

# Age-related macular degeneration: collaborating to find a cure



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## EXECUTIVE SUMMARY

Age-related macular degeneration (AMD) is the most common cause of sight loss in the developed world and the third most common globally. It is therefore one of our most urgent public health issues.

With our ageing society we face an epidemic of AMD in coming decades. Two thirds of sight loss caused by eye disease or trauma is a result of AMD. Around 600,000 people in the UK currently have sight loss caused by AMD with around 70,000 new cases every year or nearly 200 every day.

**By 2050 that number will more than double to 1.3m.**

AMD is currently incurable and largely untreatable. For a minority of people drugs injected into their eyes can limit the damage caused by the condition, but they are not a cure.

Older people describe losing their sight as being like bereavement and the impact is equated with suffering a stroke or having an advanced form of cancer.

With this personal loss comes a vast and growing economic burden. AMD has been estimated to cost the UK at least £1.6bn a year. The NHS is already unable to cope with the demand for AMD treatment. Outpatient appointments in ophthalmology have risen 30% in recent years. Current treatments are very expensive and the drug costs alone for AMD are now more than £200m a year. And still only half of all AMD is treatable.

Despite this, the disease has a low priority when it comes to research. Of the £3bn of public money spent on medical research in 2014, only £22.7m was spent on eye disease, and of that only £6m was spent on the biggest cause of sight loss – AMD. Charities in the sight loss sector raised nearly three quarters of a billion pounds in 2014 but gave only £1.5m to AMD research.

There is exciting, world-leading work going on in our universities, research institutions and the NHS. Many researchers say they believe a solution to AMD is possible and so there are compelling reasons why research into macular disease should have more investment.

With this paper we begin a mission:

- to bring researchers together to create a truly collaborative approach to AMD research and
- to find a new funding model to support it.

AMD has been estimated to cost the UK at least £1.6bn a year

Around 600,000 people in the UK currently have sight loss caused by AMD

By 2050 that number will more than double to 1.3m



We invite the research community, research funders and eye charities to join together to campaign for greater investment in eye research in general, and AMD in particular.

We must bring together the best brains in all the diverse areas needed to solve the problem of AMD and to create a platform from which to integrate understanding, define key questions and orchestrate their resolution as swiftly as possible.

**The UK is globally the logical place to drive this initiative given**

- the very high proportion of top universities in the world rankings;
- the power of the combination of the NHS and National Institute for Health Research, and;
- our track record of successful delivery of collaborative projects.

We believe we must do this; for the sake of society, our NHS, our economy, for people with AMD today and the many millions more around the world who will otherwise lose their sight in the decades ahead.

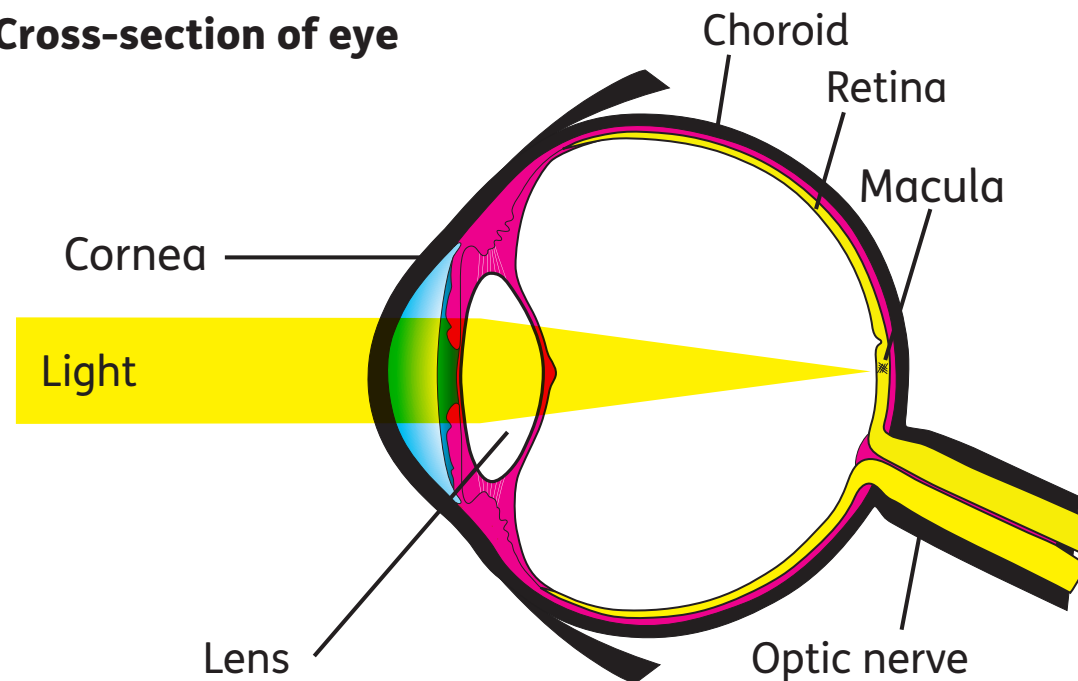
Of the £3bn of public money spent on medical research in 2014 only £22.7m was spent on eye disease and of that only £6m was spent on the biggest cause of sight loss – AMD.

## ••What is AMD?

AMD is a progressive, destructive disease of the central part of the retina called the macula.

The macula is only about 5 mm across, but it has a very high concentration of cone photo-receptors and is responsible for most of our vision.

**Cross-section of eye**



All our central vision, our detailed vision and much of our colour vision relies on the health of the macula. People with advanced macular degeneration cannot drive, read or recognise faces for example.

The early stages of AMD occur before there is any effect on vision. Clinically there may be pigmentary and other changes

to the retinal cells and, usually, the development of small deposits of cellular waste material known as drusen.

As the disease develops the cells of the underlying layer of the retina, known as the retinal pigment epithelium (RPE), begin to die. The RPE's function is to support the photoreceptors above it, so when the RPE cells of the macula die, the photoreceptors it supports die too. This is the point at which people begin to notice changes to their sight. It gets harder to see at night, vision starts to become less sharp and colours fade.

As more photoreceptors die, irregular gaps start to develop in the vision. Eventually the whole of the central area is lost and only unfocused, peripheral vision remains. This form of the disease is often called 'geographic atrophy' (GA). GA may take many months or years to progress to the final stages when all central vision is lost.



**Progression of AMD from normal vision to late stage macular degeneration**

Some people develop a different form of AMD known as ‘wet’ AMD. This gets its name from the development of abnormal blood vessels that grow into the macula. The blood vessels leak blood and fluid. The leakage makes the macula misshapen and causes distorted vision. It also scars the macula and can lead to rapid and devastating loss of sight in just a few days or weeks. This process is called ‘choroidal neovascularisation’ (CNV) and so wet AMD is also known as neovascular AMD (nAMD).

In this document GA and nAMD or wet AMD are collectively referred to as ‘late’ AMD. By that, we mean the point in the disease at which sight is affected. The stages before this point will be referred to as ‘early’ AMD.\*

## ••How common is AMD?

The RNIB report **Future Sight loss** estimates that there are around two million people in the UK with visual impairment. Half of these people have uncorrected refractive error (that is their vision could be corrected with the right spectacles). Of the other million two thirds have AMD.

AMD is the third most common cause of sight loss in the world and the most common cause in developed countries where cataract and glaucoma are treatable.<sup>1</sup>

\*Some sources refer to all AMD that is not ‘wet’ as ‘dry’, including the early stages before visual loss. This leads to the often quoted and somewhat confusing statistics that ‘90% of AMD is dry’ but also that ‘90% of visual loss in AMD is caused by wet AMD’. When the terms ‘early’ and ‘late’ are used as in the Owen study then the proportion of late-stage wet to dry cases is broadly equal.

As its name suggests, AMD overwhelmingly affects older people. One study estimates that at least 10% of people over 60 in the UK, i.e. between 1.5m and 1.8m people, have early AMD.<sup>2</sup> This means they have changes to their retina but sight is not yet affected. Another recent study gives a higher estimate, suggesting that 54% of people over 60 have early AMD.<sup>3</sup>

It is also possible that early AMD may be more prevalent in younger people than traditionally recognised. Korb et al. found evidence of AMD in nearly 4% of people in their 30s and 40s.<sup>4</sup> About 4% of people with early AMD progress to late AMD within a year. Over 2–3 years, 32% of people go from mild to moderate visual impairment and 46% of those with moderate sight loss progress to severe visual impairment.<sup>5</sup>

The largest analysis of late AMD in the UK population was conducted in 2010 by Owen et al.<sup>6</sup> in a study commissioned by Vision2020 UK and funded by the Macular Society. The study was unusual because it took very elderly populations into account.

The investigators estimated the age-specific prevalence of late AMD, GA and nAMD (for men, women and genders combined) using a Bayesian meta-analysis of 31 population studies with a combined population of 57,173.

These estimates represent the most complete meta-analysis of AMD prevalence in white populations (from Europe, North America and Australia) largely similar to the middle-aged and older population of the UK. Populations aged 50 to 97 years were included.

The results suggested that, while late AMD is relatively rare in people aged 60, the prevalence increases exponentially



through the later decades of life, roughly quadrupling in each successive decade. At age 60, prevalence is around 1:250 but by age 90 it is more than 1:5.

**The number of people with late AMD in the UK was put at 513,000 in 2010, rising to 680,000 by 2020.**

Owen found that there are around 70,000 newly diagnosed cases of late AMD every year in the UK; about 40,000 cases of GA and a similar number of nAMD.<sup>7</sup>

New figures from the Office of National Statistics show how our population is ageing. By 2039 more than one person in every 12 will be over 80, i.e. more than 6m people.<sup>8</sup>

The trend means that the number of people with AMD will rise. In the UK it is estimated that 1.3m will have late AMD by 2050, double today's number.<sup>9</sup>

AMD is fast becoming a major issue globally and is already the third most common cause of sight loss worldwide.

Improvements in treatment, access to treatment and education have led to a significant decline in many eye diseases caused by infectious agents such trachoma and river blindness. Cataract too, the biggest cause of sight loss globally, is also reducing with wider access to surgery.

The World Health Organisation estimates that 12 countries in Africa; Benin, Burundi, Chad, Kenya, Mali, Guinea-Bissau, Guinea, Malawi, Niger, Senegal, Sierra Leone and Togo will have eliminated river blindness by 2020. In South America, Ecuador, Colombia and Mexico have already done so.<sup>10</sup>

Trachoma, the world's leading infectious cause of blindness, has been eliminated as a public health problem in Mexico, Morocco, and Oman. More than 185,000 trachoma patients had surgery for trichiasis worldwide and more than 56 million people received antibiotics in 2015 alone.<sup>11</sup>

However as populations in developing countries live longer, and adopt more western lifestyles, diseases of the retina including diabetic macular disease and AMD are increasing.

A systematic review and meta-analysis of over 20 years of data, conducted by the Vision Loss Expert Group of the Global Burden of Disease Study, has identified a significant worldwide **increase** in blindness and vision impairment. The analysis, showed that the number of people who were blind due to macular diseases during the period from 1990 to 2010, increased by 36%, or 600,000 people, while those suffering vision impairment increased by 81%, or 2.7 million people. Global population rose 30% over the same period. (This excludes diabetic eye disease but includes AMD and other rarer conditions such as myopic maculopathy and macular hole.)<sup>12</sup>

A meta-analysis by Wong et al, published in the Lancet in 2014 predicted that incidence of late-stage (causing sight loss) AMD globally would double from 10m to 20m by 2040 (taking a mean estimate).

An estimated 288m will have some form of AMD by 2040. This will be mostly early, asymptomatic disease, but this population is therefore at risk of sight loss.

Half of this AMD will be in Asia. The authors point out that many of these people will not have access to expensive anti-VEGF

medicine for wet AMD. The drugs are too costly and the sterile surroundings required for safe use are unavailable.<sup>13</sup>

It is even possible that these predictions are an underestimate of the true picture.

Kenya-based ophthalmologist Andrew Bastawrous wrote to the British Journal of Ophthalmology in 2012:

“Posterior segment eye diseases (PSED): Glaucoma; Age-Related Macular Degeneration (ARMD); and Diabetic Retinopathy (DR) are now recognised as a major cause of VI worldwide and are more prevalent than infectious causes of VI such as trachoma and corneal ulcers. The majority of data collated in the last ten years from which these figures are estimated likely underestimate the true prevalence of PSED for three reasons: (a) The majority of surveys used the WHO coding instructions, which use the “principal disorder responsible for visual loss in the individual after considering disorders in either eye which are most amenable to treatment or prevention”(2), i.e. if a patient has co-existent PSED with cataract it will be deemed that cataract is the primary cause of VI. Therefore most VI prevalence data available in which cataract is the primary cause will underestimate the actual prevalence of PSED; (b) The Rapid Assessment of Avoidable Blindness (RAAB) methodology, which forms one of the most employed methods of gathering VI data in the last ten years (20 published from Africa, Latin America and Asia) does not allow for accurate diagnosis of PSED or differentiation between PSED; and (c) VI surveys have been designed to diagnose the cause of disease in those with varying degrees of visual impairment (?6/18 Snellen acuity) and thus pre-visually impairing disease is not detected. This is particularly important in the detection of PSED where cessation rather than cure is currently our only realistic

management option. If VISION 2020: The Right to Sight’s aims of alleviating suffering from avoidable blindness is to be met, the growing impact of PSED needs to be a focus of policy makers.”<sup>14</sup>

It is clear that there is an urgent, worldwide, need for a concerted, organised approach to finding effective and affordable treatments for diseases such as AMD.

## ●● Certification of visual impairment

In the UK, people with visual loss can be ‘certified’ to that effect by their ophthalmologist and then registered with their local social services department. Registration is the gateway to some welfare benefits and social care services. The certificates describe people as ‘sight impaired’ or ‘severely sight impaired’. (This used to be known as ‘partially-sighted’ and ‘blind’). Certification is voluntary and is known to be patchy and incomplete with significant variations between local authority areas. It is generally agreed that the **Certificate of Vision Impairment (CVI)** data underestimate the true number of visually impaired people because some people choose not to be certified and others are never offered it.

Furthermore, many people with AMD have sight loss that affects their daily lives but does not reach the threshold for certification. There is no definitive data on how many people have ‘low vision’ i.e. visual impairment that cannot be corrected by spectacles or contact lenses. A recent analysis of CVIs shows that 49% of all certifications in England and Wales in 2013/14 were a result of AMD.<sup>15</sup>

**AMD is responsible for as much registerable sight loss as all the other causes combined.**



## ••What causes AMD?

The causes of AMD are not entirely understood. There are recognised risk factors, age being the most important; the older we get the more likely we are to get AMD.

Genes make a major contribution to AMD risk. Faults on two particular chromosomes, 1 and 10, may account for most of the susceptibility to AMD.<sup>16</sup> The gene implicated on chromosome 1 is part of the 'complement' system that regulates part of our immune response. Other genes also contribute to risk including other complement system genes.

In addition to genetic predisposition, environmental factors are also important. Of these smoking is the most significant. Smokers are at least three times more likely to develop AMD than non-smokers.<sup>17, 18</sup> Smokers with certain genetic characteristics are up to 20 times more likely to develop AMD.<sup>19</sup> The latest report on smoking by the Surgeon General of the USA concludes that the evidence is sufficient to infer a causal relationship between cigarette smoking and the wet and dry forms of AMD.<sup>20</sup>

Other risk factors for AMD are very similar to those for stroke and heart disease: high blood pressure, obesity, a diet low in antioxidants.<sup>21</sup> There is some evidence that high exposure to ultraviolet light may also increase risk.<sup>22</sup>

Interest is growing in the role of beta-amyloid in AMD. This is the same protein thought to underpin the development of dementia.<sup>23</sup>

AMD is a complex, multifactorial disease and so it presents many challenges to those seeking ways to overcome it.

**As Phil Luthert, Director of the Institute of Ophthalmology, University College London, says:**



“Age-related macular degeneration is increasingly recognised as a colossal healthcare challenge and, despite major advances in genetics, epidemiology, pathogenesis and imaging, we still don’t understand how to prevent early disease progressing to blinding disease in the form of choroidal neovascularisation (CNV) or geographic atrophy.”

## ••How does AMD affect people?

Many people with AMD describe the impact of losing their sight as like bereavement. They ‘mourn’ the loss of their sight and experience many of the same stages of grief: denial, anger, bargaining, depression and eventually some acceptance.

People fear blindness. One survey found that 76% of people would rather lose a limb than their sight.<sup>24</sup> Another study found that patients ‘equate the impact of loss of vision with suffering a stroke or having an advanced form of cancer’.<sup>25</sup>

The impact of sight loss from AMD includes:

- Depression – people with AMD are seven times more likely to feel distressed or depressed than people with no sight loss.<sup>26</sup>
- Social isolation – sight loss restricts lives.<sup>27</sup>
- Falls – people with sight loss are 1.7 times more likely to fall.<sup>28</sup> Fear of falling restricts activity.<sup>29</sup>
- Risks to wellbeing – ability to self-care is reduced, e.g. managing medication, cooking and eating well.<sup>30, 31</sup>
- Increased costs – many people need assistive aids and home support.
- Reduced ability to work or take part in voluntary activities.
- Reduced ability to care for others such as partners or grandchildren.

- Reduced quality of life – people with AMD are increasingly unable to undertake and participate in important aspects of life such as family interactions, driving, reading, walking, using public transport and hobbies. In the advanced stage of the disease, this has been calculated to be a 60% drop in quality of life.<sup>32</sup>
- Up to half of people with sight loss caused by AMD will experience visual hallucinations known as Charles Bonnet Syndrome. A third will have hallucinations that are distressing and intrusive and interfere with daily activities. Many are unaware that AMD can cause hallucinations and live in fear that they have mental illness.<sup>33</sup>

A recent study at the University of Manchester for the Thomas Pocklington Trust found that people whose vision deteriorated from good or very good to fair or poor were found to have levels of depression that increased by 29% and a fall in income levels of 19% compared with those whose vision remained stable.<sup>34</sup>

The families and carers of people with AMD are also affected by the condition.

The ‘burden of care’ for informal carers of people with nAMD is equivalent to caregivers for rheumatoid arthritis and multiple sclerosis and higher than patients with colorectal cancer.

It is also similar to the experiences of caregivers of patients with atrial fibrillation who require regular hospital appointments for monitoring their thromboprophylaxis.<sup>35</sup>

## AMD is a life-changing condition

I used to own my own pet store and gardening business and employed eight staff members. But with the onset of AMD it became increasingly hard to manage my team and check their work. Some staff began to make fun of my condition and stopped doing jobs that I set them. I could've managed doing the gardening, but not the way my staff took advantage of my sight loss.

**Bob Shields**

I would see insects and at one point any black shadows turned into beetles and I would be thinking 'oh please don't let this be happening'. It is important for people to know, to know that they are not going mad. It is horrifying. It is keeping a mental grip on yourself and believing in yourself. But you really don't want to risk telling people. I tried to tell a family member one time, at first they snorted with laughter and then they said 'you are joking aren't you?' So I backed off as it was clear what they were thinking.

**Isobel Torrance**

Being diagnosed with macular disease has had a huge impact on my life. The key things are not being able to read without assistance, greater difficulty with shopping and the fact I've had to stop driving – essentially the ability to fully take part in society. It's difficult now to be in a busy situation as I feel lonely and isolated, it means that I have to socialise differently and I spend much more time at home.

**Julia McHugh**



*Isobel Torrance*



*Julia McHugh*



## ●● Treatment of AMD

### **There is no treatment for dry AMD (GA).**

There is some evidence that high doses of certain micronutrients can slow the progression of AMD. This comes from two large studies, the Age-Related Eye Disease Studies (AREDS).

AREDS I suggested that antioxidant vitamins A, C and E together with zinc can slow progression to late AMD by 25% in people with intermediate AMD. AREDS II added omega 3 to the first formula in one study arm and the carotenoids lutein and zeaxanthin to another arm. The addition of omega 3 did not have any effect but the addition of the carotenoids did appear to further slow disease progression in a subset of participants who had low levels of these substances in their daily diet.

A great many nutritional supplements are marketed at people with dry AMD but many have little or no high quality evidence to support their claims. Some ophthalmologists support the use of AREDS formula supplements but their benefit is not universally accepted.

### **Treatment for wet AMD has made better progress.**

The first available treatment was laser therapy. Argon laser treatment could destroy proliferating blood vessels but caused severe collateral damage and so could not be used in the central area of the macula without causing more damage than the disease.

Photodynamic therapy brought some improvement. A photosensitising dye, verteporfin (Visudyne®, Novartis), is given intravenously, followed by the delivery of cold laser light. The energy from the laser is taken up by the verteporfin and blocks the blood vessels within the CNV lesion. The advantage of this approach is that there is minimal damage to the overlying retina. However, it is only appropriate for a minority of patients.

The major breakthrough was the discovery of anti-VEGF drugs. Vascular endothelial growth factor (VEGF) is a protein that promotes the growth of blood vessels throughout the body. In wet AMD there is an over-production of VEGF leading to the development of abnormal blood vessels. Anti-VEGF drugs therefore inhibit the growth of the blood vessels.

The drugs have to be injected into the eyeball (an intravitreal injection) in order to get them to the back of the eye. This is because the eye has a very efficient blood-retinal barrier and is effectively a self-contained capsule designed to prevent foreign objects reaching the retina.

The first licensed anti-VEGF drug was ranibizumab (Lucentis®, Genentech) and was introduced in the NHS in 2008. A second anti-VEGF became available in 2013: aflibercept (Eylea®, Bayer).

A third drug, bevacizumab (Avastin®, Genentech) is widely used in some parts of the world. It is a cancer drug, used off-label, or unlicensed for AMD. This use is controversial and opposed by the pharmaceutical industry.

While anti-VEGF drugs have had a considerable impact, eight years on it is clear that they are not the solution to wet AMD.

Demand for wet AMD treatment is severely straining NHS ophthalmology departments. The number of ophthalmology outpatient appointments increased by 30% between 2008 and 2012.<sup>36</sup> In 2013/14, 8.5% of all NHS outpatient appointments were in ophthalmology. Intravitreal injections have to be given in a sterile environment by a trained ophthalmologist or, increasingly, a nurse or theatre technician as there are insufficient ophthalmologists to provide the service.

Surveys by the Macular Society and the Royal College of Ophthalmologists, and the RNIB, consistently show that many clinics fail to meet recommended waiting times for wet AMD treatment and some clinicians frankly admit that patients have lost sight as a result.<sup>37, 38</sup>

The pressures in the medical retina area of ophthalmology have had knock-on effects on other services such as glaucoma and cataract clinics. Many areas of the NHS are now restricting access to cataract surgery to save money. One recent report found that half of commissioners are restricting access to cataract surgery by the application of clinical thresholds and one in three make no allowance for second eye surgery.<sup>39</sup>

Anti-VEGF drugs have to be given promptly and regularly (every few weeks) to maintain vision as, once the macula is scarred, it cannot be repaired and the drugs are only effective on new blood vessels.

The disease is slowed in 90% of patients treated promptly and about 30% will experience an improvement in their vision. Even so, many will still develop 'low vision' over time

and for the 10% of people for whom the treatment does not work, sight loss will be very significant. Most people need the treatment for life and there are now many patients who have had in excess of 70 injections.

The Seven-Up Research Group found that after seven years of treatment with Lucentis® one third of patients demonstrated good visual outcomes, whereas another third had poor outcomes.

Compared with baseline, almost half of eyes were stable, whereas one third had experienced significant vision loss.<sup>40</sup> The findings indicate that even this late in the therapeutic course the risk of visual decline and disease activity persists, and the need for anti-VEGF treatment continues in a substantial portion of patients.

In addition there is now some evidence that the drugs affect the wider retina and may actually accelerate the progression of underlying dry AMD.<sup>41</sup>



**An intravitreal injection**



## ••Low vision services

Most people with late AMD will eventually have 'low vision'. This means their visual impairment restricts their everyday life and cannot be remedied by conventional spectacles, contact lenses or medical intervention.

Many can benefit from the use of low vision aids such as magnifiers and techniques to make best use of remaining vision. However, access to low vision services is patchy and limited. Local government has faced unprecedented cuts over the last few years that have impacted dramatically on capacity in adult social care.<sup>42</sup>

A review of the visual impairment sector by New Philanthropy Capital found a consensus view that the personal impact of sight loss is underestimated and the emotional and practical support offered is inadequate. The provision of counselling services, low vision services, rehabilitation and mobility training for people with sight loss was highly variable. This patchy provision means some people cannot access services that they need to participate fully in society.<sup>43</sup>

A report from the University of York<sup>44</sup> also found a wide variety of vision rehabilitation provision across England, in terms of the type of providers, specialism within the teams, caseloads and waiting times. Nearly a quarter of services have had their budgets cut and a fifth has had staff cuts in the previous year.

Vision rehabilitation is concentrated on mobility, independent living skills, aids and adaptations. Emotional support and counselling are less likely to be offered.

## ••The cost of AMD

The cost of AMD is enormous and growing.

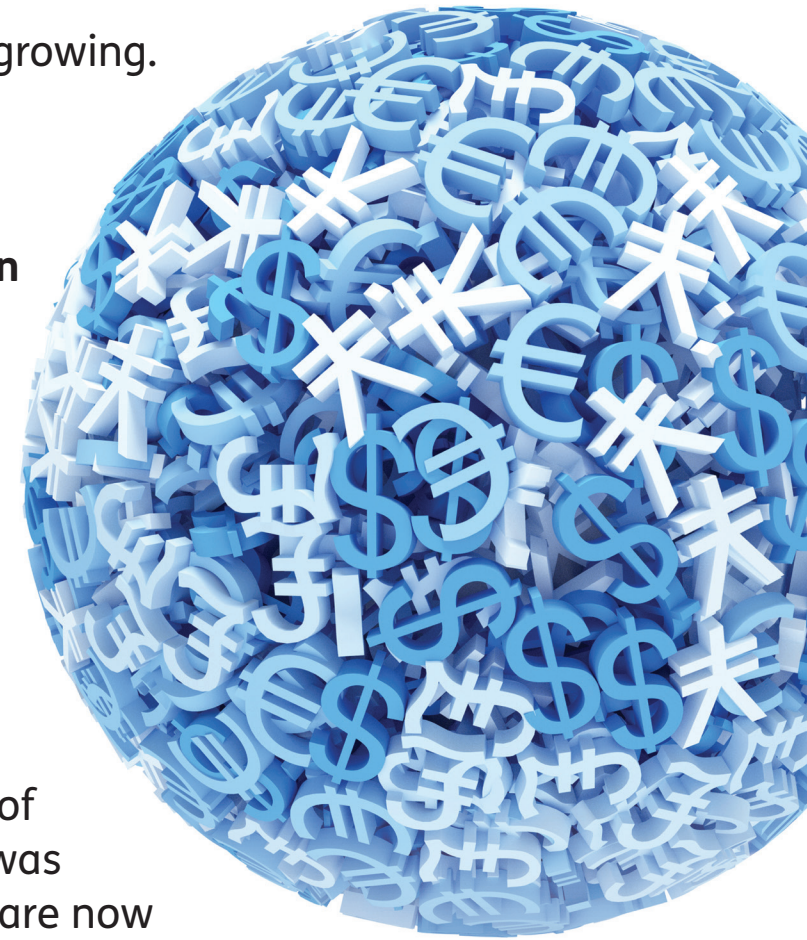
**The global AMD drug market was valued at \$5.4bn in 2014 and is expected to grow to nearly \$7.9bn by 2019, a compound annual growth rate of 7.8%.<sup>45</sup>**

Anti-VEGF drugs represented a real breakthrough in wet AMD treatment when they arrived and they came with 'block-buster' price tags.

Lucentis® was launched at a cost of £761.20 (+ VAT) per dose. Eylea® was £816 (+ VAT) per dose. Both drugs are now the subject of confidential discount schemes so the current prices are unknown.

However, in 2014–15 the total cost of these drugs to the NHS in England alone was more than £287m. The total spend on Lucentis® is the second highest of any prescribed drug appraised by NICE.<sup>46</sup> This is for all the uses of the drugs not just AMD; however, most is used in AMD.

Data for Gloucestershire derived from the electronic patient records system Medisoft show that in 2015 75% of anti-VEGF injections were given to treat wet AMD. The other 25% was for treatment of retinal vein occlusion and diabetic macular oedema.<sup>47</sup>





The relative percentages are likely to change with time but using these figures and extrapolating from the population of Gloucestershire (600,000) to the UK population (64m), this would suggest a total of 997,440 anti-VEGF injections per annum for all indications.

If the cost to the NHS is about £500 per injection (for the drug) then the total drug cost to the NHS would be expected to be £500m (997,440 x 500) in 2015. This is around double the figure of £287m quoted by Health and Social Care Information Centre (HSCIC).

The reason for this apparent discrepancy is not clear. One interpretation might be that it supports the view that there is very considerable under-treatment of retinal disease. This is likely to be the result of lack of capacity in eye clinics.

However, without knowing how much the NHS is paying for the drugs it is difficult to make a judgement.

Administering the drugs is estimated at a further £255 per procedure,<sup>48</sup> a total of just over £250m in 2015 plus the cost of assessment visits where no injections are given. These are estimated at £60 per visit.

The high price of licensed anti-VEGFs is the reason for the use of Avastin® off-label in many countries, particularly those where the cost of treatment falls on individual patients. Although Avastin® is as expensive as a cancer drug, it costs only around £100 when split into the tiny quantities needed for eye treatment.

A new drug for dry AMD is in stage III clinical trials. The drug, lampalizumab (Roche) is a monoclonal antibody that targets

the inflammatory component of the condition. Early trials suggest that the drug may reduce the progression of dry AMD by 20% overall and by 40% in a subset of patients. However, like the current anti-VEGFs for wet AMD, it has to be given as a regular intravitreal injection. If this does become the first effective therapy for dry AMD, the drug is likely to be expensive and will put even more strain on ophthalmology services.

A wider economic analysis of the costs of AMD to the UK has estimated the cost of detection, treatment and provision of state and family social care for everyone with AMD as more than £1.6bn in 2010.<sup>49</sup>

This is under the assumed 75% levels of anti-VEGF treatment for wet AMD and assuming status quo for low vision services for AMD.

The estimated cumulative cost over the decade from 2010 to 2020, under the same conditions but allowing for demographic change, is more than £16.4bn. The healthcare treatment component amounts to 17.8% of the total, i.e. more than £2.9bn. The personal and social costs are 76% which is more than £12.5bn.



## ●● Burden of disease compared to research spend

The UK Clinical Research Collaboration has produced two Health Research Analysis Reports. The most recent report<sup>50</sup> gives details of research expenditure by major government funders and 64 charities in 2014, and shows that the proportion devoted to research into eye conditions remained stable, comprising 0.9% of all the included research funding in 2004/5, 2009/10 and 2014.

The reports also compare the proportions of research spend and the burden of disease as reflected in disability adjusted life years (DALYs). In this data, ear and eye conditions are combined.

The 2009/10 report<sup>51</sup>, based on research spending in 2009/10 and DALY data from 2004, showed a mismatch between the burden of disease, expressed in disability adjusted life years, and research spending. Eye and ear disease was responsible for about 7% of DALYs but received only about 2% of research funds.

However, the 2014 report shows that the proportion of research spend is similar to the proportion of total DALYs in 2012 – both about 2%. This contrasts with the 2009/10 data which show a similar proportion of research spend, but the much higher proportion of DALYs.

We therefore have a curious phenomenon of ‘disappearing DALYs’ between 2004 and 2012. Since eye and ear DALYs are reported as a proportion of all DALYs, the drop could be either

a true reduction in eye and ear DALYs, or increases in DALYs due to other conditions.

The paucity of good, current data on the specific costs of AMD is a barrier to good decision making and prioritisation of resources; both clinical and research.

Similarly, there are no data available of the potential savings to UK society of reducing the burden of AMD. Even modest progress in slowing the progression of AMD could have a substantial effect on costs.

**In an article for Webvision, an online journal, the respected US ophthalmologist, Gregory S. Hageman, wrote:**

“A recent analysis of AMD in Australia predicts that the disease costs \$2.6bn per year.<sup>52</sup> This is projected to grow to \$6.5bn by 2025, a total cost of \$59bn over the next 20 years. A treatment that reduced the progression by only 10% would save Australia \$5.7bn over that same period of time. Similar analyses for the United States are lacking, but given the demographics and higher cost of medical care in the US, the costs would be projected to as much as 20-fold higher.”<sup>53</sup>



Public funding of AMD research

In spite of the vast and growing burden of AMD, the disease does not have a high priority when it comes to research.

The UK Health Research Analysis 2014 shows that, in that year, £3.01bn of public funding (from taxpayers and charitable donations) was invested directly in medical research. More than £400m was spent on cancer research in the year 2013/14. Only £22.7m (0.76%) was spent on eye research. (Appendix A)

Table 1: Total spend on AMD research 2014

| Funders                      | £ Spend on AMD research 2014 |
|------------------------------|------------------------------|
| Medical Research Council     | 2,392,761                    |
| NIHR                         | 655,916                      |
| Innovate UK                  | 564,482                      |
| BBSRC                        | 25,380                       |
| EPSRC                        | 21,300                       |
| NC3RS                        | 5,000                        |
| Wellcome Trust               | 961,935                      |
| Fight for Sight              | 892,589                      |
| Macular Society              | 175,529                      |
| Moorfields Charities         | 137,636                      |
| Dunhill Medical Trust        | 119,851                      |
| National Eye Research Centre | 69,150                       |
| TOTAL                        | 6,021,529                    |

Further analysis (Table 1) shows that only £6.02m (27%) of the £22.7m was spent on AMD – the biggest cause of blindness.

Research spend on AMD over the five years from 2010 to 2014 was £23.7m so, over this period, research into macular disease was only 21% of the total amount (Table 2).

AMD represents 49% of registered sight loss but attracts only 27% of eye research funding.

Table 2: Total spend on AMD research 2010-2014

| Funders                                     | £ Spend on AMD research 2010–2014 |
|---|-----------------------------------|
| Medical Research Council                    | 10,248,907                        |
| NIHR  | 3,760,704                         |
| Innovate UK                                 | 732,748                           |
| BBSRC                                       | 167,102                           |
| EPSRC                                       | 318,102                           |
| NC3RS                                       | 30,000                            |
| Wellcome Trust                              | 3,830,681                         |
| Fight for Sight                             | 3,411,874                         |
| Macular Society                             | 313,159                           |
| Moorfields Charities                        | 411,728                           |
| Dunhill Medical Trust                       | 259,784                           |
| National Eye Research Centre                | 115,044                           |
| British Council for Prevention of Blindness | 109,820                           |
| TOTAL                                       | 23,709,653                        |



In terms of where research is focused, the UK Health Research Analysis 2014 shows that the greatest proportion of health research spend is in the Underpinning and Aetiology activities.

Health Research Classification System (HRCS) Sector Distribution 2014 (RA)

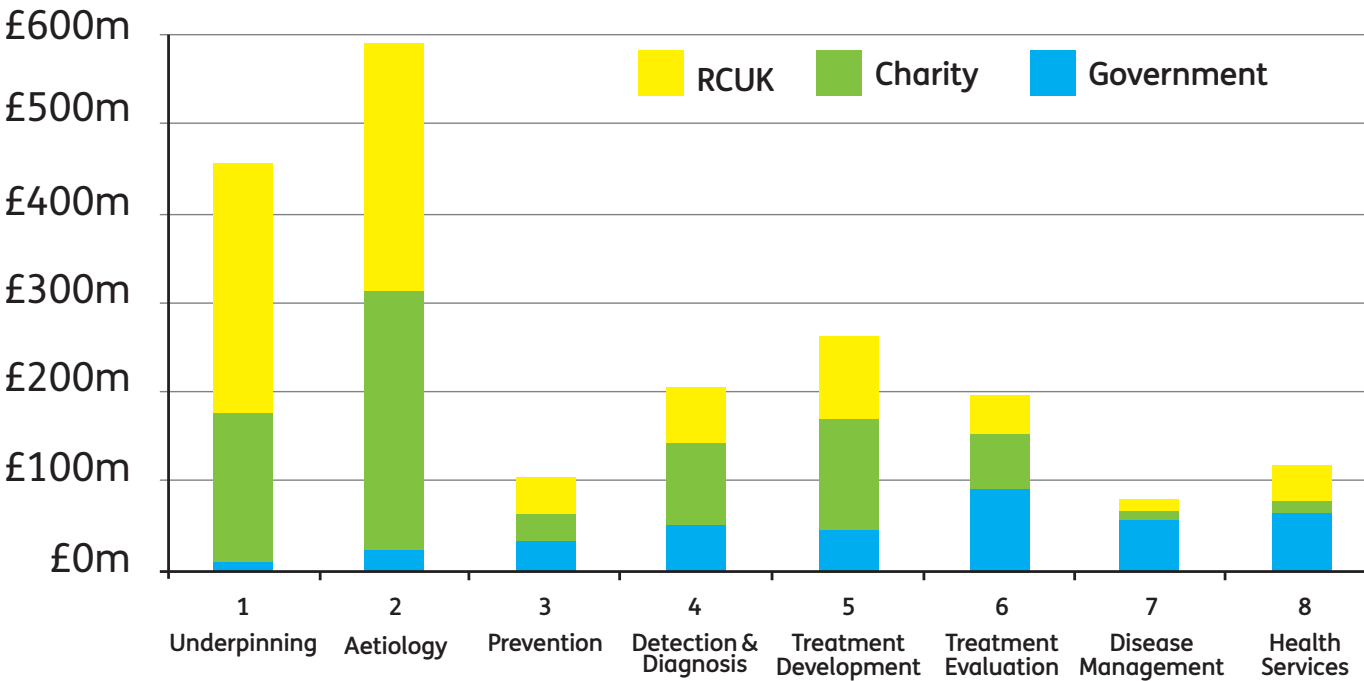


Figure 1. Distribution of combined spend by research activity by charity, Research Council and other Government funders.

Distribution of Research Spend on AMD 2014

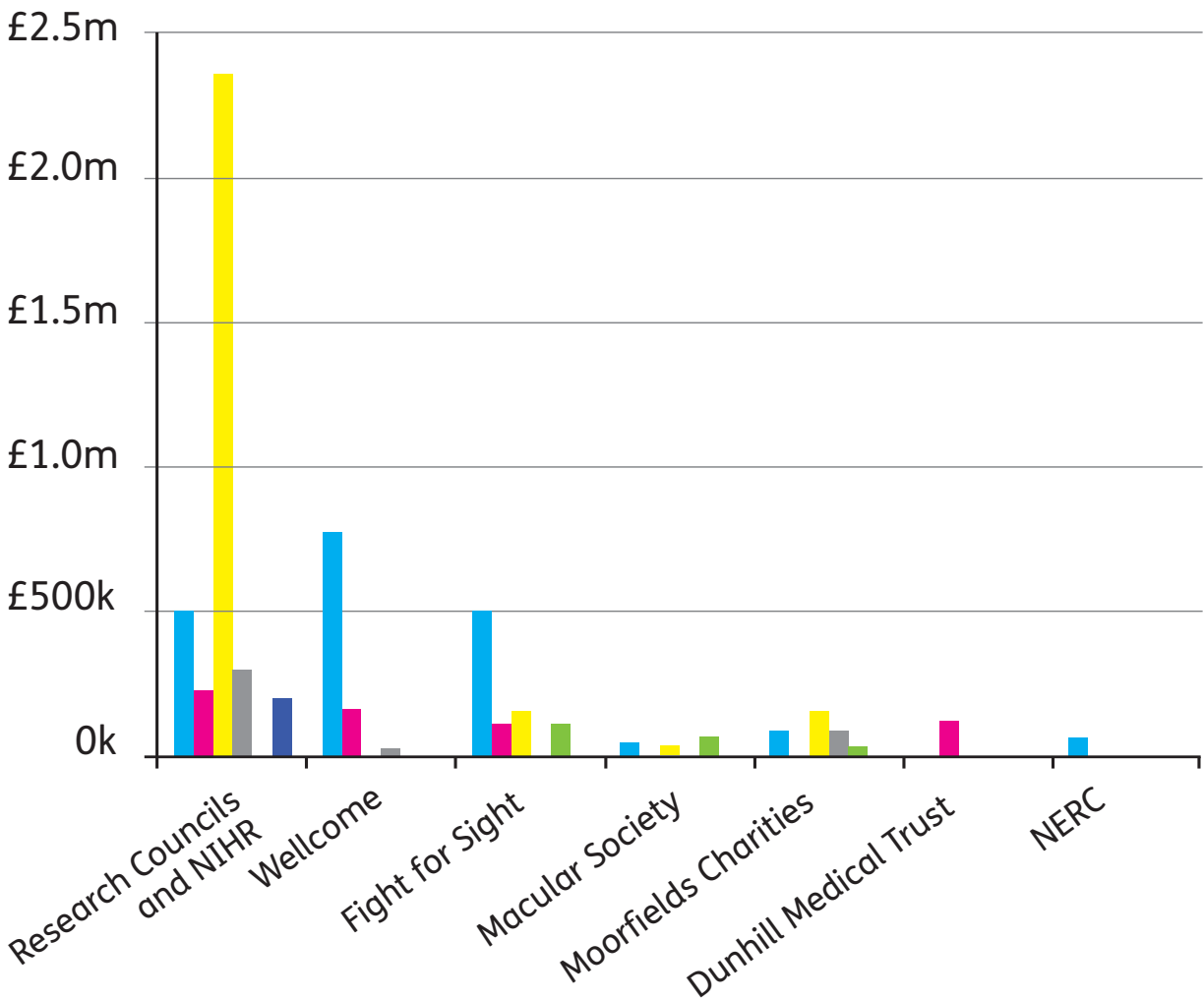


Figure 2. Distribution of 2014 research spend on AMD by HRCS activity.

- 2 Aetiology
- 4 Detection, Screening and Diagnosis
- 5 Development of Treatments and Therapeutic Interventions
- 6 Evaluation of Treatments and Therapeutic Interventions
- 7 Management of Diseases and Conditions
- 8 Health and Social Care Services Research

Charitable funding of eye research

In 2014, health-related charities gave a total of £1.3bn to medical research, constituting more than a third of all public funding of research. The big charities in sectors such as cancer, heart disease, arthritis and dementia are all significant funders of research.

Table 3: Charitable income and research spend 2014

| Charity                                  | Income<br>£m   | Research<br>spend £m |
|--|----------------|----------------------|
| Cancer Research UK <sup>54</sup>         | 665.0          | 358                  |
| British Heart Foundation <sup>55</sup>   | 118.7          | 82                   |
| Arthritis Research UK <sup>56</sup>      | 101.4          | 20                   |
| Diabetes UK <sup>57</sup>                | 81.8           | 7.0                  |
| Alzheimer’s UK <sup>58</sup>             | 26.8           | 9.0                  |
| Alzheimer’s Research UK <sup>59</sup>    | 15.1           | 8.7                  |
| Parkinsons’s UK <sup>60</sup>            | 8.5            | 4.7                  |
| Prostate Cancer UK <sup>61</sup>         | 8.5            | 12.6                 |
| Multiple Sclerosis Society <sup>62</sup> | 7.0            | 4.6                  |
| Stroke Association <sup>63</sup>         | 7.0            | 4.2                  |
| <b>TOTAL</b>                             | <b>1,117.7</b> | <b>510.8</b>         |

It is an unusual feature of the sight loss sector that there are no large charities funding medical research. Of the UK sight loss charities with an income of over £3m p.a. only four fund medical research: Macular Society, Fight for Sight, Moorfields Eye Charity and Moorfields Special Trustees (these latter two are merging). In addition the National Eye Research Centre had an

income of around £409k in 2015 and made research grants of £747k. The largest charities in the sector, RNIB, Guide Dogs, Sense, SeeAbility, Blind Veterans and Thomas Pocklington Trust do not fund any medical research. Their total income in 2014 was more than £388m.

The vast majority of sight loss charities, of which there are more than 600, are relatively small. Most were formed in the late 19th or early 20th centuries and have long and honourable histories of providing local support to people who are blind or visually impaired. The majority are what were often called ‘societies for the blind’. They range in income from a few tens of thousands to £10m. The total income from these local societies is estimated to be £164m. None funds any medical research.

Altogether in 2014, sight loss charities in the UK had a joint income of around £774m (see Appendix B).

Of that total just £1.5m was used to fund research into AMD in 2014: in other words, less than one fifth of one per cent raised by sight loss sector charities in that year was spent on research into a cure for the biggest cause of sight loss.

Table 4: Sight loss sector charitable income 2014

|                            | 2014 income<br>£m |
|----------------------------|-------------------|
| Major sight loss charities | 599.90            |
| Other sight loss charities | 10.39             |
| Local sight loss charities | 164.16            |
| <b>TOTAL</b>               | <b>774.45</b>     |

The emphasis on support in the sector does not just mean that very little money is spent on research. It is also given very little strategic importance generally. The UK Vision Strategy began as a VISION 2020 UK initiative which was led by the RNIB. It was first launched in 2008 and is intended to set the direction for the whole eye care sector. It has three strategic outcomes:

1. Everyone in the UK looks after their eyes and their sight.
2. Everyone with an eye condition receives timely treatment and, if permanent sight loss occurs, early and appropriate services and support are available and accessible to all.
3. A society in which people with sight loss can fully participate.

While these issues are undoubtedly important, there is no mention of medical or scientific research into treatments or cures to prevent sight loss. (The 2015–18 VISION 2020UK does state that one of their key documents is the Sight Loss and Vision Priority Setting Partnership Report and its Priority 2 ‘promoting the ongoing need for eye research to reduce sight loss and improve eye health’.)

The ‘Seeing it my way’ outcomes are those apparently identified as ‘most important by blind and partially sighted people...to drive how services are delivered to ensure that blind and partially sighted people benefit from these outcomes’. They are based on research by Action for Blind People. They do not include any mention of conducting research to find better treatments or cures for sight loss.<sup>64</sup>

While the purpose of this work is entirely valid there is no space in either exercise for blind and partially sighted people to voice

a desire for more research to help stop people going blind. Interestingly, the research we do with our own members clearly shows that people with AMD rate ‘research into new treatments and cures’ as equally important as or even slightly more important than providing support services<sup>65</sup> (see Appendix C).

Charities in other sectors work hard to influence politicians about the need for research investment. The small charities in the visual impairment sector make efforts to do so and the National Eye Research Centre published a manifesto in 2015 ‘Insights into a healthy future’ which was launched at a House of Commons reception and was aimed at raising the awareness of the need to fund more eye research.

However, this is not the focus of the lobbying work done by the big sight loss charities, which are focused on developing better support services for blind and partially sighted people. The RNIB and the College of Optometrists jointly provide the secretariat for the All Party Parliamentary Group for Eye Health. Eye research has been discussed only once since 2011.<sup>66</sup>

Many charities attend political party conferences in order to develop their profile and influence legislators. In 2014 RNIB, Guide Dogs and Sense attended the Conservative (governing) Party conference. The much smaller, research funding charities, Macular Society and Fight for Sight did not do so owing to the high cost of attendance.

The major research funders in other sectors did attend. Among them were Arthritis Research UK, Cancer Research UK, British Heart Foundation, MS Society, Stroke Association, Diabetes UK and Prostate Cancer UK.



Charities and industry

As governments around the world try to contain rising healthcare costs, the pharmaceutical industry is under pressure to demonstrate the added value of new therapies. The high cost of drug development means the industry is increasingly risk-averse. As a result even projects with some potential may be regarded as ‘too early’ or ‘too high risk’ to be pursued.<sup>67</sup>

The Association of Medical Research Charities (AMRC) says: “Historically, this type of research was often conducted by industry using in-house facilities. In today’s climate, such early-stage work is done in academic units, either as contract research or as pre-competitive research where the results will be made available in the public domain.”

This is where medical research charities play an important role; the considerable charitable resources available for research purposes in other disease areas are not just funding more work. They are being used strategically to help industry mitigate early stage risk and so increase the pace of research.

The AMRC says: ‘Charities can play a significant role in making otherwise unattractive research appealing to industry. Some charities have taken the strategic decision to fund early-stage research to reduce the commercial risks to industry. This may include funding to increase the accuracy of diagnostics, provide greater molecular definition of new drugs and their targets, or perhaps investigate the efficacy of repurposed drugs in new diseases.’

Research-funding sight loss charities have far less resource to invest in this way, creating a ‘double-whammy’ for eye research.

The very high cost of new drug development, often put at £2bn by industry, may lead sight loss charities to believe that they can make little impact on the progress of research. However, small sight loss charities can contribute relatively modest amounts to early stage work that otherwise wouldn’t be funded and which later can leverage much higher levels of support.

Fight for Sight invested less than half a million pounds in early work on choroideremia in 2005 that has gone on to leverage many millions more.

Table 5

| Developing a gene therapy treatment for choroideremia* |  |   |   |  |  |
|--|--|---|---|--|--|
| Who?   | Patients<br>Tommy Salisbury<br>Choroideremia<br>(TSC) set up at<br>Fight for Sight | Charity   | Government/<br>Charity<br>Health innova-<br>tion Challenge<br>Fund (Depart-<br>ment of Health/<br>Wellcome) | Evergreen<br>Fund<br>Syncona<br>(Wellcome)                                       | Venture<br>Capital<br>New Enterprise<br>Associates |
| What?  | Fundraising<br>events  | TSC Fund at Fight<br>for Sight – largest<br>single funder of<br>basic / preclinical<br>work at Imperial | Funded Phase 1<br>gene therapy<br>trial at Oxford<br>taking IP from<br>Imperial                             | Funded<br>NightstaRx, an<br>Oxford spin-out.<br>Lead program is<br>choroideremia | Lead series B<br>financing for<br>NightstaRx       |
| How much?  | £440k to date  | £300k   | £1.1m   | £17m   | \$35m  |
| When?  | 2005 to date   | 2008–2011   | 2011–2013   | 2014–2015  | 2015   |

\* And other inherited eye diseases



The Macular Society and Fight for Sight both helped fund the London Project to Cure Blindness at critical, early stages of their stem cell work. Macular Society members donated a modest £100k to cover a funding gap in 2008. The Project was then able to progress to a stage where more major funding and a commercial partner came on board. The work is now in human trials.

Table 6

| Developing a stem cell treatment for AMD |  |  |   |  |   |
|--|--|--|---|--|---|
| Who?                                     | Charity<br><br>Fight for Sight   | Philanthropy<br><br>Anon US donor/<br>Macular Society  | Industry<br><br>Pfizer  | Government,<br>industry &<br>charities<br>NIHR/BMRC,<br>Pfizer, charities  | Government,<br>industry &<br>charities<br>NIHR/BMRC,<br>Pfizer, charities                         |
| What?                                    | Infrastructure investment at UCL. IOO and funding of core salaries including Professor Pete Coffey | Donation to UCL to enable launch of The London Project to Cure Blindness led by Professor Coffey | Research support expertise in manufacturing, clinical trials and regulatory affairs | Research strands:<br>1) Stem cell line<br>2) Transplantation<br>3) Surgical<br>4) GMP facilities<br>5) Clinical manufacturing<br>6) Regulatory | Safety and efficacy trial commenced at Moorfields for patients with sudden severe visual loss AMD |
| How much?                                | Millions   | £4m/£100k  | N/D   | N/D  | N/D   |
| When?                                    | 1965–2007  | 2007   | 2009 to date  | 2009 to date   | 2015  |



●● Why UK AMD research deserves public funds

Funders might question whether it is worthwhile using limited resources to support research into AMD in the UK when a great deal of money is spent on research in the US.

There is a wealth of evidence that the money spent on research in this country supports the UK economy. The UK also has the NHS and the National Institute for Health Research (NIHR) which promote, fund and support research in the UK, making it an attractive place to carry out clinical research.

Investing in UK research also maintains expertise in an area where we have world class researchers and can demonstrate that we punch above our weight on the world stage.

Royle and Waugh reviewed the performance of UK research into macular conditions, as reflected in the number of published articles and citations to UK macular research in high quality journals.<sup>68</sup> They reported:

- The countries producing the highest numbers of articles on macular disease research from 2011 to 2014 were: 36.1% from the United States, 9.8% from the United Kingdom, and 9.5% and 8.3% from China and Germany respectively. Collectively these made up 64% of the world’s output of macular disease research from 2011 to 2014.

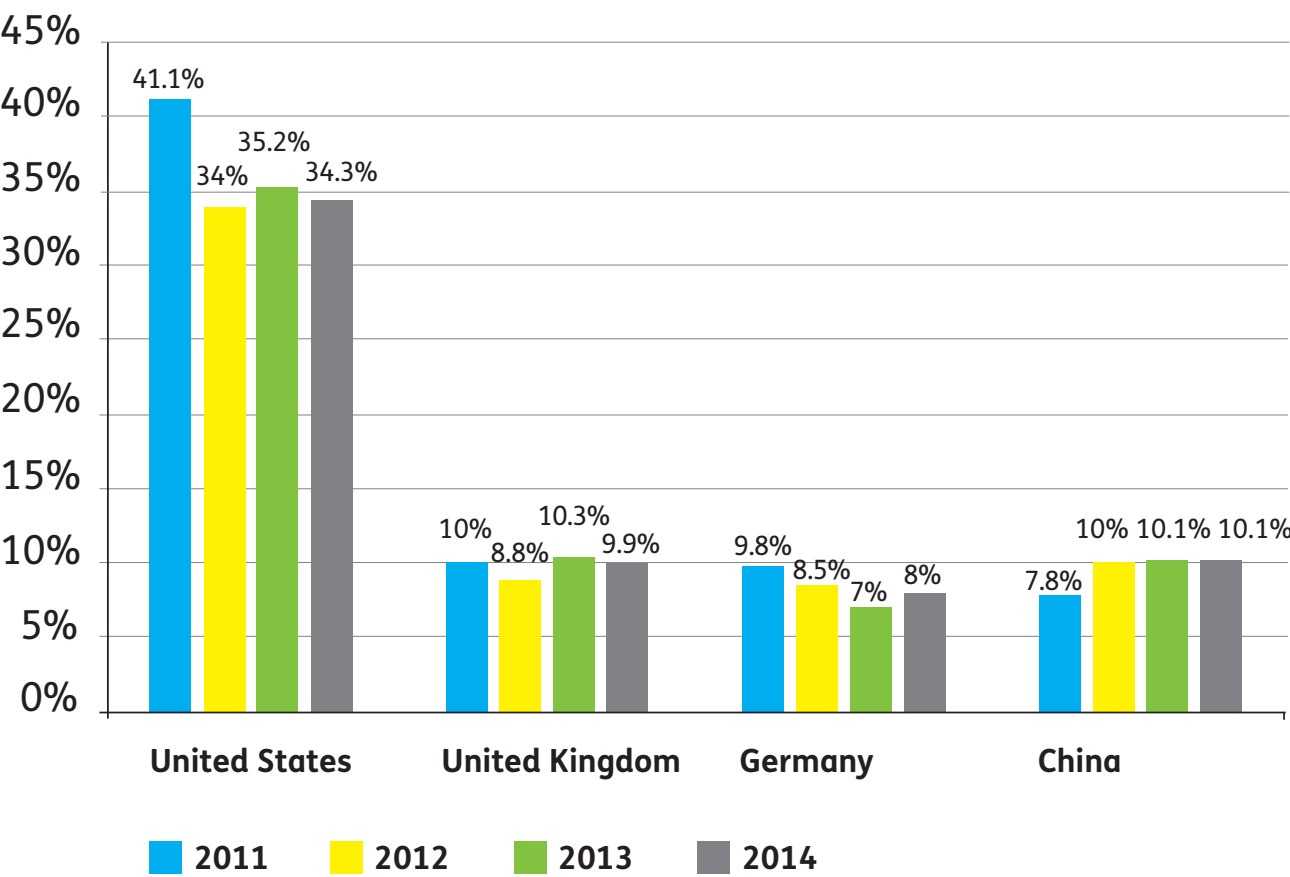


Figure 3: Percentage of world output of MD publications for the top four producing countries from 2011 to 2014.

- From 2011 to 2013, UK research produced 9.7% of the world’s output but received 14.2% of the world’s citations in macular disease; 16.2% of the top 10% of macular disease publications, ranked by citations, had a UK author.
- In terms of mean citations per article, the UK ranked third in 2011 amongst the USA, Germany and China, but rose to first ranking in 2012 and 2013.

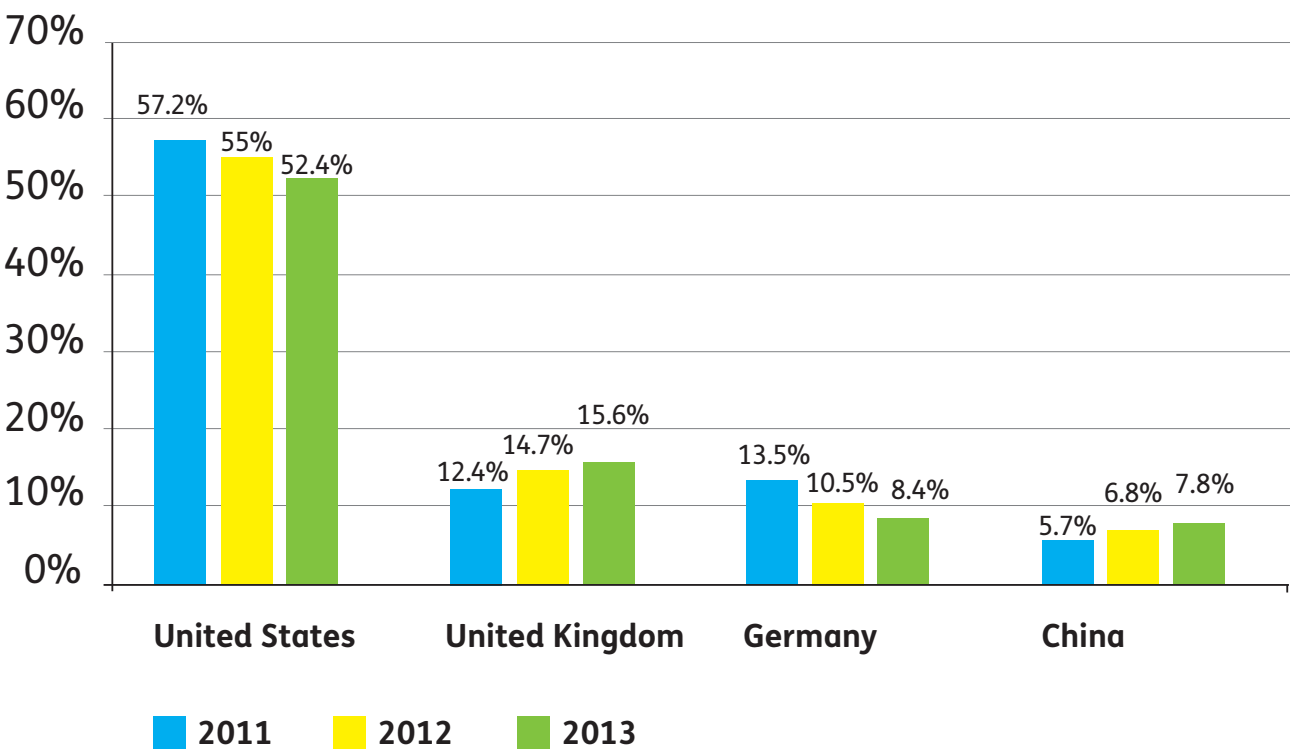


Figure 4: Percentage of world citations for macular disease for US, UK, Germany and China 2011–2013.

- In 2014, 13.2% of articles by UK authors appeared in the top 10% of journals ranked by Journal Impact Factors (JIFs), from a 9.9% share of the world’s articles.
- While the quality of UK research appears to be good, the volume of research seems low when compared to the burden of disease.



In spite of the limited funding, some excellent research is in progress which, with investment, could lead to new and improved treatments for wet and dry AMD.<sup>40, 69</sup>

Current anti-VEGF treatment regimens are burdensome for patients and health providers so research is exploring new anti-VEGF agents that might have greater potency and duration. Of the products in late stage development, conbercept, brolucizumab and Fovista® (used in combination with Lucentis®) are all in phase III trials.

Various ways to improve anti-VEGF delivery are also being investigated including using viral vectors, eye drops, nanotechnology and implants or ports to deliver drugs into the eye for a sustained period of time. However, anti-VEGF treatment does not work for all patients and can only slow the course of the disease.

Targeting of additional growth factors, specifically platelet derived growth factor (PDGF), is now established as the most promising approach in the new wave of wet AMD products. Steroids are well-established in several indications but all the other targets under investigation are more speculative, with none advanced beyond phase II at present. These alternative targets include kinases, elements of the complement system, integrins and others.

Regenerative medicine is another potential approach to wet AMD treatment, with gene therapies particularly to the fore.

Three gene therapy candidates are in development for wet AMD. Two of these are using adeno-associated viruses (AAVs) as vectors, the third a lentiviral vector. The viruses are

genetically modified to encode a therapeutic protein for treating AMD and exert an ongoing therapeutic effect.

A number of approaches are being clinically trialled with the aim of halting or reversing the decline in retinal cell function seen in dry AMD: complement system inhibition, vascular insufficiency treatment, visual cycle modulation and neuroprotective and regenerative medicine.

An approach that is generating great interest is directed against the inflammatory component of the condition, in particular the complement cascade which is part of the innate immune system. Lampalizumab is a monoclonal antibody directed against complement factor D and is currently being evaluated in a phase III clinical trial. Results of phase II trials have shown the potential to slow the progression of geographic atrophy by around 20% but regular intravitreal injections would be required.

MC-1101 is an antihypertensive drug in phase III clinical trials which is administered as an eye drop. It increases blood flow in the choroidal blood vessels, preventing the accumulation of metabolic waste products and consequent neovascularisation behind Bruch's membrane. The company which makes it, MacuCLEAR, claims that this approach has more potential than treating metabolic waste pathways involved in dry AMD as blocking one pathway may be inadequate to halt disease progression.

Modifying the visual cycle is intended to slow dry AMD progression by slowing down the activity of the photoreceptors and reducing metabolic load on these cells. By achieving this, visual cycle modulating drugs may potentially reduce the accumulation of harmful waste products.

Acucela is developing ACU-4429 (emixustat hydrochloride) as a selective modulator of the visual cycle in rod cells. ACU-4429 is believed to reduce the accumulation of toxic by-products in the retina by binding RPE65 isomerase. The phase 2/3 trial for ACU-4429 has an estimated completion date of July 2016.

Stem cells have the potential to repair and replace damaged tissues. Research is concentrating on establishing the safety and tolerability of cell transplantation and, where this has shown promise, clinical trials have begun in people with wet and dry AMD. However, this treatment option is only likely to be suitable for some patients and is many years from being widely available in the UK.

Identifying the genetic variations among people with AMD has revealed more than 30 genetic variants that influence the risk for developing AMD. The situation is complex but becoming clearer as we improve our understanding thanks to the developments in genome sequencing. Genetics may be the key to understanding the risk of developing AMD and the rate at which it progresses, as well as targeting treatments to individual patients.

Retinal implants are visual devices intended to restore functional vision and provide the user with low resolution images by electrically stimulating surviving retinal cells. Such images may be sufficient for restoring specific visual abilities, such as light perception and object recognition. The first UK trial of the Argus II retinal prosthesis system for patients with dry AMD began in 2015. Retinal implants are only likely to be suitable for patients with severe loss of central vision and require rehabilitation sessions following surgery to learn how to use the system.

Exciting though much of this is and though there are many trials underway, there are still considerable obstacles to be overcome along these avenues of investigation and there are still very many fundamental questions about AMD that cannot yet be answered.

Research into AMD is hampered by the fact that only primates have maculae. Rodents, commonly used in research, do not.

Human retinal tissue has also been difficult to obtain. Most donated eyes are used for corneal transplants and the retina is discarded. Researchers need access to retinal tissue and that means more eye banks in the UK.

The pharmaceutical industry naturally wants, and therefore seeks, a profitable solution to AMD. A recent industry report on the outlook for the AMD market highlighted both the potential size of the AMD market but also the disappointing results of trials so far.

Table 7

| Strength and weaknesses in the AMD and other retinal diseases market, 2015 <sup>70</sup>                         |  |
|--|--|
| Strengths  | Weaknesses   |
| Multiple therapeutic targets are available   | Discouraging outcomes in trials and many terminated products   |
| New products may be used in addition to, rather than instead of, existing products                               | No approved treatments for dry AMD                             |
| Dry AMD and DR (diabetic retinopathy) are almost wholly untapped and very large markets for companies to address | Lack of clear product differentiation between products         |
|  | Off-label use of Avastin detracting from use of other products |

The same report notes that a question mark that ‘hangs over the head’ of the future of the AMD and diabetic retinopathy pharmaceuticals sector is the ‘widespread belief that the best cure for these conditions is not biological or small-molecule drug interventions that can stabilise or reverse disease progression, but rather prevention: a therapeutic approach that can stop AMD and DR developing in the first place is widely seen as the major goal by scientists and clinicians working in the field’.

Wherever the solution is found, the pace of research needs to increase if we are to defeat AMD before it overwhelms health systems. The need for more funding is real and it will require a concerted approach to conquer AMD.

## ••Research that is important to patients

It is important that research effort is directed at the issues that are important to patients. Fight for Sight and the James Lind Alliance led a valuable exercise to establish patient priorities for eye research. The macular disease work stream decided that these were the priorities researchers should concentrate on:

1. Can a treatment to stop dry AMD progressing and/or developing into the wet form be devised?

2. What is the cause of AMD?
3. How can AMD be prevented?
4. Are there ways of restoring sight loss for people with AMD?
5. Can the development of AMD be predicted?
6. What is the most effective way to detect and monitor the progression of early AMD?
7. What factors influence the progression of AMD?
8. Can a non-invasive therapy be developed for wet AMD?
9. Can dietary factors, nutritional supplements, complementary therapies or lifestyle changes prevent or slow the progression of AMD?
10. What are the best enablement strategies for people with AMD?

Only 8% of the UK 2011–2014 publications matched the top priority. 34% of the 2011–2014 publications did not match any of the priorities, mainly because the priorities did not include treatment of wet AMD. (The reason for this is not clear; it may be that the expectations for anti-VEGF treatment at that time were over-optimistic.)

We believe research funders should use the patient-led priorities to encourage applications that address the issues that are important to patients, although work may be needed to help translate the priorities into terms that are meaningful to research teams.



## ••The future for macular research

We must increase the investment in and pace of research into AMD:

1. We urge researchers into blinding disease, charities for people with blinding diseases and people who are blind or visually impaired to speak out about the low levels of funding for research into sight loss in general and AMD in particular.
2. Given the rising economic and human cost of AMD we believe there is a duty on publically funded bodies to put more resources into AMD research.
3. We ask more sight loss charities to consider contributing some of their resources to medical research.
4. Given the current focus of most sight loss charities, new sources of funding for AMD research need to be identified.
5. It is vital that investigators are helped to work as collaboratively as possible and that scientists from many fields are brought together to find the solution to AMD.

An outline proposal for a multi-centre consortium to address the challenge of early AMD can be found at Appendix D.

We propose to convene an urgent meeting of leading scientists, researchers and potential funders to agree the way forward.

We must bring together the best brains in all the diverse areas needed to solve the problem, to create a platform from which to integrate understanding, define key questions and orchestrate their resolution as swiftly as possible.

The UK is globally the logical place to drive this initiative given the very high proportion of top universities in the world rankings, the power of the combination of the NHS and NIHR (National Institute for Health Research) and our track record of successful delivery of collaborative projects.

**Macular Society**



●●Appendix A

Charity, Research Council and Government funding by Health Category. UK Health Research Analysis 2014

Table 8

| Disease area                       | Total spend<br>£m |
|------------------------------------|-------------------|
| Generic health relevance           | 478.0             |
| Cancer                             | 402.2             |
| Infection                          | 227.0             |
| Neurological                       | 194.4             |
| Cardiovascular                     | 138.5             |
| Mental health                      | 112.2             |
| Inflammatory and immune            | 85.7              |
| Metabolic and endocrine            | 60.4              |
| Musculoskeletal                    | 58.7              |
| Reproductive health and childbirth | 48.0              |
| Oral and gastrointestinal          | 39.4              |
| Respiratory                        | 34.1              |
| Stroke                             | 29.0              |
| Eye                                | 22.7              |
| Renal and urogenital               | 19.8              |
| Other                              | 13.6              |
| Blood                              | 13.4              |
| Congenital disorders               | 13.2              |
| Skin                               | 13.2              |
| Ear                                | 12.3              |
| Injuries and accidents             | 9.4               |
|                                    |                   |
| <b>Total</b>                       | <b>2,025.2</b>    |

●●Appendix B

Table 9

| Sight loss charities                     | Income 2014<br>£m | UK medical<br>research spend<br>2014 £m |
|--|-------------------|---|
| Sight Savers International               | 187.6             | 0 <sup>71</sup>                         |
| RNIB                                     | 118.7             | 0                                       |
| Guide Dogs                               | 101.4             | 0                                       |
| Sense                                    | 81.8              | 0                                       |
| Blind Veterans UK                        | 26.8              | 0                                       |
| SeeAbility                               | 15.1              | 0                                       |
| Thomas Pocklington Trust                 | 8.5               | 0                                       |
| Royal London Society for<br>Blind People | 8.5               | 0                                       |
| WESC Foundation                          | 7.0               | 0                                       |
| Royal National College for<br>the Blind  | 7.0               | 0                                       |
| Orbis Charitable Trust                   | 5.7               | 0                                       |
| Catholic Blind Institute                 | 4.7               | 0                                       |
| Christian Blind Mission (UK)             | 6.3               | 0                                       |
| Deafblind UK                             | 3.3               | 0                                       |
| Clarity                                  | 3.0               | 0                                       |
| Local societies                          | 164.2             | 0                                       |
| Fight for Sight                          | 3.2               | 3.6                                     |
| Macular Society                          | 3.7               | 0.4                                     |
| Moorfields Eye Charity                   | 4.1               | 2.3                                     |
| Moorfields Special Trustees              | 3.5               | 1.0                                     |
| National Eye Research Centre             | 0.8               | 0.7                                     |
| Other charities*                         | 9.6               | 1.6                                     |
|  |                   |   |
| <b>Total</b>                             | <b>774.5</b>      | <b>9.6</b>                              |

Source: Fight for Sight. \*RP Fighting Blindness, International Glaucoma Association, Childhood Eye Cancer Trust, British Council for the Prevention of Blindness, College of Optometrists. (Note: the figures for grants made in a year may be different from the amount spent on research in a year as grants may cover research across different time periods, e.g. some are for one year others might be for three or five years.)

Appendix C

Research with members and non-members of the Macular Society 2011

Charts key

Thinking about what the Macular Disease Society might focus on in future, please rate the activities below in order of importance

- Activity 1: Campaigning for people with macular conditions.
- Activity 2: Educating health professionals on the patient perspective of living with macular conditions
- Activity 3: Support and information for people with macular conditions
- Activity 4: Funding research into treatments
- Activity 5: Funding research into a cure

Figure 5

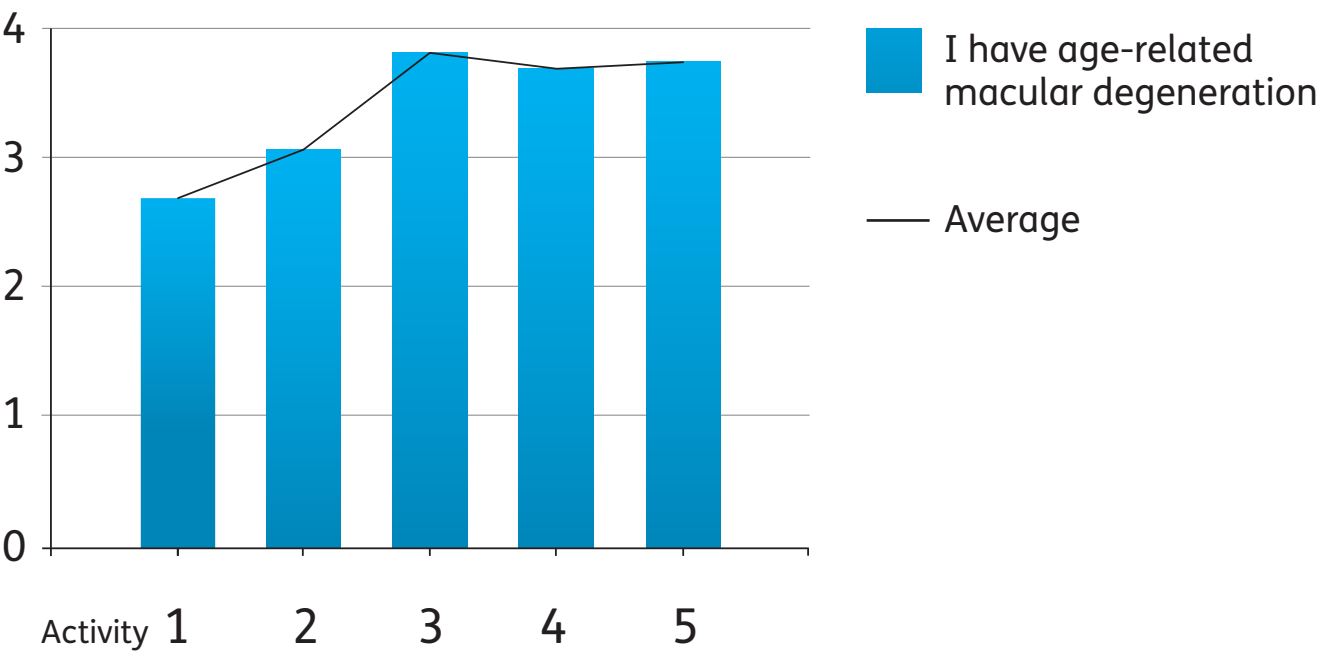


Figure 6

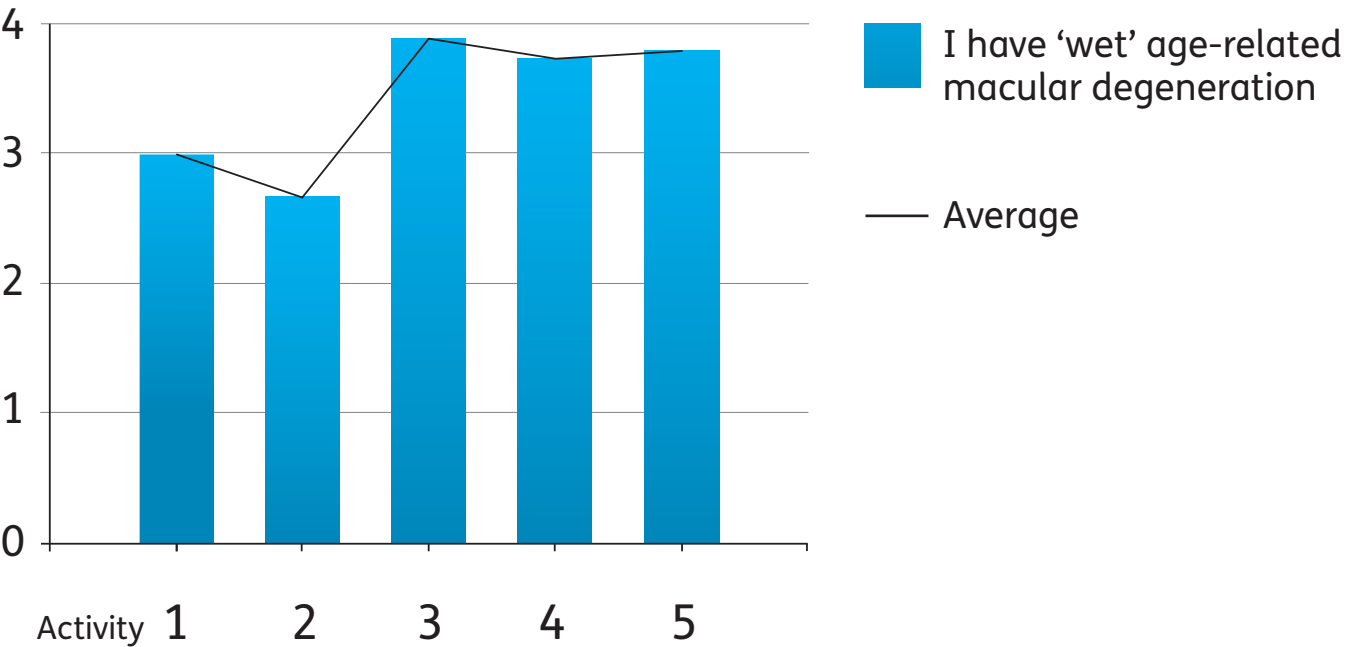
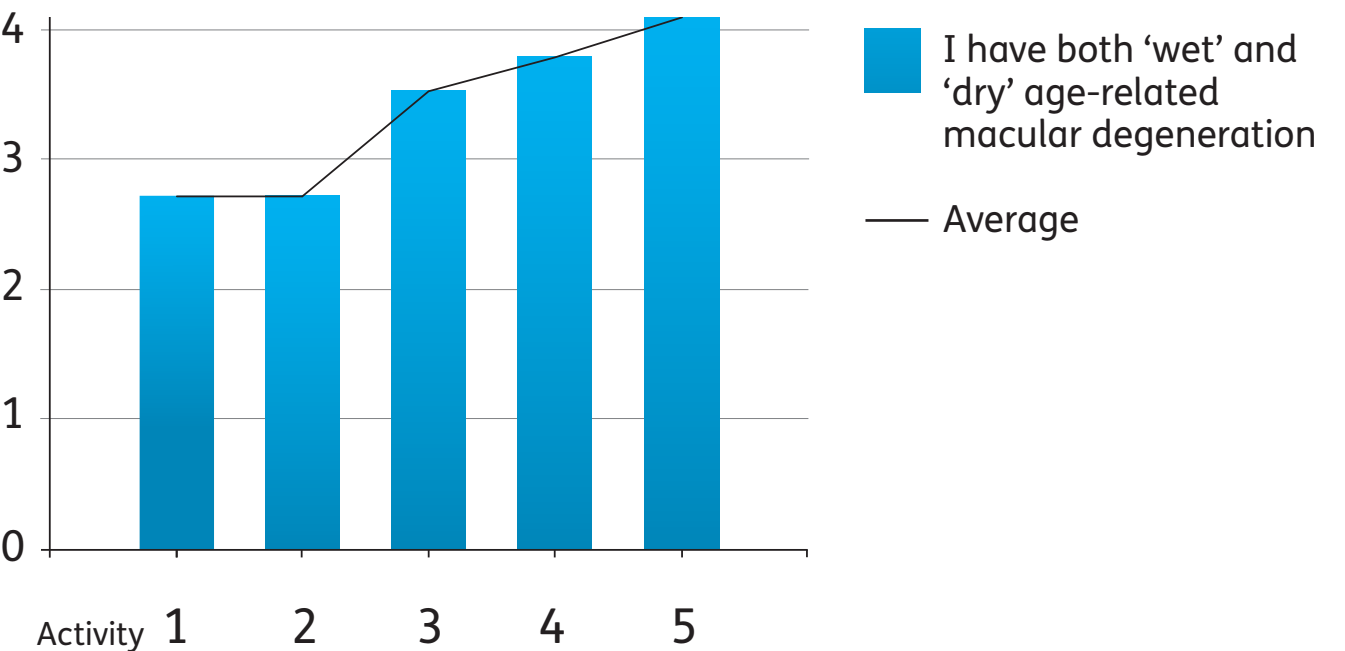


Figure 7





## ●●Appendix D

### A draft proposal for a multi-centre consortium to address the challenge of early age-related macular degeneration



By Professor Philip Luthert,  
Director, Institute of Ophthalmology

#### Background

Age-related macular degeneration is now a colossal healthcare challenge. Despite major advances and discoveries in genetics, epidemiology, pathogenesis and imaging we still don't understand what drives disease progression and therefore how to prevent the relentless march to the blinding form of either choroidal neovascularisation (CNV) or geographic atrophy (GA).

It is vital that we meet this challenge as the available and emerging therapies for late disease will never prevent the increasing burden of visual loss in our ageing population. Also treatments as they currently stand are already at breaking point and arguably unsustainable in terms of cost to patients and healthcare systems.

The complexity of age-related disease presents a formidable challenge but the excitement is that on the basis of extensive research already carried out and the new research tools that are and are to become available, we have the potential to solve this problem over the next 10 years. That is; to

substantially prevent the progression of early to late AMD, leaving many more of us with a longer healthy visual life.

#### The way forward

To meet this challenge we need to approach the problem in a concerted fashion. The critical ingredients are:

1. Substantial funding of the order of several millions per annum (in other words in a similar league as dementia).
2. A truly collaborative, consortium-based approach where we bring together, across the UK, the best brains in all of the diverse scientific and clinical areas required to solve the problem.
3. A platform with which to integrate understanding, define key questions/challenges and finally, orchestrate their resolution as swiftly as possible. This will require advanced systems-style models of disease and multiple teams to harvest, validate and integrate knowledge on an unprecedented scale.

To bring about the 'we are going to put a man on the moon' imperative to solving AMD, we need appropriate support for investigators to engage and move forward. We need to also engage the expertise beyond those traditionally working on AMD.

Whilst a detailed scientific 'road map' would have to be constructed by a carefully selected scientific advisory panel some of the key questions to be addressed and platforms to be established are as follows:

## ■ ■ Appendix D

### Key Questions

1. How many types of AMD are there? (For instance have we excluded the possibility that there is a non-drusen form of AMD because we select cases for study that have drusen?)
2. How do we identify patients at significant risk of blinding disease before their disease is so advanced preventive intervention is not realistic? (This is likely to require a combination of genetics, changes in proteins in the blood and some form of assessment of retinal structure and/or function.)
3. What are the critical pathological pathways activated in early disease, which if manipulated, will slow or prevent disease progression? This is a huge area of work that will involve development of new imaging techniques, animal models and expanding our interrogation of retinal function in patients.
4. What is the most cost-effective, safe way to interrupt disease progression?

### Enabling platforms

1. Cohorts of patients with intermediate AMD to follow prospectively with imaging and biomarkers, and to have whole genome sequencing.
2. Access to large cohorts of patients with established atrophy or CNV who can be genotyped to answer the question how many types of AMD there are?

3. National resources such as UK Biobank, 100,000 genome projects etc.
4. Access to large numbers of donor eyes so that we can study in great detail the proteomic and gene expression patterns across the retina, RPE and choroid in patients with genetically characterised intermediate AMD and to support this with in depth localisation studies.
5. A data science platform to integrate published and consortium knowledge and understanding.
6. Consortium management and funding platform.
7. Annual meetings or workshops bringing together the expertise from all disciplines to be challenged to generate new experimental paradigms.
8. Enterprise platforms to move intellectual property forward swiftly.

### Skills we might be expected to draw together in the Consortium

The multi-disciplinary consortium might be expected to combine expertise in:

- Patient phenotyping with emphasis on retinal imaging, assessment of retinal function and biomarkers.
- Analysis of human tissue.
- Cell biology and animal models including relatively large-scale gene editing/iPSC platforms.

## Appendix D

- Inflammation in the context of ageing and degenerative disease that will include focus on complement, macrophage, mast cell and dendritic cell pathobiology.
- Comprehensive 'omics capability including proteomics and next generation sequencing including RNA sequencing and epigenetic analysis.
- Cellular metabolism and bioenergetics with the ability to link cell biology to life-style factors, notably diet.
- Analysis of large-scale epidemiological datasets.
- Multi-scale, systems-style integrative modelling of disease.
- Critical target identification and small molecular screening as well as development of biologics.

It is proposed that as a matter of urgency a meeting is convened between a subset of potential scientific leads and funders to draft a more detailed plan of action.

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