Macular Society’s annual summary of the research around the world into macular diseases.

In this edition we report on the exciting progress being made at the London Project to Cure Blindness where the first patients have had stem cell implants. Our generous members and donors enabled this project to keep going in 2008 when other funding was scarce. Today it has commercial investment from the pharmaceutical company Pfizer.

Charitable funding of early stage research is vital to help prove the value of an idea and encourage commercial investment. The sight loss sector is disadvantaged in that there are no large charities dedicated to funding research as there are in other sectors such as cancer or dementia. We believe public research into macular conditions is under-funded and explain why on page 12.

Macular researchers produce high quality work as we report on page 13 but they need more support if we are to find a cure for macular disease soon. And we need to find a cure because the number of people with age-related macular degeneration (AMD) is rising fast, see page 68. By 2020 there will be around 680,000 people with sight loss caused by AMD and by 2050 that may be 1.3 million in the UK.

Once again this year we can invest at least £500k in research thanks to our members, supporters and donors who have given to our research appeal. We are very grateful to you.

If you are not yet a member of the Society please consider joining at www.macularsociety.org/become-member.

With every good wish,
John Dunston
Chairman
Research and new developments are continuing to improve treatments and investigation of macular disease. Neovascular (wet) AMD treatments have targeted VEGF, one of the proteins that causes abnormal blood vessels to grow in the retina. Whilst there are two approved treatments for neovascular AMD in the form of injections into the eye to block VEGF, these treatments have to be repeated regularly. As such the drive is to discover new drugs that last longer in the eye to reduce injection frequency. One of these is brolucizumab (or ESBA 1008) by Alcon which is now in Phase 3 studies. Similarly, a drug called Fovista that blocks the protein PDGF responsible for scar formation in treated neovascular AMD is being developed to be used in addition to Lucentis® or Eylea® injections. Hopefully, such drug combinations can reduce injection frequency, reduce scarring and improve vision gain achieved with Lucentis® or Eylea® alone.

Other researchers are looking at interfering with the messaging chemistry that enables cells to produce proteins that are needed for the development of abnormal blood vessels and scar tissue in neovascular AMD. Blocking these proteins in the eye with a monoclonal antibody may offer an entirely new method of treatment.

Even more exciting is the possibility of treating dry AMD
or geographic atrophy. Results from the latest trial of lampalizumab are awaited. Other drugs being investigated for dry AMD target different proteins including anti-PIGF which is thought to protect the retinal pigment epithelium.

Patients with AMD, including those undergoing injection treatment, often require assistance from family and friends. Recent research has provided an insight into the nature and scale of these activities by caregivers. Research also continues on how best to utilise residual vision in persons who have lost their central vision.

Stem cell transplantation in the treatment of AMD took a leap forward recently when the London Project to Cure Blindness commenced recruitment into their early phase programme. There’s a while to go before we know the potential of this type of treatment. Stem cell research is progressing in the treatment of different juvenile macular dystrophies, including Best’s disease. Using stem cells to investigate the role of the protein Bestrophin, and studying how light affects retinal pigment epithelial cells in laboratory culture prior to being implanted into the eye, will help future attempts at treating some currently untreatable conditions. The progression of retinal degeneration in Stargardt’s dystrophy has been put under the microscope by a team in London. It may be possible to intervene in ways that allow us to halt its progression.

Although we have known for some time that AMD results from an interaction of genetic and environmental factors, our understanding continues to be enhanced by research into chromosomes important in the disease. This research, based on human tissue donated for research in the USA, tells us that AMD may be a group of diseases, and may explain why some treatments may work in some people but not in others.

Establishing a national eye tissue archive for macular research in the UK will enhance further research in this direction and allow collaboration with US counterparts.
Macular Society is one of the few sight loss charities that actively fund research into macular disease. During the past 10 years we have funded £2.3 million of research, thanks to donations from members and supporters.

Macular Society has been awarded an Association of Medical Research Charities Best Practice in Medical and Health Research certificate. This confirms our use of robust methods to make funding decisions and provide support to the highest quality researchers and research.
How can we assess the quality of research into macular disease in the UK?

Professor Norman Waugh and Dr Pamela Royle, 
Division of Health Sciences, Warwick Medical School, University of Warwick

In our study we looked at macular research in the UK and how it compared internationally in terms of quality. Organisations that fund research need to know that their funds are used well. In this context “well” means that significantly useful new knowledge is generated from the research grants. The purpose of research is to add to knowledge that will ultimately help patients by making prevention or cure possible. The path to prevention or cure can be very long and among the research questions might be:

- The epidemiology of age-related macular degeneration (AMD) and the inherited macular dystrophies – who gets a condition and when? Are there differences between people who get AMD and people who don’t?
- Can we identify the causes, or at least factors that increase the risk?
- The basic science of the mechanisms that lead to AMD. What are the first changes in the eye, and can those help identify the cause? What happens between then and advanced AMD?
- The role of genes. Why do some genes increase the risk of AMD or inherited dystrophies? Can we work out why they increase the risk and will this lead to treatments?

Inevitably, some research comes to a dead end when a lot of work may go into proving that something doesn’t work, but at least useful knowledge is gained.
What are the indicators that show that the research the Macular Society funds makes a useful contribution to our knowledge? The key to contributing new scientific knowledge is publication in respected scientific journals. Publication involves ‘peer review’—other scientists in the subject area evaluate the articles and advise the Editor as to whether they are of a high enough scientific quality to publish in the journal. Peer review is not a perfect system but is the best we have.

An important indicator of useful research is the number of times a scientific article is quoted or referred to by other researchers in their published articles – the number of times it is cited. The more citations, the more academic impact the first article is deemed to have had. Citations are also important because when a researcher applies for their next funding grant, the number of citations of past research is used as a sign of research impact.

We looked at 33 research grants awarded by the Macular Society from 2005 to 2013 and the publications that resulted. We also looked more widely at macular research in the UK to see how well it rated internationally, in terms of citations, and how well macular research scored in the Research Excellence Framework (REF). This is an assessment every 5 years or so of each UK university’s research performance. Only the very best research is submitted to the REF, so we looked for any macular research studies that had been submitted. The results were:

• Most Macular Society grants were associated with publication in good quality journals. However, we could not identify publication in peer-reviewed journals for 13 grants. Five grants awarded in the years 2012-2013, were too recent to have completed the research and get it published.

• In five cases, from grants awarded in 2005, 2006, 2007, 2008 and 2011, we found no publications in scientific journals.

• Some of the research projects were very large where the
Macular Society contribution was a small part of the total funding. Other projects were quite small where all or most of the funds came from the Macular Society.

The REF publication period was from 2008 to 2013. We found 10 studies that acknowledged the Macular Society as a source of funding in the REF submissions, and thereby judged by the universities to be of international importance. When we looked worldwide at macular research output in academic journals from 2011 to 2014 we found that four countries led the way in the number of scientific articles published: USA (36.1%), UK (9.8%), Germany (9.5%), and China (8.3%) accounted for about 65% of all such publications.

We looked at the number of citations per article on macular research and found that UK research does well compared to the other three lead countries, and in 2012 and 2013 was in the lead position. So UK macular research is up with the best in the world, in quality.

In October 2013 the Sight Loss and Vision Priority Setting Partnership (SLV-PSP) published the results of a two year consultation among sight loss charities, patient groups and eye health professionals, on what were considered to be the most important topics for macular research over the next ten years.

When we looked at all the topics in 421 UK publications on macular research published during 2011-2014, only 8% of the published research dealt with the top priority of that SLV-PSP report; treatment to stop dry AMD progressing and/or developing into wet AMD.

So the news is that most research grants from the Macular Society lead to publications that add to our knowledge and that UK macular research is amongst the best in the world. However, following the priority setting of the SLV-PSP report there is not enough research being carried out on those areas ranked as the high priorities.
The Macular Society has funded medical research since its foundation in 1987. Thanks to the generosity of our members and supporters we have been able to give more than £2.3 million to research projects around the UK in the last decade.

But we now believe we must do more. Research into eye disease in general and macular disease in particular receives very little public funding in this country compared with the great cost of macular conditions.

In 2014 more than £3 billion of public money (from taxpayers and charity donations) was invested in medical research. Of that only £22.7 million was spent on eye disease and only £6.03 million on age-related macular degeneration (AMD) – the biggest cause of sight loss. In fact AMD is responsible for 49% of all sight loss registrations but receives only 27% of eye research funding.

The UK sight loss charities have a combined income of more than £774 million a year. However only a handful of smaller charities such as the Macular Society fund medical research. In 2014 only £1.5 million of that £774 million went into research into AMD. That is less than one fifth of one percent of income.

AMD is fast becoming a major health and social crisis. It is
estimated that it costs the country around £1.6 billion a year. Just the cost of treating wet AMD is estimated to be more than £300 million a year.

And then of course there is the human cost of AMD. If you or someone you love has AMD you will know how high that cost is. It is vital that we make faster progress towards better treatments for AMD and, we hope, a cure.

The price of AMD today will be dwarfed by future costs. Many more people are developing AMD as society ages. Today there are around 600,000 people with sight loss caused by AMD. Nearly 200 people are diagnosed every day. By 2050 there will be 1.3 million people with AMD. Around the world by 2040 that figure will be 196 million.

There is much exciting, high quality research being done by world-leading researchers in the UK (as you can see from this edition of Digest) but it needs investment.

The Macular Society is publishing a paper setting out our case for more funding of research. We want researchers, sight loss charities and people with macular disease to join our campaign. We ask charities that are not currently funding research to consider doing so to help prevent people losing their sight in future.

Given the high cost of AMD to society we believe public institutions have a duty to fund more research. We want to help develop a truly collaborative approach to macular research. We are working with leading researchers to establish an AMD consortium to speed up the progress of research.

Your continued support is vital and your gifts and donations are received with profound gratitude. The forthcoming edition of our member magazine Sideview will have an update on our campaign and how you can help. We believe this campaign is crucial if we are to save the sight of many thousands of people today and many millions in the decades to come.
Macular Society Research Awards 2015

Thanks to the generous donations of supporters, the Society made two major research awards and funded two PhD studentships in 2015.

Reticular pseudodrusen in AMD: a population-based study | Supervisor – Dr Ruth Hogg, Queen’s University
Belfast | PhD student – Timos Klainti Naska

Reticular pseudodrusen (RPD) are deposits found within the retinal pigment epithelium (RPE) cells. In comparison, ‘traditional’ drusen are found outside the RPE. RPD have been shown to increase the risk of AMD development and progression and can also affect visual function. This study will investigate how common RPD are in the general population and how they are associated with AMD. The researchers will also examine other lifestyle factors or health problems that commonly coexist with RPD.

Modulating mitochondrial dynamics in the retinal pigment epithelium as a therapeutic strategy for macular dystrophies | Dr Aparna Lakkaraju,
University of Wisconsin-Madison USA

The aim of this study is to investigate the mitochondria in healthy RPE and examine how these cells are affected by vitamin A and high oxygen use. The researchers will also evaluate whether drugs that promote clearance of damaged material and reduce inflammation can preserve mitochondrial function. This study will potentially benefit patients with AMD and inherited forms of macular disease.
Macular Society research

Study of molecular mechanisms driving retinal pigment epithelium (RPE) dysfunction in patients in different stages of AMD and cellular rescue as a potential future therapy | Supervisor – Dr Arjuna Ratnayaka, University of Southampton | PhD student – Ellie Keeling

Research has found a number of similarities between AMD and Alzheimer’s disease. In both conditions lysosomes, which are part of the cell’s waste disposal system, and mitochondria, which provide energy to the cell, are gradually damaged. Both lysosomes and mitochondria are vital to the health of the RPE but current knowledge about them is limited. The researchers plan to take living RPE cells from patients to study the changes to lysosomes and mitochondria at different stages of AMD. They will also test whether rescuing lysosomes and mitochondria from becoming damaged could be used as a potential treatment for early AMD.

Realising the potential of the UK Biobank resource
Professor Paul Foster, UCL Institute of Ophthalmology

UK Biobank is a large project involving more than 500,000 people who have agreed to have all of their health data collected by researchers over many years. This data is a powerful resource to help researchers discover why some people develop particular diseases and others do not. Currently, most people are diagnosed with AMD when symptoms are well advanced and they have already lost some vision.

As the Biobank includes a cross-section of the population, it allows the study of many people who have yet to develop AMD. The researchers hope to identify the risk factors for AMD by examining their underlying genetic and lifestyle data. This will provide important information on how to target the early stages of the disease and stop its progress.
Developing a database of volunteers for research into macular conditions

Geraldine Hoad
Macular Society Research Grants Officer

As an organisation dedicated to finding a cure for macular disease, supporting the painstaking medical research needed to achieve this is a major aspect of the Society’s work. Researchers tell us that they often have difficulty finding enough suitable participants for their studies. We also know that many people want to be involved in research into their condition. It therefore made sense for the Macular Society to bring the two together and in 2015 we launched a new resource called the Research Participant Database.

The database enables members and non-members, once they have signed up, to receive information about research trials that they may be eligible to volunteer for as a participant. The database covers all macular conditions, but as researchers need to find relatives of people with macular disease and healthy control subjects, it also includes these groups. The response to the launch of the database has been very positive with over 800 people joining so far.

When a research team approaches the Society for help in recruiting for their study, we identify those people on the database who fit the eligibility criteria for the study. We then send each person a letter with brief information about the project and who to contact if they wish to learn more or volunteer as a participant. For example, a team at Cardiff
University is carrying out research to improve our understanding of AMD and how changes to the blood vessels beneath the retina contribute to the condition. They were looking for people with and without AMD to undergo some tests and we were able to contact people on the database who lived in the area and might be eligible to take part. It was then up to each individual to decide whether they wanted to take part in the study and contact the university.

Over 95% of those who have signed up to the database are willing to take part in clinical studies, including clinical trials. However, people can also volunteer to take part in patient groups who may be consulted about research design or the important outcomes of research from the patient’s perspective. The database can also be used to identify those people who are happy to be contacted by the Society’s Communications team to share their story as part of any campaigns or publicity for the Society.

Signing up to the database is completely confidential and only collects basic information about a person and their macular condition. This enables us to check a person’s eligibility for each study. No information is shared with any other organisations – not even the researchers requesting volunteers.

If you would like to sign up please contact the Helpline on 0300 3030 111 and we will send you a form. Alternatively you can complete the form online at www.macularsociety.org/researchdatabase.
We are determined to find new treatments and a cure for macular conditions.

Every donation, no matter what its size, plays its part in moving us closer to that important goal. As the only national charity funding research exclusively into macular disease we aim to help the hundreds of thousands of people affected by macular conditions – dry and wet AMD and juvenile dystrophies.

We are very grateful for the generous donations to our research appeal each year from our members and supporters. Without this support our vital research programme would come to a halt. We choose projects which use your donations to make the most impact, encouraging the brightest and best scientists to work in the field. Funding PhD studentships is one of the ways we work with the leading research teams.

With your help we are confident that eventually we will defeat macular disease.

Timos Klainti Naska’s 3 year PhD has been funded by the Society. Timos graduated with a Bachelor of Science in Optics and Optometry followed by a Master’s degree in Clinical Ophthalmology & Vision Research from the University of Glasgow. His aim is to pursue a career as a researcher.

Macular Society has been awarded an Association of Medical Research Charities Best Practice in Medical and Health Research certificate.
A legacy for research given to the Macular Society is helping monitor and improve the quality of care for patients with wet age-related macular degeneration (AMD).

Miss Joyce Bushby, who died in 2012, was a long term member of the Society. She asked if her legacy could be spent on research which didn’t involve animals.

We honoured this very personal wish by spending her gift on a three year national audit of patient care for people with wet AMD. Led by Rob Johnston, Consultant Ophthalmologist at Gloucestershire Hospitals NHS Trust, the project’s findings will help establish benchmark standards of care for patients receiving wet AMD treatment; and will enable meaningful comparison between hospitals to ensure standards do not fall below acceptable levels.

In its first year, the project collated data from 45,000 medical records at 41 NHS hospitals, creating the world’s largest dataset of real-world clinical outcomes for wet AMD patients. The project is now defining measures that will allow comparison between centres and highlight excellent practice.

Selected analyses, thought to reflect best the quality of care between centres, will be presented on the RCO’s National Ophthalmology Database website and will allow centres to see their own performance against the best UK clinical practice.

Gifts in Wills play a special role in funding research, as we strive to keep up momentum towards new treatments and a cure. To ask about leaving a gift for research in your Will, please call Julie Edwards on 01264 321 965 or email legacies@macularsociety.org
Chromosomes are thread-like structures located inside the nucleus of a cell. Human cells have 23 pairs of chromosomes giving a total of 46 per cell. Each chromosome is made of protein and a single molecule of deoxyribonucleic acid (DNA).

The advent of rapid DNA sequencing methods has greatly accelerated biological and medical research and discovery. Sequencing DNA is the process of determining the precise order of genes and their component building blocks of proteins within a DNA molecule: these nucleotides determine the specific outcomes of our genetic inheritance.
**Glossary**

**Allele** – the alternative forms of a given gene are called alleles. They can be dominant or recessive. Each parent passes one set each of their alleles in all 23 chromosomes.

**Drusen** – are the tiny yellow or white deposits in a layer of the retina between Bruch’s membrane and the retinal pigment epithelium of the eye. The presence of large and numerous drusen in the macula is a common sign of age-related macular degeneration (AMD). Drusen are made up of lipids, a type of fatty protein.

**Gene** – this is a portion of the DNA molecule that serves as the basic unit of heredity.

**Genome** – the complete set of genes or genetic material present in an organism.

**Genotype** – this is your complete heritable genetic identity; it is your unique genome that would be revealed by gene sequencing. Genome sequencing is determining the order of DNA nucleotides in a genome – the order of As, Cs, Gs, and Ts that make up an organism’s DNA. The human genome is made up of over 3 billion of these genetic letters.

**Loci** – the position of a gene as determined by its linear order relative to the other genes on that chromosome.

**Phenotype** – a description of physical characteristics such as height, eye colour as well as your health, disease history, traits and behaviour.
Observing individual photoreceptors over time enables the accurate assessment of the progress of Stargardt disease in patients

Michel Michaelides, Professor of Ophthalmology, UCL Institute of Ophthalmology

In our study we are using a high-resolution imaging technique to look at individual photoreceptors in the retina of patients with Stargardt which enables an assessment of retinal structure at the individual cell level. Observing changes over time in individual cell structure will provide reliable evidence of the progress of Stargardt disease that will be crucial knowledge in the design of future gene therapy or cell replacement trials.

Stargardt disease is an inherited condition caused by faults in the ABCA4 gene and is characterized by progressive central vision loss due to the early involvement of the macula. As a recessive genetic disorder both parents will have carried the faulty gene so that two copies of the gene are present in an individual with the condition. The estimated prevalence in the population is around 1 in 10,000. Symptoms often begin in childhood, but the condition can develop in early adulthood and less frequently later adulthood. The progress of sight loss in a patient most often relates to the age of onset, with a better outcome associated with later onset of the condition.

There is a lack of certainty regarding the exact mechanism(s) leading to sight loss. But the retinal pigment epithelium (RPE) cells and the photoreceptors of the retina are both affected and progressively die off. Although it is known that the protein produced from the ABCA4 gene is active in the outer segments of the photoreceptor cells, it is
not certain if this is the primary site of death within these cells. There are no current cures or treatments for Stargardt.

However there have been recent significant advances in both gene and stem cell therapies. Gene therapy is a technique whereby a functioning copy of the ABCA4 gene is delivered to the outer retina to replace the faulty copy in the patient’s photoreceptor cells. The StarGen gene therapy trial is on-going and the final group of patients currently enrolled in its Phase I/II stage. A stem cell trial, in which human embryonic stem cell derived RPE cells are injected into the retina is underway and in its Phase I/II stage.

Our study is an investigation of the natural history of Stargardt where we examine the observable physical characteristics, or phenotype, of the retinal cells in patients with Stargardt. Patients with genetically proven Stargardt are recruited and reviewed at baseline, and then again at month 6, 12, 18, and 24, using a number of different qualitative and quantitative measurements of retinal structure and function.

We have recruited 50 patients to date.

Our custom-built adaptive optics scanning light ophthalmoscope is a high-resolution imaging system, which allows us to see individual photoreceptors; thereby allowing assessment of retinal structure at a cellular level. Repeated observations over time will enable us to assess the relationship between retinal structure and function, and determine what differences the genetic make-up of the condition may have on characteristics of the disease such as age of onset, rate of progression, and severity.

By the end of this longitudinal study we expect to be able to identify sensitive and reliable measurements needed to determine treatment effect and safety, and to identify suitable trial participants and windows of opportunity. This data will enable improved advice on predicting disease outcome, and is crucial for the design of future human clinical trials using gene therapy, cell replacement strategies and new pharmacological treatments.
New insights into the roles of chromosome 1 and chromosome 10 in the biology of inherited AMD

Significant evidence of the genetic risks associated with developing age-related macular degeneration (AMD) has been discovered during the past 10 years. There is now a body of knowledge detailing the chromosomes, genes and their variants that may influence the development and progression of this disease.

Drusen are tiny yellow or white deposits that develop in a cell layer of the retina at the back of the eye: they are a common sign of AMD. Early investigation of eyes from human donors with and without AMD led to identification of numerous proteins associated with the complement system in these drusen. The complement system plays an important role in regulating the body’s immune system and these early studies suggested that some form of breakdown in this system was occurring in the eye.

Importantly, these observations led directly to the discovery that common variants among a cluster of genes on chromosome 1 which regulate the complement system, confer significant risk for, or protection from, the development of AMD. In addition, variants within a cluster of two genes on chromosome 10 (ARMS2 and HTRA1), neither of which have any obvious relationship to the complement pathway, were also shown to have a strong association with AMD risk. (Figure 1) Other minor
genes have been shown to associate with AMD but their precise roles in the development of AMD have not been established. In combination, the AMD-associated variants in the chromosome 1 and chromosome 10 loci account for more than 80% of the disease risk. There is no other common disease for which only two genetic loci account for a majority of risk burden.

As AMD is a disease that occurs only in humans, over $30 million has been invested over the past 25 years to develop a tissue bank of more than 7,000 pairs of human donor eyes. This unique resource has been examined for its genetic and clinical characteristics: this has meant analysing the genes along with microscopic changes in the tissues of the eye and linking this to the clinical record of the donor. This has played a key role in understanding when chromosome 1 and chromosome 10 impact on the biology of the eye.

Because there is no evidence to support a direct biological interaction between the chromosome 1 and 10 genes and their protein products, we have focused on analyses of donor eyes and patients with extreme gene combinations. For instance, where the eye-tissue has the risk alleles at chromosome 1 but none of the risk alleles at chromosome 10, we have termed this ‘chromosome 1-directed AMD’ and visa-versa. This has enabled us to determine specific clinical, biological and disease features of AMD that are driven by each of these genes.

**Figure 1:** Evidence of individual genes on chromosome 1 and chromosome 10 suggest that AMD is not a single disease but at least two distinct biological diseases

<table>
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<th>Chromosome 1</th>
<th>Gene for complement factor</th>
<th>Risk associated with AMD</th>
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<td>CFH</td>
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<th>Chromosome 10</th>
<th>Gene for complement factor</th>
<th>Risk associated with AMD</th>
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<td>ARMS / HTRA1</td>
<td>40%</td>
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Data collected from this approach over the past five years suggest that AMD is not a single disease but at least two distinct biological diseases that exhibit significant overlap within the population. For example, individuals with chromosome 1-directed AMD are often characterised by the development of large, soft macular drusen in contrast to patients with chromosome 10-driven AMD, who typically do not manifest numerous large drusen. Moreover, differences in vascular density,
retinal thickness, location of neovascular disease-associated fluid and retinal function have also been identified and linked to either chromosome 1 or chromosome 10. Moreover, chromosome 1 and chromosome 10-directed AMD are characterised by marked differences in the tissues of the eye, gene expression, biomarkers, and other diseases. Microscopic tissue alterations in the Bruch’s membrane layer and ‘spheres’ with the cells of the retinal pigmented epithelium layer of the retina are both characteristics of eyes in chromosome 1-driven AMD, whereas chromosome 10-driven AMD is characterised by a loss of capillaries in the choroid layer of the eye.

Data collected from the 7,000 pairs of donated human eyes and more than 10,000 patients are helping us to elucidate ocular and systemic mechanisms and pathways underlying genetic risk at chromosomes 1 and 10. The potential implications of this approach with respect to the future of AMD diagnosis, drug development, and clinical trial design are substantial.

Come and meet us at the Macular Society Roadshows

14 April Southampton | 11 May Hull | 7 June Belfast
28 June Glasgow | 6 July Birmingham

We are holding a series of informative events across the country, which will include a low vision exhibition and talks from leading specialists on the latest on research and treatment for macular disease.

Tickets: £15, includes light lunch. Book now to secure your place – call 01264 350 551 or www.macularsociety.org/roadshows
Is now the time to introduce genetic testing for inherited sight-loss?

Dr Giuliana Silvestri, Consultant Ophthalmic Surgeon, Royal Victoria Hospital and Honorary Senior Lecturer, Queen’s University Belfast

There are many different inherited conditions of the retina that collectively are known as inherited retinal dystrophies. Retinitis Pigmentosa (RP) is a dystrophy that affects 1 in 4,000 people from a young age with a progressive loss of function of the light sensitive photoreceptor cells (rods and cones) and the supporting retinal pigment epithelium (RPE) cells.

In RP the first things that are noticed are difficulties with night vision and peripheral vision. Later the macula of the retina is affected and central vision loss occurs. Sometimes central vision loss can occur first. The age at which symptoms start varies and the rate of deterioration is generally very slow with changes occurring over years rather than months.

As our knowledge has grown and new genes have been identified, genetic testing has become more available for patients. This enables the diagnosis to be more precise and means patients can be told the gene mutation that identifies their specific form of RP. However, RP is extremely genetically diverse in character: there are currently over 260 identified genes and mutations (spelling mistakes in the genetic code). This is believed to represent only 60% of the genes thought to be involved in the disease even though progress in mapping retinal disease genes has been significant over the past 25 years (Graph 1).
In a recent study, a group of 82 RP patients and other family members were recruited at the Department of Ophthalmology and Centre for Experimental Medicine, Belfast. All patients had a detailed clinical history taken and underwent a full ophthalmic examination and testing. Retinitis pigmentosa was diagnosed on the basis of sight tests, physical features and measurements of the retina typical for the disease. Available additional family members, both affected and unaffected, were also recruited. Patient blood samples were sent for gene sequencing and molecular diagnosis at Baylor College of Medicine, Houston, USA.

Out of the 82 families in the study, 36 had two or more RP affected familial members, while the remaining 46 had only one affected member: these are simplex cases which means that the person is the only affected member in the family. DNA from one affected member of each family was selected and sequenced.

In the results for the 46 simplex RP cases 28 individuals were able to be identified with specific mutations as the genetic cause of the disease. 41 different mutations were identified, 21 were previously known while 20 were new to RP. Out of 36

Graph 1. Mapped and identified retinal disease genes 1980 - 2014

Reference: Retinal information network    https://sph.uth.edu/retnet
Genetics

Single family member affected with Retinitis Pigmentosa - simplex cases

28 simplex cases identified by specific mutations

Diagram 2

Total of 41 mutations identified.

Among the 21 solved familial cases three different patterns of inheritance (arRP, adRP and xlRP) were identified for the mutations. Because of this diversity of RP genetics, accurate molecular diagnosis is necessary for effective patient counselling as it can provide information about the likely future course and outcome of the disease. Genotyping is important not just for diagnostic reasons but because it is important to patients who want the answers to questions such as: “When will I go blind?” or “Should my daughter be concerned about having children?” The detail has meant a great deal for some of these patients where we have been able to determine whether or not an individual with hearing loss and RP is affected by Usher’s Syndrome, a disease of multiple features including RP and hearing loss; or where we have been able to determine if the daughter of an affected family member should undergo embryonic testing to prevent the transmission of RP. The genotyping methods have successfully identified specific mutations in 49 out of the 82 individuals. It has demonstrated that we can better define the disease and help more fully with family planning and patient management in future.

Researchers reconstruct ancient virus to improve gene therapy

In gene therapy a small virus is used as a carrier to deliver the correct version of a gene to faulty cells. In current UK retinal gene therapy trials the faulty gene in the retinal pigment epithelial cells (RPE) is replaced and then switched on to produce the missing protein. Gene therapy should require just one injection, as once the missing gene is delivered the DNA is incorporated into all the RPE cells.

In their normal environment a virus like the common cold infection must infiltrate a person undetected and transfer its genetic material into the host’s cells, where it replicates. If the host has had prior exposure to the virus their body will recognise and attempt to destroy it. Current gene therapy makes use of adapted adenoviruses, which are related to common cold viruses, and referred to as adeno-associated virus (AAV). Engineering such a virus to carry the extra genetic material and remain unrecognisable to the host does present difficulties. Altering one part of the virus to achieve a benefit, such as more efficient gene transfer or reduced recognition by host immune cells, can destroy the virus’ structural integrity.

To overcome this, Professor Luk H. Vandenberghe and his colleagues at Harvard Medical School have turned to evolutionary biology. Over time, AAV ancestors have undergone changes that kept the virus structure while altering some of its functions. Researchers have created an evolutionary timeline of changes and produced synthetic ancestor viruses. The reconstructed ancient virus appears to be highly effective at delivering gene therapies to the retina. Researchers believe this form of virus will be important in developing future gene therapies.

International consortium analyses data from 43,000 people to identify new genetic factors associated with AMD

An international study, involving researchers at the University of Southampton and Southampton General Hospital, has significantly expanded the number of genetic factors known to play a role in age-related macular degeneration (AMD). Professor Andrew Lotery, who led the Southampton contribution, hopes the findings may help improve the understanding of the biological processes that lead to AMD.

Professor Lotery said: ‘This is a landmark study which has identified 34 genes which when faulty increase your risk of developing this devastating disease. Identifying these genes is the key to understanding what causes AMD. As a result this could open new doors to finding more efficient ways of treating this very common disease’.

The researchers have now discovered a total of 52 genetic variations that are associated with AMD, 16 of which had not been previously associated with AMD. The study findings add to the knowledge of two particular genes, CFH and TIMP3, which had each previously been linked to AMD. CFH was the very first disease-linked gene to be found through a genome-wide association study. TIMP3 had earlier been linked to Sorsby’s dystrophy, a rare disease that is similar to AMD clinically, but that tends to affect people before the age of 45.

For the first time the researchers also identified a variation specific to ‘wet’ AMD, which may point to
reasons why injection treatment for this form of AMD is effective for some people but not everyone.

The International AMD Genomics Consortium, involving 26 centres worldwide, including Southampton, collected and analysed the genetic data from 43,566 people of predominantly European ancestry. They aimed to identify common and rare variations in genetic coding associated with AMD.

Common variations generally have an indirect association with a disease. Rare variations, by contrast, are more likely to alter protein expression or function and therefore have a direct or causal association with a disease. Rare variations were defined as those found in less than one per cent of the study population.

The study included about 23,000 participants with AMD and 20,000 without it, of which the Southampton team contributed more than 1,000 samples.

The researchers analysed DNA samples from both groups, surveying most of the genome, but also focusing on distinct loci already known or suspected to be associated with AMD. They compared the participants’ DNA to a reference dataset called the 1000 Genomes Project, yielding more than 12 million genetic variants of potential interest. Finally, they went back to the participants’ DNA samples, looking at all 12 million variants, to see if any were found more or less often in people with AMD than those without it.

Source: Insights into Rare and Common Genetic Variation from a Large Study of Age-Related Macular Degeneration, Nature Genetics, 2015. DOI:10.1038/ng.3448
Stem cell science is now in its third decade of discovery. Creating a means to replace the ageing cells of the retina is an attractive proposition as a long term treatment for a degenerative condition like AMD. Embryonic stem cells (hESC) are derived from egg cells that have been fertilised in vitro using tissue donated for research purposes with the informed consent of the donor.

Over the years, scientists have established methods to create and control the differentiation of stem cells into specific cell types such as the specialised cells of the retina.
Glossary

**Differentiation** – The differentiation of cells refers to their development into specific cell types such as muscle, liver or a particular cell layer in the retina.

Nowadays it is possible to manage the differentiation of stem cells by changing the chemical composition of the culture medium, altering the surface of the culture dish, or by modifying the cells by inserting specific genes. Through years of experimentation, scientists have established these basic protocols or recipes for directing the differentiation of stem cells into particular cell types.

**Embryonic stem cells (hESC)** – are derived from eggs that have been fertilized in vitro from tissue donated for research purposes with the informed consent of the donors.

**Pluripotent stem cells (iPSC)** – It is now possible to reprogram adult skin cells to become like embryonic stem cells and then reprogramme these cells to become specialised cells. Using a source of stem cells from an individual reduces the risk of rejection if these cells are used for tissue transplantation in the retina.

**Retina** – 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.
In a pioneering trial at Moorfields Hospital, London, the first participants have been treated with an implant of retinal pigment epithelial (RPE) cells derived from stem cells. The London Project to Cure Blindness has been working for nine years to develop the stem cell line and gain regulatory approval of this treatment for macular degeneration.

Professor Pete Coffey, who led the team that developed the cell patch at UCL Institute of Ophthalmology, says: ‘Getting the first patient was the moment of greatest breakthrough. The process, the science and the manufacturing has been a series of hurdles, but we knew that the process would work: we knew the patches would work and that with the right surgical tool we could deliver it into the correct part of the eye. All this felt achievable but having an actual patient, that has been the biggest step into the unknown.’

For this trial a bank of human embryonic stem cells (hESC) was produced. Using this an RPE cell line for the implant has been derived in partnership with Pfizer Ltd. As pharmaceutical experts in managing the Good Manufacturing Practices (GMP) required by the UK and USA medicine and drug control agencies, they ensure that the implants are of the highest quality and do not pose a risk to the patient.

The phase 1/2a trial tests for safety and looks at how well the 3mm x 6mm implant of a single layer of RPE cells works. The presence of an implant offers a uniquely practical means of assessing the results. Once the surgery is complete the researchers can observe the
patch of RPE cells and determine their viability in each patient. Using the imaging techniques of fluorescein angiography, scanning laser ophthalmoscopy and optical coherence tomography they are able to examine the patient’s eye and answer questions like, do the cells stay on the patch? Do they survive or are they attacked by the immune system?

Up to ten patients will be involved in this trial. Now the research team are wanting to publish the results on the first group of these patients.

Co-leader of the project, retinal surgeon **Professor Lyndon Da Cruz**, who carried out the operation, said ‘There is real potential that people with wet AMD will benefit in the future from transplantation of these cells.’

For the next trial, the research team have approval to use induced pluripotent stem cells – stem cells derived from human skin cells.
Bestrophinopathies is the broad term used to describe a group of conditions that arise as a consequence of mutations in the Bestrophin1 (Best1) gene. These conditions can be broadly divided into four main categories: Bests vitelliform macular dystrophy or Bests disease, Autosomal Recessive Bestrophinopathy, Autosomal Dominant Vitreoretinochoroidopathy and Retinitis Pigmentosa.

The Best1 gene is found exclusively in the retinal pigment epithelium (RPE) of the eye, a single cell layer found between the retina and the choroid. The RPE performs a number of key functions necessary to maintain sight, namely 1) regenerating the visual pigments required for vision 2) clearing up the debris shed daily by the photoreceptor cells of the retina 3) supporting and maintaining the retina by supplying nutrients and controlling the flow of ions to the retina 4) absorbing stray light and 5) secreting a variety of growth factors and molecules.

The RPE is a heavily pigmented and highly regular layer of uniform cells with distinct plasma membranes on each side of a cell. The RPE is not an intrinsic component of the light-sensing pathway in the eye; however, abnormalities in cell function, such as those caused by mutations in the Best1 gene, can result in sight loss.
Our project uses induced pluripotent stem cells (iPSCs) to gain a better understanding of the role Best1 plays in an RPE cell. iPSCs are adult cells that have been genetically reprogrammed to behave like stem cells, that is, they have the ability to turn into any cell of the body. By taking a skin sample from a patient diagnosed with a bestrophinopathy, we are able to reprogram their cells to become iPSCs. We can then use these cells to create RPE, effectively creating an endless supply of diseased patient cells that we can study in a dish.

We have been fortunate to obtain skin cells from a number of volunteer patients carrying a range of Best1 mutations, which will allow us to examine different aspects of Best1’s role in maintaining healthy vision. For example, we are currently studying a patient with a premature stop mutation, a metaphorical early full stop in the genetic code of Best1. This mutation results in a ‘null phenotype”, where no functional Best1 protein is made in the RPE cell. Comparing the behaviour of these patient RPE cells to control RPE cells that do express the Best1 protein will allow us to identify just what the role of Bestrophin1 is in the RPE cell.

Other mutations we are studying appear to result in the protein being mis-located within the cell; Bestrophin1 can normally be found along the side and base of RPE cells in the basolateral membrane.

In the first year of the project we have generated stem cells from a number of patients and these, in turn, have been differentiated into RPE using techniques developed by our research group. We have begun to characterise the effects of Best1 mutations at the molecular and cellular...
level in diseased patient RPE cells that have been reprogrammed from their skin cells.

The next stage of the project will focus on physiological testing to identify the function of Best1. Recent studies examining the structure of Best1 have suggested that it functions as an ion channel, controlling ion transport across, and regulating the electrical activity, of the RPE cell. We will examine the electrical activity of the patient-derived RPE in comparison with control samples. The data gathered will not only allow us to reveal the function of Best1 but will suggest the most appropriate avenues to explore regarding potential future therapeutic drugs.

The ultimate aim of the project is to investigate and test prospective therapeutics on the patient-derived RPE cells. The patient-derived RPE provides us with an excellent technical tool for use in the laboratory and also enables us to work towards the ethical goal of reducing the use of animals in medical research.

Dr David Carter
Investigating how light can improve the quality and function of human retinal pigment cells prior to transplantation

Dr Anthony Vugler, Lead researcher, UCL Institute of Ophthalmology

In the development of stem cells for transplant into the eye we have to develop reliable methods of growing high quality cells in the laboratory in a system that can be routinely repeated. Our work is investigating the use of light as a tool to enhance the development of the human retinal pigment epithelium (RPE) cells from stem cells, prior to their use as transplant tissue in the retina. Does a particular wavelength of light help the RPE cells to grow?

To achieve this we need to have a reliable method of measuring how well these RPE cells function; this has meant developing a suitable animal model where we can examine and quantify how well the RPE cells work when transplanted into a retina.

With this aim, Aisling Lynch, our Macular Society funded PhD student has established two particular families of mice where the RPE cells do not function adequately: we refer to these as our mouse models. In the first model we rely on a genetic mutation in the mouse that stops the animal’s own RPE cells from performing the visual cycle (a vital function of the RPE), while in the second model a drug treatment causes the mouse RPE cells to die off in a way similar to the death of human RPE cells in dry age-related macular degeneration.

Aisling has assembled a new incubator in our laboratory specifically designed to allow the delivery of light stimuli to
Stem cells

human stem cell cultures. In order to control for the effects of light on RPE cell differentiation, she also had to design and make some new tissue culture equipment. This setup now has a new computer-controlled light source that is capable of delivering a broad range of wavelengths and light intensities, either as discrete pulses of light or as light/dark cycles. This is the first incubator of its kind and is an exciting research tool. Aisling has now exposed human RPE cells to various schedules of illumination and is optimising the procedure to maximise the development of the RPE cells.

We have been successful in developing a method of cell culture that enhances the levels of an important enzyme, RPE65, in the human RPE cells: RPE65 is a key enzyme in the visual cycle. This fundamental research has uncovered a previously unappreciated aspect of RPE cell function and we are now utilising this new discovery in our human RPE transplant work. We have also made significant progress in the use of our mouse models and have established that it is necessary to eliminate the host RPE cells in order for transplanted human RPE cells to survive in the sub-retinal space of mice.

During 2016, Aisling will be assessing how well human RPE cells exposed to light will function in our chosen mouse models where the native RPE is degenerate and no longer works. The aim here will be to establish if the increased levels of the enzyme RPE65 we see in
the RPE cells in the laboratory are maintained following transplantation of these human RPE cells into the sub-retinal space of the mice with degenerate RPE. Our second line of enquiry is to ask, does the transplant of the RPE cells correlate with an enhanced cell activity and visual function in the mouse?

During the early part of 2015, Aisling’s work was selected for a talk at the prestigious annual Association for Research in Vision and Ophthalmology meeting in America. We anticipate that Aisling will be in a position to begin to publish research papers during 2016. We are also aiming to present more of her data at conferences, prior to the completion of her PhD.

Get set to fundraise!

If you’re keen to fundraise for us and enjoy a challenge, why not apply for a charity place in one of these exciting events in 2016?

• Edinburgh Marathon Festival all events 28 & 29 May
• Trekfest The Beacons (25, 50, 75 or 100k) 4 & 5 June
• British 10k London Run 10 July
• RideLondon–Surrey 100 cycle ride 31 July
• Trekfest The Peaks (25, 50, 75 or 100k) 3 & 4 September
• Great North Run (13.1 miles) 11 September
• Scottish Half Marathon 18 September
• Bournemouth Marathon Festival all events 1 & 2 October
• Royal Parks Foundation Half Marathon 9 October
• The Big Fun Run series of 5k Runs various dates/venues

New for 2016, limited places available!
Serpentine 1 mile Swim – 24 September

For further details or to apply for a place, please call Kathy King on 01264 321 964 or email kathy.k@macularsociety.org
Proteins are synthesized and regulated depending upon the functional need in each cell of the body. In the cell, RNA (ribonucleic acid) has the principal role of acting as a messenger carrying instructions from the DNA to control the synthesis of proteins. Protein expression refers to the way in which proteins are made, modified and regulated in living cells.

In the eye, the chain of biochemical reactions that first convert light into electrical signals in the retina and then regenerate the visual pigment following exposure to light is known as the visual cycle.
Blocking a particular protein with a monoclonal antibody may offer a new method of treatment for wet AMD

Professor Stephen Moss, Norman Ashton Chair of Biomedical Research, Institute of Ophthalmology, UCL London

The major interest of our laboratory is age-related macular degeneration (AMD), with a specific focus on trying to understand at a cellular level, the fundamental changes that take place in the retina during the course of the disease. The discovery around a decade ago that certain genes, that control a part of the immune system, have an indirect role in the development of AMD has opened the door to a new field of study for the eye.

Our experiments typically involve growing in culture the specialised cells of the retinal pigment epithelium (RPE): the layer of cells beneath the photoreceptors that deliver nutrients and remove waste from the retina. Investigating how these cells respond to the kind of stresses that they meet in the eye under AMD is a major area of our interest. However, it remains largely unknown why it is that in AMD certain proteins involved in the immune system cause the RPE cells to cease working properly and in some instances die. What we have discovered is that normal healthy RPE cells are able to deal with attack from the innate immune system very effectively, by capturing potentially harmful proteins and then destroying them in specialised compartments within the cells.

What we now want to know is why the RPE cells in AMD patients are less able to overcome the harmful effects of attack by the innate immune system.
system. To answer this question our plan is to use cells isolated from patients with AMD and then through the processes developed in stem cell technology to convert those cells in culture into RPE cells. We can then investigate how these RPE cells respond when exposed to the same conditions that cause the cells to malfunction in AMD.

Although these studies are particularly relevant to dry AMD, we also have a long-standing interest in wet AMD, in which risk of the disease is controlled by the same set of immune system genes. However, in wet AMD the disease takes on a different form, in that new blood vessels develop in the choroid layer of the retina, and grow through the RPE cells, and into the retina where they leak and cause irreversible damage to the photoreceptors. The damage is especially significant in the macula due to the enrichment of cones at this site, and the critical importance of the macula for vision. For some years wet AMD has been treated with drugs that inhibit growth of new blood vessels – the anti-vascular endothelial growth factor (VEGF) drugs. However, not all patients respond to anti-VEGF treatment and for some patients its effectiveness lessens over time. There is therefore an urgent need to identify new molecular targets that may be developed for the treatment of wet AMD. To address this challenge, our group together with the group of Professor John Greenwood at the Institute of Ophthalmology, undertook a search for novel genes involved in the abnormal growth of blood vessels: a process known as angiogenesis.

This investigation led us to the discovery of a protein of unknown function called LRG1 that we showed through a series of cellular studies to be a potent stimulator of angiogenesis. Furthermore we showed that this protein works by a completely different mechanism to VEGF: it stimulates tissue the growth factor β (TGFβ) to activate angiogenesis. It has been known for many years that TGFβ has the potential to drive abnormal blood
vessel growth, but because it has so many useful housekeeping functions in the eye (and almost everywhere else in the body) it is more or less impossible to target therapeutically itself. However, we showed that by blocking the protein LRG1 we can deactivate this pathway, which has the critical advantage of leaving the beneficial activities of TGFβ unchanged.

We considered that LRG1 could be a good or even better target then VEGF in the treatment of wet AMD, and that inhibiting LRG1 could work well in combination with VEGF blocking. We therefore embarked on the lengthy process of developing a monoclonal antibody that would block the function of the protein LRG1 with a view to eventually testing this antibody in patients.

The work to develop the antibody was completed in 2015, and funding of almost £6 million was recently awarded by the MRC to take the antibody into an early stage trial in patients with wet AMD. The LABINA trial will be conducted at Moorfields Eye Hospital with our clinical colleagues Adnan Tufail and James Bainbridge, and support from the UCL Comprehensive Clinical Trials Unit, and the UCL Translational Research Office.

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**Do you have dry age-related macular degeneration?**

**Would you like to participate in a research study?**

City University London is inviting people with dry age-related macular degeneration to participate in a study investigating the effects of the condition on their ability to carry out daily tasks.

Volunteers will need to visit London for a day but your travel expenses will be paid. If you are willing to perform some computer-based tasks and be interviewed, please telephone us for more information.

Deanna Taylor 0207 040 3226
RNA compound aims to prevent retinal scarring in wet AMD

The biotechnology company RXi Pharmaceuticals Corporation has announced a clinical study to evaluate the safety and clinical activity of RXI-109, an RNA compound that aims to prevent the progression of retinal scarring in participants with ‘wet’ age-related macular degeneration (AMD).

‘Currently, there is no effective way to prevent the formation or progression of retinal scars that may occur as a consequence of several devastating ocular diseases. In wet AMD, our first area of study, retinal scarring can result in continued vision loss,’ said Dr. Pamela Pavco, Chief Development Officer of RXi Pharmaceuticals.

RNA interference is a biological process in which molecules of RNA prevent a particular gene from being active and so stop the manufacture of a particular protein. RXI-109 is an RNA interference compound developed to target the control of connective tissue growth protein, a key regulator of scar formation and known to be involved in retinal scarring.

In this Phase 1/2 trial, each participant will receive a total of four doses of RXI-109 at one-month intervals. RXI-109 will be administered by intravitreal injection in one eye only.

The 3 month period of dosing will be followed by a 4-month observation period. The safety and tolerability of RXI-109, as well as the potential for clinical activity, will be evaluated over the course of the study using numerous assessments to monitor eye health and visual acuity. The ultimate goal is to reduce the scarring that is secondary to advanced wet AMD and in doing so, preserve vision for a longer period of time.

Source: www.rxipharma.com
There is increasing evidence to support the view that the time it takes for a person’s eyes to adjust to darkness after being exposed to a bright light is a good indicator of that individual developing age-related macular degeneration (AMD). Adults whose eyes are slow to adjust to the dark have a greater risk of developing AMD. The eye uses photoreceptor cells of rods and cones to convert light into a visual signal in the brain. The rods contribute to low light vision and night vision more so than cones.

In the late 1990s, with my colleague Greg Jackson, PhD, at the University of Alabama at Birmingham (UAB), we discussed the possibility that dark adaptation might play a role in AMD. We had noted that many patients with AMD, and also some older adults in normal macular health, complained of poor night vision.

Greg Jackson built a prototype machine to measure dark adaptation (DA). DA refers to the time it takes for a person’s eyes to adjust to darkness after being exposed to bright light. The device exposes a subject’s eye to a flash of bright light in an otherwise completely dark environment, a process known as bleaching. The length of time that passes before the patient detects a series of visual cues is measured to determine DA. From this initial concept to securing funding, arranging licensing of
In a recent study we recruited participants aged 60 years and above from ophthalmology clinics. Eligibility required both eyes to have a healthy macula with no degeneration.

Participants made a first visit for a baseline measurement of their DA in one eye using the commercially available MacuLogix AdaptDx®, a computerised dark adaptometer that delivers a bright light, a photobleach and measures the time of recovery of the rods. An abnormal speed of DA was defined as a rod-intercept value of more than 12.3 minutes. Demographic characteristics, visual acuity, and smoking status were also assessed for each participant.

Both baseline and follow-up visits were completed by 325 individuals who had an average age of 68 years. At baseline, 263 participants had normal DA with an average of 9.1 minutes and 62 participants had an abnormal DA with an average rod-intercept of 15.1 minutes. After adjustment for age and smoking, those with the abnormal DA recovery time in the tested eye at baseline were approximately twice as likely to have early AMD in that eye by the time of the follow-up visit three years later, compared with those who had normal DA at baseline.

Dark adaptation has a strong biological plausibility in terms of retinal aging and the development of AMD. Our work suggests that rod-mediated DA may be a useful method of assessment for identifying persons who have higher risk of developing AMD. However, the results do not suggest that the DA protocol we have used is a suitable screening test for early AMD as it does not, identify with a high enough sensitivity, patients who will develop AMD. Nor does it rule out with enough sensitivity all those who will not develop AMD.

Information to help those with macular disease

Macular Society is committed to supporting those with macular disease through the provision of information and support services.

Our range of patient information is available online or from our helpline.

Professionals can order free patient information for patients and carers. Order online at www.macularsociety.org/order-patient-information Download in pdf or audio at www.macularsociety.org/resources

‘The hallucinations were really frightening’

Alice Sadler began experiencing Charles Bonnet Syndrome hallucinations soon after her AMD became advanced. She was terrified by them and began to worry about her mental health.

‘Right from my first counselling session I experienced such a sense of relief. I had someone to actually listen to what I had been going through. Here was someone who knew about Charles Bonnet Syndrome and could talk to me about it.’

Our telephone counselling service is free to anyone who needs advice or 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 qualified counsellors through the Macular Society’s helpline: 0300 3030 111 help@macularsociety.org
Treatments and trials

The eye has two primary light-sensing cells, the photoreceptors in the retina. Cones, which are concentrated in the macula area, process colour vision under daylight (photopic light levels). The Rods detect movement in the peripheral vision and are predominant in darkness (scotopic conditions).
Over the past few years there have been major advances in our understanding of the causes of age-related macular degeneration (AMD). As the name of the condition implies, the older an individual gets the more likely they are to be affected by AMD. Lifestyle factors have been identified that increase risk and the most important one is smoking. However, it is now clear that the biggest risk factors are genetic.

Whilst we have treatments that limit damage in wet AMD, we do not yet have treatments for dry AMD. The best form of treatment would of course be to prevent people getting these advanced forms of AMD that cause visual loss, but we do not yet have any effective preventative treatments other than modifying lifestyle. In order to develop new treatments we need to understand more about the condition.

The recent advances in AMD genetics have identified the main genetic variants that alter AMD risk. The affected genes are codes for the production of protein, and it is the alterations in the proteins and the consequences of these for the eye that we need to understand in order to develop new treatments. So there is much more we need to learn about what happens to the eye in AMD at a biochemical and cellular level. In order to study the eye itself there are two possible approaches; one is to use...
animal models and the other is to study human eye tissue. Unfortunately, whilst animal studies do provide some information, there are no good animal models of AMD. Therefore we need to study human macular tissue to learn more about AMD. This presents its own challenges as the only way to do this is to study post mortem eyes.

With a grant from the Macular Society we have been able to take this approach forward. Central to our work is access to donor eye tissue from Manchester Eye Bank, one of two national eye banks in the country. When people generously donate their eyes after life, the primary purpose is to donate their corneas, the transparent windows of their eyes, for transplantation. These donated corneas are transplanted into patients who cannot see because of corneal clouding and this is a very effective treatment. In addition, people will often donate the rest of their eyes for research and this allows us to collect the macular tissue for future research. When we obtain the eye tissue we often do not know whether the donor had AMD or not, so we collect and process as many samples as we can on the basis that a proportion will have had AMD, or have been at risk of AMD.

One of the attractions of this approach is that we can analyse DNA from the eye tissue and identify macular tissue from donors who had a high risk of developing AMD, but had not actually developed visual problems. Our belief is that by studying the eyes at an early stage we will be able to find biochemical triggers for the condition that would
represent good targets for the development of new drugs to prevent or treat AMD.

Our stated aim is to collect and store macular eye tissue from 1,000 donors during this 3 year project. We started in January 2015 and in the first 12 months have collected tissue from over 400 donors, so we are well ahead of schedule. This archive will provide an invaluable resource, not only for our own research, but also for other researchers who share our view that one of the best ways to develop new treatments for AMD is to study macular tissue.

To this end we have recently applied for ethical permission to have the archive, which we call ‘The Manchester Eye Tissue Repository’, designated as a Research Tissue Bank. This will enable us to distribute tissue samples to other investigators: we have already had several requests for tissue. Once we have approval we plan to start sending out donor tissue to other researchers in the first half of 2016.
Anti-PIGF treatment may offer therapeutic pathway for dry AMD

Researchers at Gifu Pharmaceutical University, Japan have identified a potential target for future therapies to slow dry AMD progression. The research examines the effect of placental growth factor (PIGF) protein on dry AMD. PIGF has been implicated in wet AMD progression. ‘Currently, blocking PIGF in wet AMD has a therapeutic effect,’ says Hideaki Hara, PhD. The researchers thought the opposite effect was true for dry AMD.

Exposure of retina cells to intense light can age cells and in the laboratory will produce a condition like dry AMD. The Japanese team had previously shown that injecting PIGF into mice retinal cells reduced light-induced damage, but this latest study contradicts this. The researchers were surprised to learn that PIGF made the retinal damage and thinning of the retina worse. Dr Hara said, ‘Instead, PIGF aggravated the degeneration.’

Therefore, they decided to inject the mice with anti-PIGF before light exposure and subsequently discovered that the breakdown of the retinal pigmented epithelium was suppressed. The antibody to PIGF seems to protect the retinal cells from damage.

Wet AMD treatment aflibercept (Eylea®) already acts as an anti-PIGF antibody. Hara and his team ‘think there is a very great likelihood that aflibercept shows efficacy in dry AMD.’ Using an existing drug in trials could reduce the time to determine if anti-PIGF treatment could treat dry AMD.

Can treatment for wet AMD in the ‘real world’ of the hospital clinic match the results of drug trials?

James S Talks, Consultant, Royal Victoria Hospital, Newcastle upon Tyne

The best treatments we currently have for treating wet macular degeneration involve repeat injections of an anti-VEGF drug into the eye with the hope of improving or at least stabilising the patient’s vision.

When the ‘real world’ outcomes of how well the patients’ vision responds to treatment are compared to the results of the drug’s clinical trials they are often not as good as might be expected. This is partly because trial patients tend to be a selected group but also because best results require regular monitoring and often repeat treatment which can be a problem for patients, carers and eye departments to comply with.

What is needed is a drug therapy that can be given less often or doesn’t need repeating. A potential step in that direction is the use of Eylea® (aflibercept) which in the original licensing trials was given two monthly for a year compared to the monthly treatment with Lucentis® (ranibizumab). Both drugs had the same benefits on vision implying that fewer visits are needed for the same result using Eylea®.

Our study has looked at the visual outcomes of year one patients from 16 clinical centres in the UK where the protocol of the original clinical trial, the VIEW study, was followed: an initial three monthly injections of Eylea® followed by treatment
Treatments and trials

every two months for the first year of treatment for wet macular degeneration.

In our study 1,840 eyes from 1,682 patients were given an average number of 7 injections over one year. The average starting visual acuity was 53.7 rising to 58.8 letters, a +5.1 letter gain. The proportion of patients with 70 letters or more, which is 6/12 vision and about driving standard, improved from 16.4% at baseline to 33.7% at one year. In the VIEW studies the proportion of patients seeing 70 letters or over at one year was 32.6%.

Patients treated outside clinical trials, in the ‘real world’, tend to have a wider range of retinal pathology and visual acuity is not measured with the same degree of accuracy as that in trials. However, by having large patient numbers we do think this study gives a reasonable measure of how well this treatment regime is performing in practice. Our results show that a two monthly treatment strategy after the initial three monthly doses produces reasonable visual acuity outcomes which are similar to that seen in clinical trials and better than previous ‘real world’ data collections have shown.

A collection of data of this kind is made possible with the use of electronic patient records which are increasingly being used in hospital eye clinics. Plans for larger data collections from more clinics are underway as we believe such data is important to understand the benefit and in part to justify the expense of the treatment. It may also be possible to use such large data sets to compare centres and hopefully make sure all centres are performing equally well.

James Talks MRCP FRCOphth is the corresponding author and Chair of the UK aflibercept users group. Co-researchers are Andrew J Lotery MD, FRCOphth; Faruque Ghanchi FRCOphth; Sobha Sivaprasad FRCOphth; Robert L Johnston FRCOphth; Nishal Patel MD, FRCOphth; Martin McKibbin FRCOphth; Clare Bailey FRCOphth; Sajjad Mahmood FRCOphth.
Treatments and trials

News release

New drug brolucizumab aims to reduce the frequency of treatment for wet AMD

One of the key considerations in the research of new treatments for wet age-related macular degeneration (AMD) is reducing the burden of treatment on patients by offering longer acting drugs to reduce the number of clinic visits needed. Brolucizumab is a new monoclonal antibody drug that offers the hope of reducing treatment frequency for wet AMD. With a significantly smaller molecule size than the currently available anti-VEGF drugs, half the size of Lucentis® (ranibizumab), it is thought to offer better penetration of the target retinal tissues.

In a Phase 2 study patients treated every three months with a single injection of brolucizumab produced results that indicated it may have more potent effects than a single dose of Eylea® (aflibercept). A total of 90 patients diagnosed with wet AMD participated in the trial that compared the effectiveness of brolucizumab with Eylea®; the primary measurement being how well patients could read differently sized letters on a test chart from a distance of six metres, the standard test of visual acuity using a Snellen chart.

Alcon Laboratories, the company developing brolucizumab, are now moving to a Phase 3 study and expect to recruit around 1,700 patients in more than 50 countries worldwide. Sabri Markabi, Senior Vice-President at Alcon, said ‘We have initiated our Phase 3 study program based on the encouraging results we received from the Phase 2 studies.’ UK trial sites are in development.


Euretina 15th Congress. Frank. Holz@ukb.uni-bonn.de
Eye health management

In planning any treatment or health care it is crucial to have accurate data on the number of patients and the particular form of their sight loss. The number of people in a population that is affected with a particular disease at a given time is referred to as the prevalence.

When discussing the likely number of new cases of a condition within a period of time this figure is normally expressed as the incidence of cases.
Electronically connecting community optometry to hospital ophthalmology departments: the Eyecare Integration Project in Scotland

Jacintha Gong, Specialist Registrar, Ophthalmology, Caroline Styles, Lead consultant for macular disease, Roshini Sanders, National clinical lead (Eyecare Integration), NHS Fife

Ophthalmic services throughout the UK are faced with the challenge of providing world-class, long-term sight care to facilitate an independent, enjoyable lifestyle for patients for as long as possible. Health boards are under increased pressure to reduce referral and treatment waiting times, in the hope that prompt treatment will not only be beneficial to patients, but also more economical in the long run.

The burden on hospital ophthalmology departments is undisputed. Ophthalmology care is responsible for approximately 10% of all outpatient work in secondary care. Without innovation, the system is not sustainable, as patient numbers are only predicted to increase.

The basis of improving ophthalmic services is centred on improving the efficiency of the referral system and reducing unnecessary hospital visits, by way of promoting communication between the relevant healthcare teams, optometry practices, the general practitioner (GP), and the hospital eye service. It calls for an integrative approach to eye care, ensuring that the speediest attention is reserved for those who need it most.

NHS Fife in Scotland successfully implemented the Central Ophthalmic electronic
Eye health management

Referral Unit (COeRU) between 2007-2011. Patients were electronically referred by community optometrists to the hospital using secure NHS mail, with attached digital images.

The GP, who was copied in, forwarded on the patient’s health summary using established pathways (Scottish Care Information (SCI) Gateway). Analysis of the scheme has shown that 37% of these images enabled diagnosis to be made without the patient requiring a hospital appointment. Along with the removal of a complex paper referral pathway, it has reduced waiting times from 32 to 4 weeks, and freed up resources for sight threatening conditions to be identified and treated within days.

NHS Fife’s successful record with the system led to the Scottish Government Health Department pledging £6.6 million to fund the

Examples of digital images used for electronic referral.

Image A
**Diagnosis** – Dry AMD
**Action** – Hospital review not required

Image B
**Diagnosis** – Advanced wet AMD with vision worse than 6/96
**Action** – Directed to low vision services
Eyecare Integration Project, as a nationally supported electronic link between community optometrists and hospital ophthalmology departments.

One key development has been the implementation of a unified electronic referral form that divides referable pathology into glaucoma, macular, cataract, paediatric or general ophthalmic pathology. This aids triaging and helps the referrer to include specific clinical information relevant to the subspecialty presentation.

Under the national agreement the system functions during working hours of the week, and referrals are screened within 48 hours. The referring optometrist will receive automatic feedback regarding the referral decision, which will be one of four outcomes: an urgent appointment, a routine appointment, an e-diagnosis not requiring a hospital appointment, or that further information is required from hospital notes, the GP or optometry practice.

Other advantages of an electronic system include quick and accurate funding payments to optometry services, research opportunities around the epidemiology of ocular pathology, and anonymised education and training material in digital format.

Rolling out an electronic referral system necessitates adequate computing infrastructure in community optometry practices, which can support secure connections to the NHS network over a Virtual Private Network.

Ongoing funding is required for maintenance of the electronic referral system and as the project continues to be implemented across Scotland.

This redesign of national ophthalmic services uses technology to revamp previous referral pathways to meet the challenges of future healthcare and community resources. Ophthalmic services will need to continue innovating in this way to provide vision care that is evidence-based, efficient, patient-centred and viable.
Registration for sight impairment – what is epidemiological analysis?

**Catey Bunce**, NIHR Moorfields Biomedical Research Centre and **Richard Wormald**, Consultant Ophthalmologist, Moorfields Eye Hospital

When a patient’s sight has fallen below a particular level their consultant ophthalmologist might offer registration as sight impaired (partially sighted) or severely sight impaired (blind). Registration entitles individuals to certain benefits.

A copy of each certificate is sent to the certifications office for what is called “epidemiological analysis” – but what does this involve? Epidemiology is formally defined as “the study of distribution and determinants of disease in man”. In this context it means the study of the distribution and causes of sight impairment. Information from the form (e.g. age, cause of sight impairment) is entered...
onto a secure database at the certifications office which is based at Moorfields Eye Hospital.

The system operates under the auspices of the Royal College of Ophthalmologists and all staff involved in data management have received training in the governance issues. Anonymised reports are then provided to the Welsh and England governments so that they know how many people have lost sight due to particular eye conditions each year. Anonymised information is available for England from the public health outcomes framework which can be accessed by anyone with internet access (see link below).

Studying data captured during the certification/registration process means that important facts about individuals with sight impairment can be determined and this can be fed back to those who are charged with providing support to people with the condition. For example, less than 5% of certifications for age-related macular degeneration are for people aged less than 70.

The average age at certification was 86 years. If those who provide support for sight impaired people know this, they can ensure that the services provided to those with sight loss are tailored accordingly.

The number of blind people has been captured in one form or another since 1853. The only way we know the prevalence of a particular eye condition is by examining the certification data. When forms are sent to the certifications office, professionals are providing information that is of use in the planning and care for people with sight loss.

We would like to thank those professionals who help in this way and the NIHR Moorfields Biomedical Research Centre Patient and Public Involvement Team.

Public Health data: www.phoutcomes.info/search/sight%20loss

Eye health management
Eye health management

An audit of certification forms for severely sight impaired and sight impaired in Northern Ireland for 2014

A J Jackson, J Lindsay, T Moutray, Royal Victoria Hospital, Belfast Health and Social Care Trust

In Northern Ireland we are looking at ways to modernise the process of certification of sight impairment. In England and Wales the original Blind and Partially Sighted Registration Form (BD8) was replaced by a series of new forms, including the Certificate of Vision Impairment (CVI) form in 2003: in Northern Ireland the equivalent (A655) was not replaced until 2007.

The Departmental guidance concerning eligibility for certification, as either Severely Sight Impaired (SSI) or Sight Impaired (SI), are however identical to guidance linked to the certification process in England and Wales. Here we report on the results of an audit of CVI submitted in Northern Ireland during 2014.

We analysed a total of 334 certification returns: 185 of which were for SSI; 141 were for SI; 8 were unspecified. Of the total number of individuals certified, 200 were female, 132 male and 2 were unspecified. The average age of those certified was 72.2 years (Females – Mean 74.4, Median 81, Range 3 to 102 years) (Males - Mean 78.1, Median 70, Range 4 to 96 years).

The distribution of Visual Acuities of those certified differed according to certification category. In both the SSI and SI categories those with better acuities were most likely to have been certified as a result of limitations to their peripheral vision. When analysed according to the underlying cause of vision impairment, AMD accounted for
approximately 55% of registrations in both the SSI and SI categories. The second and third major causes of vision impairment in both groups were glaucoma and diabetic eye disease respectively.

In comparison to currently available UK data, further analysis of the Northern Ireland data would tend to indicate that there is a greater tendency to certify younger, as opposed to older visually impaired individuals in Northern Ireland.

While trends relating to visual acuity and underlying cause are similar to those reported from the UK as a whole, the incidence of newly identified vision impairment, by certification alone, is considerably lower in Northern Ireland. For 2014, the incidence of certification in Northern Ireland was 0.018%, compared to 0.058% in England.

However this audit does not reflect the true incidence or prevalence rates in Northern Ireland but rather a snapshot of ocular conditions affecting the population. It provides a basis for more rigorous mechanisms to be put in place to accurately record population-based visual impairment statistics in NI.
How many people will be affected by AMD in 2050?

Dr Alicja R Rudnicka, Professor Christopher G Owen, Population Health Research Institute, St George’s, University of London

Our previous work published in 2012 estimated that there were 513,000 people with late stage age-related macular degeneration (AMD) in the UK; where late stage refers to people with an identified loss of vision.

This figure includes 276,000 cases of the dry form known as geographic atrophy (GA) and 263,000 cases of the wet form, neovascular AMD (nvAMD). Because an individual person may have the dry form in one eye and wet in the other there will be an apparent discrepancy in the total figure.

The work also suggested that the number of late stage AMD cases might increase to 679,000 by 2020. These estimates were based on prevalence estimates obtained from a systematic review and analysis of several studies, carried out among populations of people of European ancestry. Using the yearly UK population data from 2007-2009, it was also possible to estimate incidence, which suggested that there were 71,000 new cases of late AMD in the UK per year.

For the number of cases in 2015, we estimate that there were 588,000 cases of late AMD, where this comprised 323,000 cases of GA and 309,000 cases of nvAMD. The number of people
with late AMD we now estimate will increase to 645,000 in 2020. By 2050 we estimate there will be almost 1.3 million people with late stage AMD (where this consists of 720,000 with GA and 683,000 with nvAMD).

For the number of incident cases, we estimate that there were 80,000 new cases of late AMD in 2015. The corresponding number of new cases per year for 2020 being 83,000, and 157,000 for 2050.

These estimates assume that there are no changes in the underlying prevalence and incidence rate of AMD overtime, i.e. the same prevalence and incidence rates have been applied to all years and weighted by predicted population changes for males and females combined. It assumes that the risk factors for AMD remain the same and no cure is forthcoming.

These estimates are based on 5 year population data (for males and females combined) and not the yearly data as used previously.

While these figures are likely to be less accurate than our earlier published estimates, our 2020 predictions are reassuringly similar. In 2012 we had estimated an increase to 679,000 late AMD cases by 2020 while our new estimate for cases of late AMD is 645,000 cases in 2020. Note, confidence limits associated with these revised estimates are not provided. An updated review and more detailed population data would be needed to limit these caveats.

Broadly these estimates suggest that we can expect a near doubling in the number of prevalent and incident cases of late AMD, GA and nvAMD from current day to 2050, based on population ageing alone.

The similarity in the number of GA cases and nvAMD cases is of particular note, with important implications for current and future health care provision.
Does a higher macular pigment density preserve vision in low light conditions in AMD?

Dr Raymond Beirne, Lecturer in Optometry, School of Biomedical Sciences, Ulster University

Individuals with moderate dry age-related macular degeneration (AMD) have an increased risk of disease progression and subsequent future vision loss. There is a need to better understand factors which may preserve visual function at this disease stage. In an ongoing study at Ulster University researchers are investigating how macular pigment (MP) level may influence visual performance in individuals with moderate AMD.

The MP is a yellow pigmented spot in the centre of the retina known as the macula. Made up of two carotenoids, lutein and zeaxanthin, the MP protects the macula from harmful blue light and in helping maintain the macula function. MP is not synthesized by the human body and is entirely of dietary origin. Lutein and zeaxanthin reach their peak concentrations in the macula, far higher than in any other tissue of the body. The thickness or the density of the MP varies by person.

There has been much interest in the potential role of the MP in AMD as the levels can be improved through a diet rich in green vegetables or by taking supplements. Lutein and zeaxanthin are included in the recommendations from the AREDS 2 study group for reducing the risk of progression for those with moderate AMD. However, we don’t know if differing MP levels of those at the moderate disease stage has a significant
This study is concentrating on how MP influences rod photoreceptor function in the retina. Rods are responsible for vision in low light levels and in the ageing process slowly die and are not replaced. Measuring how well the eye reacts to low light levels can identify the number of rod cells in the eye. Research shows that rod cells in the retina are selectively damaged in AMD, resulting in a corresponding functional loss. We are measuring a part of the rod-mediated dark adaptation using a device, the Maculogix AdaptDx. The instrument measures how quickly the eye recovers to a bright flash of light at a retinal location where rod numbers are high, and vulnerable to loss with AMD. The faster the individual recovers, the better the rod function. Assessing rod-mediated visual function with the AdaptDx has shown potential for assessing visual function in AMD patients.

Preliminary results from the 20 participants show that rod-mediated visual function is significantly reduced in individuals with moderate AMD, with rod-mediated recovery, on average, over 3 times slower than that of a healthy control group.

Individuals with moderate AMD do not have significantly different levels of macular pigment when compared to healthy individuals but just over 50% do take some form of daily supplement which may enhance MP levels. Rod function appears to be better, on average, in individuals with above average levels of MP compared to those with below average levels within the moderate AMD group. This suggests MP level does influence rod-mediated performance for patients thought to be at similar risk for disease progression based on graded eye fundus photography alone.

Recruitment for the study is ongoing and when completed will allow the relationship between rod-mediated dark adaptation speed and macular pigment optical density to be fully examined. For patients with moderate AMD the study will provide evidence as to how baseline levels of MP influence dark adaptation at this stage.
Which visual assessment best predicts the power of magnifier suitable for the AMD patient?

Professor Gary Rubin and Graham Brown
UCL Institute of Ophthalmology and Moorfields Eye Hospital

The purpose of this study was to find out which vision test would best predict the power of magnifier for patients with either wet or dry age-related macular degeneration (AMD) and treated or untreated. 173 participants were recruited from Moorfields Eye Hospital clinics. They consisted of 102 female and 71 male patients with AMD who were fluent in English, with an average age of 80.4 and no other eye problems other than mild cataract.

They undertook four routine baseline visual assessments which each present a different test of a person’s vision. These were the:

**Distance ETDRS LogMar letter chart**: equal numbers of letters on each line and a steady decrease in size.

**MARS contrast sensitivity**: near vision chart where the letters reduce in contrast whilst remaining the same size.

**MNRead**: a near vision test consisting of short sentences in everyday language of decreasing print size. It can be used to measure Critical print size which is a measure of the smallest size print where a reasonable speed of reading is still achievable. Maximum Reading Speed is the fastest speed recorded in words per minute and MNRead Acuity is the smallest size print read correctly.

**IREST** is a near vision test consisting of two different size texts (Large and Small) in everyday language, the passages are longer than MNRead.
The time taken to read the passages and any mistakes are recorded to calculate the number of correct words per minute.

The participants then had a standard NHS hospital low vision assessment of spectacles and magnifiers, with new visual aids issued if needed.

Five optometrists provided the low vision assessments and provided limited training in the use of the prescribed low vision aids. Participants’ best vision ranged from 6/12 to 3/60 (average of 6/30+2). The magnifiers dispensed ranged from 1x to 14x with an average of 5x.

The visual assessment that best predicted the power of the dispensed magnification was the MNRead acuity, correctly predicting about a third of the magnifiers issued. Also strongly predictive were the MNRead critical print size, and MNRead reading speed. There was no real practical difference between the prescribing habits of the study optometrists, or AMD type when adjusted for visual acuity.

These results agree with previous findings. They suggest that MNRead could provide a useful guide for low vision practitioners in prescribing magnifiers for AMD patients. Further research would be needed to determine whether these results would hold true with other eye conditions.
**Devices**

**Visual acuity** is a measure of a person’s central vision and reveals the ability to distinguish the detail and shape of objects. It is tested using a Snellen chart with differently sized letters that a person reads from a distance of six metres away.

**Microperimetry** is a specific form of visual measurement made to produce a sensitivity map of a person’s retina. Several different technical devices can be used to quantify how much light is perceived in different parts of the retina.
Using a low-cost portable tablet device to measure retinal sensitivity in AMD

Identifying the severity and progress of age-related macular degeneration (AMD) is particularly important since changes in a patient’s vision can go unnoticed in the early stages of the disease. It is well established that the standard measurement of visual acuity (VA) using a Snellen eye chart does not sufficiently detect the deficits in vision which occur in the early stages of the condition.

The Snellen chart with progressively smaller lines of text letters measures VA only: it does not measure peripheral vision, depth perception, colour perception or the ability to perceive contrast. Such measurements are typically performed in a clinical or research setting using microperimetry and the scanning laser ophthalmoscope to assess functional and structural changes to the retina.

Researchers at the Centre for Eye Research Australia and the Royal Victorian Eye and Ear Hospital, Melbourne, Australia have been working on a way to use a relatively inexpensive, portable tablet device such as an Apple iPad to measure patients’ retinal sensitivity without the need to visit a major eye hospital for this testing. Such relatively simple equipment could enable more frequent testing by eye care professionals or even self-testing by the patient. It could enable much earlier identification of the signs of vision-threatening complications or vision loss through macular degeneration.

The development that has made this possible is PsyPad: a customisable software system that enables the display of a library of highly specialised test images on an Apple iPad tablet device. A battery of clinical
visual function tests are presented as images: they all have a uniform dark background with a fixed level of reflectance. The images include test stimuli where circular white targets are presented as visual stimuli in a range of light intensity from a maximum to minimum level in discrete increments, Image 1.

Patients respond to the test images by entering a key stroke on the device. The critical assessment in such testing procedures is identifying the

Image 1
The test on the PsyPad platform to measure central retinal sensitivity. The location of the five test stimuli are shown. Participants respond to seeing a stimulus by pressing the grey response square at the bottom right hand corner.
threshold when the participant does or does not perceive an individual white target stimulus. To achieve this researchers use what is known as the staircase procedure: the target stimuli start out at a high light level and get reduced in small steps after each of the participant’s responses until the participant does not report seeing the target. At that point, the light level is made higher until they report seeing it again, at which point it is made lower in light level. In this way the researcher is able to zero in on the threshold at which the participant is seeing the stimuli.

Instead of being presented in ascending or descending order, the targets and light levels are presented randomly. This prevents the participant from attempting to predict the next target stimulus and therefore reduces any errors from participants guessing or learning any patterns of response.

In the study the research team compared the measurements of central retinal sensitivity using the tablet device with the established method of microperimetry. The inclusion criteria for all the participants were: being aged 50 years or older; having at least intermediate AMD in both eyes; and already participating in another research study where microperimetry testing was being carried out.

Comparing the results from the microperimetry and the PsyPad examination of each eye the results were not significantly different using the two methods.

The ability to obtain measurements on a tablet device that closely represents those obtained under controlled clinical or research settings has been established. The researchers hope that such tests can also be introduced in the future on other low-cost devices, including smartphones and computers.

Tiny electronic chip implanted at the back of the retina to replace damaged photoreceptors

Eye surgeons at Oxford’s John Radcliffe Hospital have implanted a tiny electronic chip at the back of a patient’s retina as part of ongoing NHS-funded research of the technology.

Rhian Lewis was diagnosed with retinitis pigmentosa when she was five. This disorder destroys the photoreceptors in the retina that leads to a gradual loss of vision. Completely blind in her right eye and with virtually no vision in her left eye as a result of the condition there has been no treatment available. Although this disease destroys the rods and cones that normally convert light into nerve signals, most of the retinal nerve tissue remains intact.

The wafer-thin retinal implant chip, measuring 3x3mm, is inserted into the back of the eye to replace the damaged photoreceptors in a delicate six hour operation. The implant is located behind the retina where it exactly replaces the photoreceptors that have been lost. The chip only has 1,600 pixels but the image is refreshed regularly as the eye moves. Each of these pixel cells contains a light-sensitive photodiode, an amplifier, and a 50 × 50 micrometre iridium electrode into which the electrical stimuli at the retina are guided.

The device is connected to a tiny computer that sits underneath the skin behind the ear. This is powered by a magnetic coil which is applied to the skin. From the outside this looks similar to a hearing aid. The device is switched on once everything has healed up after the surgery. The image is black and white and grainy, rather like early television pictures, but for
patients who have spent years without any sight at all this improvement can be life changing.

Rhian said: ‘The problem with having no sight is that, because you lose your mobility, you also lose your confidence. I don’t go out and about on my own. Around the house, you rely on other people to find things for you – it’s very frustrating. Now, when I locate something, like a spoon or a fork on the table, it’s pure elation. I just get so excited that I’ve got something right.’

Rhian is the first patient outside Germany to be implanted with this second generation device. Using dials on a small wireless power supply held in the hand, she can adjust the sensitivity, contrast and frequency to obtain the best possible signal for different conditions.

Professor Robert Maclaren, Nuffield Laboratory of Ophthalmology said: ‘It’s an amazing process because what Rhian and others are trying to do is reactivate a part of the brain that hasn’t been doing anything for the last 10 years or so and there is a lot of rehabilitation because basically they are learning to see again.’

A total of six patients will be taking part in this trial at the John Radcliffe Hospital.

Source: www.ox.ac.uk/news/2016-01-05-blind-woman’s-joy-she-able-read-time-thanks-bionic-eye
Macular Society is committed to supporting those with macular disease by providing information and support services. Our patient information covers topics including nutrition, diabetic macular oedema and treatments. Our services include a confidential helpline; counselling to help with the emotional impact of sight loss; and telephone befriending to help reduce feelings of loneliness.
The experiences of caregivers and recipients of support and assistance for AMD

Emily Boxell, PhD student and Clare Bradley, Professor of Health Psychology, Royal Holloway University of London.

There has been very little research looking at the experiences of people who support someone living with macular degeneration. Research carried out with carers of people with other long-term conditions such as dementia, diabetes and survivors of stroke suggests caring can have a considerable impact on the partners, relatives or friends who care for them. There are many different forms of support including emotional and practical support, information and advice.

Our initial investigation into the extent to which people with macular conditions received support related to their eye condition was undertaken in the Macular Society 2013 survey. This survey found that 845 respondents (54%) reported that someone provided unpaid care, support or assistance to them because of their macular condition. Of these, 47% reported receiving support for 7 hours or more a week. However little is known about the impact of providing this support on the carers themselves or those with macular conditions for whom they care; we designed a follow-up study to investigate this.

We asked Macular Society members who were the respondents to the Macular Society 2013 survey, to indicate their interest in participating in follow-up research. For this initial follow-up study we selected only those respondents who had age-related macular
Living with macular conditions

degeneration (AMD). After applying this inclusion criterion this left 138 members who had provided their own and their carer’s contact details.

Questionnaire packs were posted separately to the members with AMD and their carers in October and November 2015. Telephone assistance with survey completion was offered.

Members were asked how much difficulty they have carrying out everyday tasks (e.g. housework) and if they receive help with these tasks. Additionally the Daily Living Tasks Dependent on Vision scale measured the extent to which their AMD impacted on vision-related tasks. We added questions on current driving status and whether their carer drives them to places.

Carers completed the Caregiver Reaction Assessment. This questionnaire explores the impact of providing support on various aspects of life (e.g. impact on finances, daily schedule, health). The questions cover both positive and negative reactions to providing support.

All respondents were asked to complete a measure of well-being (W-BQ16). Two questions assessing quality of life were included from the MacDQoL measure of macular-disease specific quality of life, and were adapted to be relevant to the carer. This information was collected alongside demographic information (e.g. age, gender), details about the AMD including any treatment for AMD, and questions on general health e.g. any other long-term health conditions.

Further information was collected on the support received/provided (as applicable), for instance: an estimation of the average number of hours a week of support received/provided, if anyone else assists with providing support, the length of time respondents have been receiving/ providing support associated with AMD, and the relationship between the person with AMD and the carer.
We received 73 completed questionnaires from person-with-AMD/carer pairs. Those who completed the questionnaires could volunteer to take part in one-to-one telephone interviews with the lead researcher. Of these, we purposively sampled 12 person-with-AMD/carer pairs to interview. This was to ensure that we would be talking to people with a range of different experiences.

The interviews are exploring the topics raised in the questionnaires in more detail. Interviewees can raise new points which help us to get an overview of the impact of receiving/providing support for someone with AMD. An important focus for the interviews is to understand how best to support carers in their role, whilst also maintaining the independence of the person with AMD as much as possible.

Analysis of the questionnaire and interview responses is underway. The findings from both research studies will be used to develop services that may be needed, to inform Macular Society campaigns and to help inform future research.

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**Macular Society Helpline**

0300 3030 111

Monday – Friday, 9am to 5pm

**Affected by macular disease?**

Our helpline team holds a wealth of knowledge and is ready to answer questions on all aspects of macular disease.

**Helping a patient?**

We encourage eye care professionals to refer their patients to us. We have time to talk through issues and can signpost people to relevant support services.
The Macular Society have provided Eccentric Viewing (EV) training across the UK since 2006, by training volunteers to deliver a community-based model. Trainers deliver free one-to-one training during 1-hour sessions over a 2–3 month period; usually between 1 and 3 sessions in learners’ homes.

A total of 58 trainers and 200 learners participated in the study between October 2012 and April 2014, and 121 learners completed all stages of the study. The researchers used telephone interviews to gather detailed information from learners and trainers spread across the UK.

The organisation of the programme was in general very well received by the learners. The best feature of the training was perceived to be the trainers themselves: they were felt to be knowledgeable, well-trained and friendly. 75% of learners felt that the trainer had given them helpful advice in addition to the EV training. The learners welcomed the fact that the training could be conducted in their own home.

Learners usually have the goal of improving their reading or seeing
better in general. Around 65% of them feel they have achieved a positive effect at the end of the programme.

In addition to the interviews, each trainer also audio-recorded their learner reading sample print of various sizes, before and after the training. When these recordings were analysed, no improvement in reading speed was found, on average. It seems that many of the learners already had good reading speed, so there was not much scope for improvement. After the training, the learners could, on average, read print which was slightly smaller, and equivalent to the size of large print, but the frequency and duration of reading did not increase.

There was a borderline significant increase in “life satisfaction” following the training, and this did seem to be linked to those individuals who had an improvement in their reading speed. However, there was no change in health or vision-related quality of life, or in the difficulty experienced in performing everyday tasks.

The Macular Society will now be able to use these findings to decide whether any changes need to be made to the EV training programme to make sure that it is as effective as possible.

Disclosure:
The study was conducted by the researchers on behalf of the Macular Society, to assess the effectiveness of the programme.
Living with macular conditions

Caregiver burden in patients receiving Lucentis® for wet AMD

Rishma Gohil, Roxanne Crosby-Nwaobi, Angus Forbes, Phil Hykin, and Sobha Sivaprasad, NIHR Moorfields Biomedical Research Centre. Ben Burton, James Paget University Hospital, Great Yarmouth

Caring for partners, dependents or relatives with chronic disease can substantially impact caregivers. Burden on caregivers has not been considered in clinical research despite the need for frequent eye clinic visits by patients for monitoring and treatment.

It is important to capture the caregiver burden for this condition and to evaluate factors that determine burden given the prevalence of unpaid caregivers. This study was designed as a cross-sectional questionnaire-based survey of caregivers for people with wet AMD undergoing Lucentis® therapy in 3 NHS trusts. Purposive sampling of caregivers was used to maximise the likelihood of obtaining a complete range of views and included caregivers with different relationships to patients. Caregivers were approached and consented separately from the patient. Caregiver inclusion criteria was that they were aged 18 years or older and self-identified as providing care to the patient receiving anti-VEGF therapy. Individuals who received financial compensation or did not speak fluent English were excluded.

250 caregivers and 250 patients were enrolled. Response rates were 80% for caregivers. The sample of 250 caregivers was 65.3% women, 34.7% men. Approximately 57% of caregiver participants were employed outside the home either full-time or part-time.
In terms of patients being taken care of, 100 (40%) were spouse/partner, 115 (46%) parent or sibling, and 35 (14%) “other.”

Subjective caregiver burden was evaluated using Caregiver Reaction Assessment (CRA)\(^8\). This self-rated burden scale consists of 24 items representing 5 caregiving dimensions (impact on caregiver’s schedule, impact on caregiver’s financial situation, degree of family support, impact on caregiver’s health status and degree of caregiver self-esteem).

Each item is answered using a 5-point Likert scale with responses from 1 (strongly agree) to 5 (strongly disagree). See Table 1.

We assessed caregiver perceptions of patient’s visual difficulty due to wet AMD by classifying visual disability as mild, moderate or severe, allowing correlation of CRA scores with caregiver perception of visual disability. We then analysed the significant patient and caregiver characteristics in a linear regression model. Patient health status also negatively impacted caregiver’s schedule and health.

More importantly, the lower the visual acuity in the patient’s better eye, the greater impact on caregiver finance, schedule, health and self-esteem.

A clear pattern of informal care tasks emerged. The most common caregiver activities included taking to hospital appointments, transport, shopping, organising medical appointments and dealing with health professionals.

This objective estimation of the burden correlated well with the CRA scores that showed that disrupted schedule is the most affected domain. Surprisingly, the number of hospital appointments and length of follow-up did not significantly affect any CRA domains. This indicates that caregivers do not consider taking patients to many hospital appointments overburdensome, as long as the visual acuity in the better eye is maintained so the patient remains independent and not further reliant on his/her caregiver.
Table 1: Caregiver Reaction Assessment: responses to a sample of questions from the five domains.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Disagree/ Strongly disagree</th>
<th>Neither agree nor disagree</th>
<th>Agree/ Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disrupted Schedule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit family/friends less</td>
<td>53.6%</td>
<td>15.6%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Stop work to care</td>
<td>54.4%</td>
<td>18%</td>
<td>27.6%</td>
</tr>
<tr>
<td>Financial problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial resources adequate</td>
<td>16.4%</td>
<td>24.4%</td>
<td>59.2%</td>
</tr>
<tr>
<td>Lack of family support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty in getting help</td>
<td>62.4%</td>
<td>18.8%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Health problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health has become worse</td>
<td>68.4%</td>
<td>13.2%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Self-esteem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I enjoy caring</td>
<td>2.8%</td>
<td>14.4%</td>
<td>82.8%</td>
</tr>
</tbody>
</table>

Finance was significantly affected in younger caregivers, perhaps reflecting reduced income or childcare costs due to taking time off work or transport costs to attend hospital appointments.

The study also found that caregivers of patients with wet AMD do not receive sufficient support from their patients’ health professionals, charitable societies or social services. It is important to identify caregivers who may require additional support for caring for patients with poor visual acuity and poor general health. The greatest burden to caregivers of wet AMD patients occurs due to schedule disruption. Healthcare providers should be aware of this when managing these patients. Treatment strategies should be tailored to allow optimal visual outcomes in these patients.

‘Dry’ age-related macular degeneration (AMD) is believed to affect around 90% of all people diagnosed with AMD. The standard eye test chart measures vision but does not directly relate to everyday tasks. Being able to read letters on a chart is a different ‘visual function’ to searching for your house keys, recognising faces or navigating stairs. Surprisingly there is little research looking into these everyday visual functions in people with dry AMD.

Our work here at City University London seeks to better understand how dry AMD impacts on everyday visual activities. We do this using a number of computer-based tests that mimic everyday tasks using film and still images: for example, face recognition, searching for objects in everyday scenes and hazard detection. We also interview participants about their experiences and symptoms of AMD.

For example in a search task, participants were asked to find items within photographs of everyday indoor and outdoor scenes. Average search times across the images were recorded for each participant. In a face recognition task participants completed a modified version of the Cambridge Face Memory Test and the percentage of correctly identified faces was measured for each participant. We compared the results for both tasks against the same tests on similar aged people with healthy vision.
We have recruited 16 patients out of a target number of 30. Among these 16 participants, two were categorised as having early stage AMD, ten intermediate and four late AMD respectively. In our preliminary results, eight (50%) exceeded the 90% normative limits for average search time and this number was statistically significant (Fisher’s Exact Test, p=0.0026). Three (19%) recorded a face recognition performance worse than the 90% limit (p=0.38); two of these had late stage AMD, geographic atrophy.

So people with dry AMD, certainly those with the more advanced stage of the disease, are likely to have measurable difficulties in these tasks. We hope that further results will lead to better understanding of the impact of dry AMD on day-to-day living, help clinicians in advising their patients about their visual impairment, and raise awareness of the functional implications of dry AMD. In addition, the new tests designed for this study have the potential to act as ‘real-world’ outcome measures in clinical trials for new treatments for dry AMD.

If you are interested in taking part in this study, please see our advertisement (page 47) for details.

www.staff.city.ac.uk/crabblab

Declaration: This research is funded by Roche Products Ltd

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