Eye Research – an equal partner

A Report entitled “Eye Research – an equal partner”, compiled and edited by Julian Jackson, featuring contributions from leading researchers in the UK

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17/09/2020

VISION BRIDGE
Fighting Sight Loss - Supporting Sight

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1.0 Introduction

This Report aims to drive vision and eye health up the list of public health priorities, raise awareness of the tremendous legacy and potential of eye research, highlight the challenges facing eye research including the critical need for greater investment and indeed provide added momentum to the debate around increasing biotech and bioincubator support for translational research. It provides a snapshot of the wide range of eye research ongoing in the UK and further afield and points to the vital link between laboratory work and positive clinical outcomes.

It not only makes the case for eye research as a major stakeholder and key influencer in the provision of quality eye care but also justifies the position of eye research as an equal partner in delivering an improved quality of life for the visually impaired alongside the provision of key services such as accessible transport, disability benefits, counselling and rehabilitation and social support.

This Report appears at a time when there is widespread concern over our growing and ageing population with their associated health problems and the increasing pressures this applies to our eye care infrastructure, resulting in greater patient demand, missed appointments and longer waiting times.

It is also generally acknowledged that eye health is still a low priority for many Clinical Commissioning Groups (CCG's) in England, despite the projected doubling of those with sight loss to 4m by 2040, the many and varied impacts experienced by those with sight loss, the cost to the economy and the surveys indicating that over 80% of people say that sight is the one sense they most fear losing.

Therefore, it is suggested that much more clinical leadership is required at local level as well as greater collaboration between local eye health networks and commissioners alongside greater collaboration and less duplication between voluntary organisations to ensure that eye health and the provision of eye care is given the top billing that it deserves.

It is equally important to look upstream of the eye clinics and hospitals to assess the past and ongoing contribution that eye research continues to make in the fight against avoidable and unavoidable sight loss.

This Report is confident in stating that eye research continues to be a world of discovery, innovation and achievement which can undoubtedly assist in the development of an eyecare system that is safe, efficient, effective, flexible, proactive, responsive, understanding, intelligible to patients and value for money.

Over the last 50 years, eye research has delivered some vast improvements in our understanding of the patterns and processes of eye disease and produced step changes in detection, diagnosis and prognosis, treatment and the rehabilitation of patients. However, it remains little understood amongst policy makers, stakeholders, practitioners and providers within eye care. So, the level of awareness and understanding of sight loss needs to be greatly increased, but just as crucially the role that eye research plays in the prediction, treatment and prevention of further sight loss, the enhancement of remaining vision and the restoration of sight must be proactively highlighted. In addition to this, downstream of eye research, the urgent need to improve patient access and funding of eye care services in the UK is having to compete with a range of increasingly pressing social priorities and a constant focus on historically prioritized diseases such as cancer and dementia.

With the scenarios outlined above, it is imperative that we continue to press the case for the need for a sustainable and effective eye care system that can unlock people's potential and access to employment, improve quality of life, confidence and self-esteem, expand social connectivity, avoid

costs associated with falls and mental illness, boost productivity and deliver value for money. However, in support of this, we must also continue to highlight the important role that eye research can play in educating up practitioners and related healthcare professionals, the crucial position that eye research holds in support of such an eye care system and the critical link between eye research and follow on reduced pressures in secondary care, shorter waiting times and improved patient access to appropriate assistive technology, swifter and safer procedures, positive clinical outcomes and generally improved eye health. We believe that the current and ground breaking research examples contributed by leading researchers, clinician scientists and developers featured in this Report help in this regard.

2.0 Understanding the patterns and processes of disease

Understanding the patterns and processes of disease is a fundamental prerequisite for delivering sustainable, effective and cost-efficient treatments, providing long term benefits to patients and cost savings to the health care system. The ability to identify the drivers of disease and new therapeutic targets, create opportunities for earlier and preventative therapeutic interventions and alternative treatments, predict the onset and rate of disease progression and gauge the way in which individual patients may react to treatments are all crucial weapons in the fight against sight loss.

2.1 Harnessing human diversity to better understand and treat immune mediated ocular diseases

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Our immune system defines our health. It protects us from infectious diseases and constantly interacts with the billions of microorganisms that live inside us and on our skin. When we become ill it responds and sometimes loses its balance. Occasionally it directly causes self-harm. All these characteristics of immunity are as true in the eye as they are elsewhere in the body. The challenge is to understand and correct these imbalances when they occur to restore and maintain the ability of the eye to see.

Each one of us has a unique life-course through which we are exposed to multiple environmental influences, including our own particular history of exposure to bacteria and viruses, some of which stay with us forever and all of which interact with us in a manner shaped by our basic genetic code. When this leads to inflammation and is manifested in the parts of the eye that threaten sight, we typically resort to the types of treatments used for arthritis and the prevention of organ transplant rejection to bring it under control. However, when inflammation is low grade and insidious, for example in diabetic retinopathy or age-related macular degeneration, we have yet to work out how to medically respond.

It turns out that there is no single solution that works for all of us when our immune system is out of kilter. This is most evident when common drugs are used to suppress harmful inflammation. Some people get better and others do not, some people feel fine and others find the side effects intolerable. We are trying to understand this diversity by modelling key immune cells in a dish in order to develop new diagnostic tests that tell us who will respond well to treatment and who would be better to try something else. We are also seeking to exploit the wonderful transparency of the eye to directly observe the way immune cells interact in a range of sight threatening scenarios.

In all this we are applying the latest technologies in characterising immune responses to compare individuals and understand both our similarities and differences to develop precision diagnostics and medicines. This is achieved by harnessing multiple collaborations across the globe, both in academia and in industry, with the goal of generating new insights into the features of our biology that distinguish between a good and a bad visual prognosis, and ultimately to harness the power of our immune system to restore health and improve lives.

2.2 The case for 'basic science'

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The Queen's ophthalmology programme holds a distinctive and important position in UK eye research, with its success being underpinned by synergy between basic scientists and clinicians who are focused on the same retinal diseases and through multidisciplinary teamwork, drive, innovation and impact.

Our investigator profile consists of academic ophthalmologists, optometrists, surgeons, pharmacists, nutritionists, physicists and NHS consultants who work closely with basic scientists who maintain their core interests in vascular and endothelial pathophysiology, stem cell biology, neural and glial degeneration and ocular drug delivery across discipline themes relating to angiogenesis, inflammation, metabolism and regenerative medicine. Together, these investigators have a track-record of working together to advance understanding of retinal disease and some of this discovery science has formed an essential foundation for follow-on local and international clinical trials.

In the clinical realm, our academics have assembled unique cohorts of highly characterised patients, telemedicine infrastructure, national screening networks, and ophthalmic trial knowhow has resulted in Queen's achieving unprecedented success in leading government and commercial-sponsored multicentre, international clinical trials. These clinical trials, combined with the eye-health pillar of the NI Cohort of Longitudinal Ageing (NICOLA), are led by Queen's in partnership with the Belfast Health & Social Care Trust. Together they have already had impact on Northern Ireland healthcare with ~3500 patients receiving uniquely comprehensive ocular evaluation within NICOLA, and ~2500 patients being enrolled (nationwide) in AMD, DR and glaucoma trials thereby receiving significantly enhanced clinical care.

Benefits for people in the UK & globally

Beyond Northern Ireland, the ophthalmology programme has driven advances in our understanding of key retinal diseases and this knowledge base has led to appreciable improvements on the standard of care and policy decision making. Queen's has been leading studies on European, Indian and African population environmental and nutritional risks associated with AMD and DR for many years. As a direct result of these efforts the burden of vision loss has been reduced, quality of life improved and significant economic savings made across the UK and worldwide.

The following are some examples of the impact achieved:

- The IVAN trial led by Prof Chakravarthy provided definitive evidence that an off-label drug for treating the wet form of AMD was equally efficacious as the more expensive drugs prescribed for the same condition. As a result of IVAN, bevacizumab was placed on the WHO Essential Medicines List and led to policy recommendations in the United States and a number of European countries. Based on evidence provided by IVAN, recent high court outcomes in the UK will save the NHS £500 million per year and the trial has been credited with creating a new era, giving doctors the freedom to prescribe cheaper unlicensed drugs in the UK (1) .

- The NIHR-sponsored EAGLE trial, led by Prof Azuara-Blanco, provided evidence that supported change of current practice and cost-benefits for treating primary angle-closure glaucoma with better clinical and patient-reported outcomes (2).

- Cataract is the world's leading cause of blindness, treatable only by surgery which often carries bad outcomes in the developed world. Innovative research by the Queen's team led by Prof Congdon has improved the accuracy of immediate post-operative outcomes through a free Smartphone App called BOOST. This has been translated into six languages and adopted by the WHO, multiple vision NGOs, national ophthalmic societies, and leading surgical facilities in low/middle income countries (LMICs). BOOST has significantly reduced vision loss from cataract in developing countries (3).

- As a recent recruit from Moorfield's Eye Hospital, Prof Peto leads the Queen's Retinal Reading Centre which plays an essential role in ophthalmic image analysis for major international image-based trials and interventions, such as the European Eye Epidemiology Group, the EyeRisk EU Consortium and in the provision of data to the Global Burden of Diseases database (4) . The Centre provides international training in DR screening/grading and delivery of treatment to all levels of healthcare providers. Prof Peto's leadership underpins the success of the Queen's Diamond Jubilee Trust Diabetic Retinopathy Screening Programme which has already led to several thousands of patients being screened and treated in the Commonwealth, who otherwise would have gone blind.

In addition to "conventional" eye diseases significant pioneering programs are also run at QUB to introduce the eye and eye imaging as a surrogate to neurodegeneration in diseases like Alzheimer's disease, Multiple Sclerosis, Down Syndrome as well as cardiovascular disease, cytosis fibrosis and arthritis.

In a year of profound change triggered by the Covid-19 crisis and a renewed focus on public health, Queen's has continued to support the outstanding work being undertaken in vision science as part of our Vision 2020 programme. Vision 2020 was an ambitious, global project first envisaged in the late 1990s with the aim to eradicate preventable blindness while raising awareness of the importance of eye health and its impact on the world. Progress has been strong and steady with many notable milestones along the way thanks to the focus and dedication of thousands of clinicians, researchers and basic scientist.

Queen's made the decision to celebrate the year 2020 with a 12 month special timetable of seminars, workshops and conferences to mark this important milestone, playing a key leadership role in international efforts to find real solutions to complex and critical issues facing our society.

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2.3 Building a Living Lens to Fight Diseases of the Eye

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Regarding ophthalmology, the main aim of my research is to produce a 3D bioengineered 'LensMimic' made from lens epithelial cells. Thanks to an award from the Rosetrees Trust, we are developing world leading materials technology that will facilitate the generation of future ophthalmic solutions for lens and eye diseases. Research published in Nature in 2016 showed that lens epithelial stem/progenitor cells can self-renew, forming a 3D transparent lens-like

structure that refracts light. And hence modernisation of the accepted surgical procedure with bioengineered solutions that harness the natural regenerative properties of the lens have been proposed.

In order to facilitate the translations of bioengineered breakthroughs from the laboratory to the clinic, we are generating lens-like structures (aka 'LensMimic') and are optimising their transparency and accommodative power. We anticipate that success will enable researchers to address key fundamental biological and medical questions; questions which cannot be answered using animal or donor lenses.

My second area of interest is the development of insightful mathematical models such as Durham's ordered pull-through model of the cell-density profile for the mammalian lens epithelium. Together with Durham colleagues, and through generating new experimental data, a universal model covering lenses varying by an order of magnitude from bovine (approx. 18 mm) to mouse (approx. 2 mm) was created. The research included human lenses and confirmed that mammalian lenses scale with size. The validated model was published in the Royal Society Journal Interface (J. R. Soc. Interface).

2.4 Eye Related Research

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The main focus of my research in the area of ophthalmology is to develop advanced optical instrumentation to both study the development of the eye, and also to help advance clinical practice. In the clinical case we are also looking at opportunities of using the eye, and its intimate connection to the brain, as a route to probing more systematic health related conditions.

In terms of the development of the eye the focus of the current research is to use advanced methods of optical microscopy to study the developing lens within a Zebrafish for extended periods of time. The lens develops roughly 24-48 hours post fertilisation in a Zebrafish and using a novel light sheet microscope we have developed (1), we are looking at not only how the shape is formed and controlled but also the exquisite control over the local refractive index within the lens. This is linked with both the possible use of such chemical control of graded index materials in industry, but also in the longer-term formation of cataracts within human subjects.

The second area of interest is to develop new methods of imaging the retina at high speed and with high spatial resolution to study the blood circulation within the retina and choroid. Due to the link with the brains blood flow and hence the core flow within the body we are looking to link these measurements with the development of major complications in health, such as septic shock and monitoring of patients within intensive care. This work highlights the fundamentally close relationship between the eye and the overall health of a patient.

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2.5 Harnessing genetic information to discover what causes myopia

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Myopia (short-sightedness) typically develops in childhood, through excessive growth of the size of the eye. This means light is brought to a focus in front of the retina leading to blurry vision, which requires spectacles or contact lenses to be worn to achieve sharp vision. Patients with myopia, especially high-degree myopia, are at a much-increased risk of retinal detachment and degenerative changes to the retina, making myopia a common cause of visual impairment.

In recent decades the prevalence of myopia has doubled in Europe, and reached staggeringly high levels in parts of South East Asia (for example, 70-80% of young adults are myopic in Taiwan, Singapore, and parts of China).

International collaborations of genetics researchers (including from Cardiff and London) studying many thousands of participants has led to the discovery of more than 150 'myopia susceptibility' sites scattered across the human genome. Each site contributes a small increased risk of myopia. However, for the majority of these sites, the underlying biology of how they confer an increased risk of myopia is not known. Recent research suggests these genomic sites interact with lifestyle factors to exert their effects.

One recent study, researchers from Cardiff and Bristol investigated the role of education. Years spent in education has long been implicated as a risk-factor for myopia, but since it would be unethical to conduct a randomised controlled trial of high vs. low education, the issue has been controversial. Using a technique called 'Mendelian randomisation', which leverages the increased risk conferred by genetic variation between individuals to draw causal inferences, the new study yielded very strong evidence that some aspect of education does indeed increase the risk of myopia.

2.6 Challenges and therapeutic opportunities for Age-related Macular Degeneration Proteostasis mechanisms in healthy, ageing and diseased Retinal Pigment Epithelium

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Age-related macular degeneration (AMD) is a complex, multifactorial disease characterised by a progressive degeneration of the central part of the retina (macula) directly linked to the dysfunction of the essential, supporting monolayer of cells – retinal pigment epithelium, RPE. The resulting visual impairment has been associated with a broad range of causative factors, both genetic and environmental, alongside ageing as a major risk factor. Despite the multitude of these factors, multifaceted functional interactions between these highlighted a relatively small number of common fundamental cellular processes that are affected. In addition, increasing evidence from other age-related diseases that affect different parts of the central nervous system supports the notion that the impaired cellular processes are substantially similar with those in other degenerative diseases especially in terms of abnormal extracellular deposits, protein processing and trafficking, metabolic and oxidative stress, inflammation and microvascular abnormalities, thus pointing to similar pathogenic cellular mechanisms.

While vision loss and blindness are not a normal part of ageing, age is one of the strongest risk factors for developing AMD/age-related degenerative diseases. All structures of the eye undergo ageing changes leading to varied effects. However, cells that maintain a non-proliferative state and a long lifespan, as well as their support structures – such as the retinal pigment epithelium and Bruch's membrane, RPE/BrM, which are key sites for AMD pathogenesis – are particularly susceptible to age-related changes affecting essential cellular processes in the retina.

Proteostasis, or protein homeostasis, is a key achievement of cells that impacts critically on virtually every aspect of cell physiology, functions and lifespan. The cellular machinery that underpins proteostasis integrates complex, multi-layered regulatory networks that control the biogenesis, folding, trafficking and degradation of proteins present within and outside the cell. Loss of proteostasis, or failure of mechanisms responsible for maintenance of protein homeostasis, both intra- and extracellularly, is central to understanding the cause of AMD associated with different levels/forms of proteins, excessive protein misfolding, aggregation and degradation leading to loss-/gain-of-function phenotypes.

In this respect, the Ocular Molecular Biology and Mechanisms of Disease Group in the Department of Eye and Vision Science, University of Liverpool is studying various aspects of proteostasis that are essential for the normal functions of the RPE that become impaired in (neuro)degenerative processes. One area that the group has been focusing on is the identification and characterisation of the key effectors of proteolysis (protein degradation) and its regulation in healthy, ageing and diseased RPE cells. Specific proteolytic events, both intra- and extracellularly underpin major functions of the RPE – phagocytosis of spent photoreceptor outer segments, response to oxidative stress, authophagy, modulation of extracellular matrix, etc. The regulation of proteolysis therefore defines to a great extent RPE physiology and is implicated widely in pathophysiological processes associated with its ageing and disease. Not surprisingly from this point of view, the RPE invests a remarkable metabolic effort in synthesising and maintaining appropriate levels of a broad range of proteolytic enzymes and their inhibitors; these are some of the most abundantly expressed proteins by RPE; and one of the most potent regulators of proteolysis, the cysteine proteinase inhibitor cystatin C, is among the top 2% abundantly expressed genes by RPE. This inhibitor proved to be one of the models for studying mechanisms of impaired intracellular trafficking, organelles interactions, protein mis-processing and aggregation, imbalance of proteolytic activities.

The group has been studying the expression profile of cathepsins and their inhibitors, their processing in relation to normal and pathophysiological/ageing states of the RPE and thus identified significant imbalances in their activity, targeting and interactions in response to cellular stress leading to AMD development. For example, the basolateral secretion profile of cystatin C in RPE cells suggested a role in relation to maintaining the structure and function of Bruch's membrane/choroid. A variant of cystatin C has been associated with increased risk of developing exudative age-related macular degeneration (AMD) and presents leader sequence-related dysfunctional intracellular trafficking, leading to reduced efficiency of processing through the secretory pathway, altered folding and increased aggregation. Remarkably, the same variant was the first one for which a genetic association for increased risk of both Alzheimer's Diseases and AMD was described in different studies.

Overall the findings suggest that the RPE has a significant control over extracellular proteolytic events, via the secretion of highly active proteases, and their inhibitors. Molecular stress associated with natural ageing can alter the protease/inhibitor balance in/around RPE, which alongside misfolding of soluble proteins have the potential to contribute to pathological features of AMD, such as breakage of blood-retina barrier, formation of toxic aggregates, and structural abnormalities.

Evidence emerging from ours and other groups indicates that understanding of proteostasis as a salient feature shared by age-related and neurodegenerative processes is of outstanding importance for targeting early disease, for identifying interventions amenable to possible prevention or slow down of disease, and for rationale identification and design of more precise AMD therapies, efficiently

targeting impaired intracellular trafficking, protein misfolding, aggregation and proteolytic imbalances.

2.7 The importance of earlier interventions and alternative treatments

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Despite enormous progress in recent years in treating eye disease where there are major vascular problems (such as in wet age related macular degeneration and diabetic retinopathy) there remains an urgent clinical need for new therapies, especially those that intervene early in the disease process. The aim of earlier intervention is to halt or slow down the disease progression before abnormal blood vessel growth causes significant retinal damage and sight loss. New therapies, that hit completely different targets than the current approved drugs used to target abnormal blood vessels, may be effective at an earlier stage. Moreover they may prove to be even more effective when combined with current drugs, such as those targeting VEGF, or may even provide benefit to patients when current standard of care treatments fail.

In response to this growing clinical need the Greenwood and Moss laboratories at UCL Institute of Ophthalmology have been searching for new therapeutic targets that may be involved in the early disease changes that precede the more obvious and macroscopic manifestations of disease (gross pathology). For many years, they have been studying the fundamental causes of vascular problems in retinal disease, with the aim of identifying new therapeutic targets. This work has led to the discovery of a molecule, LRG1, that is increased in many diseases and plays an important role in promoting the growth of unwanted diseased blood vessels. They have now established that the disruptive action of this molecule can be blocked with a drug.

The uncontrolled growth of highly abnormal blood vessels is a feature of a number of sight-threatening diseases including wet age-related macular degeneration, proliferative diabetic retinopathy and retinopathy of prematurity. It is also a characteristic of life-threatening conditions such as cancer and atherosclerosis (clogging of arteries with fat deposits leading to hardening of arteries and then possibly stroke and heart attack). These new blood vessels are highly damaging as they often fail to deliver a sufficient blood supply, leak fluid and can rupture causing tissue haemorrhage. As a consequence, dysfunctional vessels contribute towards the incidence of a disease (morbidity) and the death rate amongst patients (mortality) associated with many diseases.

Although considerable advances have been made in preventing abnormal vessel growth in the eye, it may be preferable to devise new therapies that prevent the early blood vessel changes that underpin abnormal vessel growth or, when they do occur, promote the growth of normal vessels. The Greenwood and Moss labs have discovered that the molecule LRG1 not only promotes disorganised new vessel growth but also disrupts the function of existing vessels. Following the development of a therapeutic agent (Magacizumab) that blocks the disrupting effect of LRG1, the Greenwood and Moss teams have found that they can improve existing vessel function and reduce abnormal vessel growth not only in the eye but also in solid cancers. This finding that inhibition of LRG1 reduces early vascular dysfunction, that often precedes the onset of new vessel growth, raises the possibility that earlier intervention in diseases such as diabetic retinopathy may be possible. The group has now developed a smaller sized therapeutic molecule for ocular administration and have created, with UCL Business, a spin-out company (PanAngium Therapeutics) to raise funding to take this into patients. The aim is to embark on clinical trials at Moorfields Eye Hospital in 2022/3 for the treatment of wet age-related macular degeneration and diabetic retinopathy.

In conclusion, despite the many years it takes (usually 15-20 years) from discovery to patient benefit, this work demonstrates the importance of discovery science as this allows for greater step changes in new treatments to be achieved. Taking what is known and tinkering with it only delivers small incremental improvements and the way medicine is going shows that single treatments are insufficient and providers of eyecare will need to use combination therapies to enhance efficacy.

2.8 Major advances in genomic research in ophthalmology

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Several developments in human genomics have been made in recent years that have been facilitated by rapid advances in high throughout DNA sequencing technology and the increasing affordability of such techniques.

Research in genetics was historically a time-consuming process, involving the painstaking analysis of single genes and their function. For example, research by Dr Atan and her team showed how certain genes are important to pathways in the retina responsible for our night vision (PNAS, 2015; Sci Report 2018) – if any of these genes are faulty, one would expect patients affected by these gene defects to have 'night blindness' (difficulty seeing in the dark).

In the last 10-15 years, however, high throughput DNA sequencing has revolutionised this process, such that it is now possible to analyse all of a person's DNA sequence or 'genome' at one time. As a result, genetic testing for rare eye conditions has become much more efficient and the probability of finding faulty gene defects which are responsible for causing rare eye conditions is now much higher, allowing opportunities for earlier diagnosis, management, and screening. So that more people could benefit from the power of genomics, NHS England rolled out its Genomic Medicine Service at the end of 2018 enabling genomic sequencing to become part of routine hospital care.

The benefits of genomic medicine also apply to more common eye disorders, such as age-related macular degeneration (AMD), which are caused by a combination of several genes and environmental risk factors. Research by Dr Atan and her team showed how variations in the VEGF gene can influence risk of AMD (Hum Mol Genetics, 2006) and Vascular Endothelial Growth Factor is the main stimulant for neovascularization in AMD that is targeted by modern therapies like Lucentis and Avastin. With current technology, it is now achievable to analyse all of the genetic risk factors for AMD at once to determine one's individual risk of developing AMD in future.

Armed with this knowledge, it is possible to make lifestyle changes that might mitigate against one's genetic risk of AMD, such as eating a well-balanced diet and cutting out smoking. Although this type of genetic risk assessment of future eye disease is not offered by the Genomic Medicine Service in the NHS, several private companies offer whole genome DNA sequencing as a commercial service to members of the public.

Finally, genomic tools can be used to measure the causal relationship of one risk factor or disease on another, in a way that was not ethically or practically possible before. Myopia, or short-sight, is one of leading causes of visual disability in the World, but why the global prevalence should be rising so rapidly in recent decades was not clearly understood. Numerous observational studies had reported strong associations between educational outcomes and myopia, but whether our schooling methods cause myopia or children with myopia are more studious was not known with any certainty, since randomising children to different levels of education would be unethical. Using a technique called mendelian randomisation, Dr Atan and her team found that more time spent in education is a causal

risk factor for a greater level of myopia, but little evidence that myopia itself leads to better educational outcomes (BMJ, 2018). Consequently, increasing the length of education in developed and developing countries may inadvertently increase myopia prevalence and potential future visual disability, with implications for policymakers who influence our educational practices.

2.9 The pre-Descemet's layer and its relationship with the trabecular meshwork - implications for eye pressure control, glaucoma and its management

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The discovery of a new layer in the human cornea (the clear window in the front of the eye) in 2013 changed the way we look at the cornea, especially with regard to corneal surgery and understanding corneal pathology. The work leading to the discovery and characterisation of the layer was acknowledged by the Times Higher Education Award for 'Research project of the year' in 2014. The layer was termed the pre-Descemet's layer or Dua's layer (DL). It is now largely accepted in the ophthalmic community with inclusion in over 225 books, 314 citations to the original paper, and recent endorsement by the American Association of Ophthalmic Oncologists and Pathologists who have termed it the Dua-Fine layer. It has considerably improved our understanding of the transplant procedure used to replace diseased corneal tissue, leaving the unaffected and critical endothelial layer intact – Deep anterior lamellar keratoplasty (DALK) and made the procedure safer. It has led to the innovation of three new surgical procedures, namely the DALK-triple, suture management of acute hydrops in keratoconus and pre-Descemets endothelial keratoplasty. It has resulted in paradigm shifts in our understanding of Descemetoceles, acute hydrops, Descemet's membrane detachment and spread of micro-organisms in the deep cornea layers.

Of greater potential significance is the fact that the collagen fibres and elastin content of thelayer are like that of the trabecular beams in the trabecular meshwork. At the periphery, beyond the termination of the Descemet's membrane, the DL imperceptibly merges with the trabecular meshwork. Recently we have published results demonstrating that the DL has more elastin (elastic fibres) than any other part of the cornea and this matches the elastin content of the trabecular meshwork. These previously unappreciated relationships between the DL and the trabecular meshwork have considerable importance in the context of control of drainage of the eye fluid (aqueous humour) from the eye and maintenance of eye pressure control with implications for occurrence of glaucoma.

Glaucoma (sustained rise in eye pressure causing tissue damage) is a blinding condition with more than 70 million affected worldwide. Eye pressure is maintained by controlled outflow of eye fluid (aqueous). The DL is hypothesised to exert biomechanical influence on the TM to keep it functioning. Degradation of elastic fibres is known to affect eye pressure by disruption of the morphology of the trabecular beams. It is very likely that degradation of the DL, both in its elasticity and collagen structure, can lead to loss of its biomechanical effects on the functioning of the trabecular meshwork with consequent loss of eye pressure control.

We have designed a series of studies and experiments on human eye bank eyes in an laboratory (ex-vivo) organ culture model, to test various aspects of eye pressure control in relation to the function of the DL, which will be modified by surgery and enzymatic degradation to simulate real life conditions. This brings an entirely new approach to understanding mechanism of eye pressure control and glaucoma, which will lead to newer approaches in preventing and treating glaucoma.

Support is sought to fund this research and a post-doctoral fellow to generate preliminary data to enable applications to the major eye charities in the UK for ongoing funding of the research. It is

envisaged that more than one aspect of the research will be patentable for development of treatment strategies for glaucoma.

2.10 If there is no struggle, there is no progress

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Often it is easy to forget the amount of time, effort, and regrettably money, it takes to conduct research into how diseases happen and how best to intervene. AMD is certainly no different in this regard, but there are signs that all that research effort is beginning to bear fruit. We have known of a strong genetic link between a persons' immune system and AMD, particularly the dry form of the disease, for almost fifteen years. Mutations in genes that affect the complement system make individuals particularly at risk of developing the disease, where an over-active complement system in the back of the eye drives inflammation and tissue damage. Our greater understanding of the genetic link has also made it possible to refine which patients would benefit from treatments designed to take back control of this aberrant immune response. But the early clinical trials targeting complement all failed to halt, or even slow, the progression of dry AMD. The success of these trials, however, was to give us a better understanding of dosing and delivery, with new methods being designed and refined all the time.

The very latest complement modifying therapeutic, APL2, has shown great promise in phase II clinical trials, where an ~20% reduction in the speed of progression of dry AMD was observed. A modified Compstatin molecule, APL2 can reach the part of the eye where it is needed and, although not currently a perfect solution, is the first time we have tangible evidence that targeting the complement system is a viable therapeutic intervention strategy. With the emergence of new delivery methods, such as gene therapy, we are likely to see another step-change in efficacy in the next few years. Certainly, there has been a marked increase in the levels of confidence in this emerging technology with large investments from pharmaceutical companies. These companies do not heavily invest in new areas of technology without a lot of due diligence, and when they do they make sure all effort is put into making it a success.

So, it serves us well to remember that with every passing year of effort, every call for more funding for research, and every clinical trial that does not reach its intended outcome, that we are in fact still making measured progress to the ultimate goal, of a deliverable treatment for dry AMD.

2.11 From basic cell biology to ocular disease and new therapies

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Tissues and organs in our bodies are formed by sheets of cells that interact with each other via molecular complexes that join the cells together and seal the gaps between neighbouring cells. These complexes do not just act as glue: they function as sensors that transmit information to the cell interior about the environment, such as the presence or absence of
neighbouring cells or whether the neighbouring cells are in a normal or stressed state. This sensing mechanism guides tissue formation and maintenance, and how tissues respond to damage and different types of stress such as inflammation.

In the eye, examples of such cell sheets include the corneal epithelium, a cell sheet that protects the surface of the eye, and the retinal pigment epithelium at the back of the eye, a cell layer that supports the survival and function of photoreceptors, the cells that harvest light and directly mediate vision. The photoreceptors themselves also form a layer of cells by interacting with each other. Defects in the mechanisms by which cells interact with each other cause serious diseases that lead to strongly reduced vision and blindness. Examples include retinitis pigmentosa, an inherited disease leading to blindness due to defects in photoreceptors and the retinal pigment epithelium, and acute and chronic inflammatory conditions affecting the ocular surface and the retinal pigment epithelium.

We are investigating the molecular mechanisms by which cells interact with others and how they transmit information to cells and guide their behaviour. We have discovered such mechanisms using cell biological approaches and then asked if and how they play a role in human disease, and if we can manipulate these mechanisms to treat such diseases.

Example 1 – 15 years ago, we discovered a new component of cell-cell interactions that we are targeting now to develop therapies for acute and autoimmune inflammatory diseases. Inflammation of the ocular surface (e.g. conjunctivitis) and the retina (e.g. uveitis) are very common and difficult to treat effectively. Inflammation is also a major driver of age-related macular degeneration, a very common cause of reduced vision and blindness. Debilitating chronic, allergic and autoimmune inflammatory diseases affect other organs in our bodies such as the lungs (e.g., chronic obstructive pulmonary disease) and the nervous system (e.g., multiple sclerosis) and, as in the eye, are generally difficult to treat effectively.

Subsequent research demonstrated that the protein we had discovered signals to cells and thereby controls their behaviour and survival. Using samples from human eyes and tissues donated to research, we found that this protein is expressed at very low levels in healthy tissue but is upregulated in response to inflammation and other forms of tissue damage such as wounding. We therefore asked whether inhibition of this signalling protein can block inflammation and degenerative processes leading to blindness.

To do so, we have developed a group of compounds that can block the function of this signalling protein. We then demonstrated that these compounds indeed work in cultured cells of different types that play an important role in inflammatory eye diseases, and have now successfully tested the more effective of these molecules in animal disease models. Upon further refinement of these approaches, we aim to start clinical trials with the goal to develop therapeutic drugs that are either applied locally (e.g. eye drops for ocular diseases) or to the entire body (e.g. pills/injections for internal organs).

Example 2 – We postulated that cells make molecules that help them to form and stabilise cell-cell interactions. By looking at a distinct group of molecules encoded in our genes, we discovered such a molecule that is required for the formation of stable cell-cell interactions in many different tissues. Last year, we discovered that inherited defects in this molecule cause retinitis pigmentosa.

We now started to investigate how these defective molecules induce disease and to explore different strategies to correct malfunctioning of this molecule with the aim to develop an effective therapy. This research is at an early stage but we have already made significant progress as we can rely on tools that we have developed over the last years. The aim of this project is to develop a therapy based on replacing the defective gene (e.g., gene therapy). For this purpose, we are now generating disease models that we can study and manipulate in the laboratory that are based on cells obtained from patients and hence carry the defective gene.

Example 3 – Cells do not only interact with neighbouring cells within the same sheet but they also provide support for neighbouring cells. For example, the retinal pigment epithelium is important for

vision because it supports the functions for photoreceptors that reside on top of the retinal pigment epithelium. Photoreceptors develop a specialized domain that senses light and they constantly renew this domain, which is important to maintain their function. This renewal process involves the shedding of old material, which needs to be removed to maintain functionality of the retina. Removal of this old material is mediated by the retinal pigment epithelium, which internalizes this debris and breaks it down. This internalization process is called phagocytosis. If the retinal pigment epithelium is defective, phagocytosis does not occur, the shed photoreceptor debris accumulates, and the retina degenerates.

We discovered a new molecule responsible for activating phagocytosis. Phagocytosis requires a molecular motor: an engine that drives the internalization of debris. The molecule we discovered turns on this motor. In cells from patients that suffer from retinitis pigmentosa because of defects in phagocytosis, this molecule is not activated. We have now discovered how we can jump start phagocytosis using engineered versions of the molecule we discovered. Delivering such engineered versions into cells derived from retinitis pigmentosa patients rescues phagocytosis. We are now testing this approach in animal models with the aim to develop this approach as a therapy for patients suffering from diseases affecting phagocytosis and RPE function, such as some forms of retinitis pigmentosa and age-related macular degeneration.

2.12 Taking care of your eyes – the hidden risk of ionizing radiation and the real impact of cataract on our society and health in general

Professor Roy Quinlan
Professor of Biomedical Sciences
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Miss Alice Uwineza
PhD student
Durham University

Ionising radiation is released during diverse processes, including medical imaging (X-rays, fluoroscopy, CT and PET scans), radiation therapy and nuclear energy production. Recently, a significant correlation was found between exposure to low dose ionising radiation and cataract formation in the eyes, which has led regulatory bodies to substantially reduce the maximal acceptable exposure limits. While we know that the eye lens is one of the most sensitive tissues to ionising radiation in the human body, our understanding of the way in which radiation contributes to the development of cataract is at its early stages. This is an important problem that needs our attention so that the appropriate guidance and evidence base is available, especially because for some their exposure to low doses of ionising radiation is part and parcel of the job, such as cardiologists, radiologists, aviation workers and nuclear facility workers.

In our research, we study the effects on and the damage caused by ionising radiation to the cells in the lens. We measure the chemical modification of proteins, lipids and DNA. Lens cells have a high content of cholesterol and we have shown that exposure to X-rays converts cholesterol into oxidised cholesterol moieties. These affect cell membrane structure, a key aspect in understanding the damaging effects of ionising radiation on the eye lens. Ionising radiation also affects cell proliferation and therefore lens growth. The more we increase our understanding of the biological processes involved in radiation-induced cataract formation, the better the radiation protection community can take action towards protecting those at risk.

2.13 Partner Diagnostics and Therapeutics for genetic eye disease - Ulster university

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World-leading ophthalmology research at Ulster University specialises in the discovery of specific mutations in genes linked to inherited eye disease

In collaboration with industrial partner Avellino Labs USA, Tara and her team are developing genetic testing for a number of inherited eye diseases including but not limited to a range of Corneal Dystrophies alongside a relative genetic risk test for Keratoconus. If an individual harbours certain mutations, this can influence the response to environmental stimuli, medical intervention or ocular injury. For example, numerous studies have shown patients receiving elective refractive surgery, who carry a mutation in TGFBI, display a post-operative accelerated deposition of mutant protein and develop symptoms of Corneal Dystrophy, which otherwise may not have developed for decades. Avellino Labs USA provides a genetic test for TGFBI gene mutations, which allows candidates considering corrective laser eye surgery to be advised on the risk of adverse corneal dystrophy related pathology post surgery. To date, Avellino has tested almost 800,000 individuals worldwide and prevented over 1,000 people from having a potentially blinding reaction post laser eye surgery. Whilst the diagnostic provision for TGFBI mutations is well established, our efforts must now extend to complex diseases that require a greater appreciation of not only genetic variants, but non-genetic regulatory influence that contributes to disease. For example, the genetic testing for Keratoconus is more complex in nature and increasingly challenging.

In terms of developing novel treatments for genetic disease of the eye, the eye itself offers distinct benefits in the field of genome engineering. A high proportion of genetic ocular diseases are monogenic with the causative gene elucidated in many cases. In addition, the eye offers unique anatomical and physiological qualities that make it amenable to treatment; it is easily accessible, has a small surface area and is propped to hold an immune-privileged status making ocular diseases an ideal system in which to develop for CRISPR/Cas9 gene therapy.

The team's continual drive and passion to understand genetic variants associated with monogenic disease, for which a single gene is accountable, has demonstrated new and novel treatment options. Their ability to modify the genome using molecular surgery has emerged as a promising therapy for inherited disease, many of which would otherwise have no effective treatment. The team were the first in the world to show CRISPR/Cas9 gene editing in vivo for corneal dystrophy, demonstrating knock out of the mutant allele. In the era of personalised medicine, by knowing the DNA sequence of an individual and detecting the mistakes which relate to disease, pre-screening of all family members allows a bespoke gene therapy to be designed and administered prior to disease symptoms developing.

The advancements in genome engineering have accelerated the prospect of personalised medicine as a therapeutic option.

Recently, Editas Medicine published results detailing the development of EDIT-101, a CRISPR engineered treatment for Leber congenital amaurosis (LCA). EDIT-101 is targeted to delete or invert a mutation within CEP290, which causes a miss-splicing of the transcribed mRNA. In vitro experiments in human cells and retinal explants were able to restore functional CEP290 expression. It has been reported that in mice and non-human primates
subretinal delivery of EDIT-101 was well tolerated, and sustained CEP290 editing in photoreceptor

cells was achieved that met or exceeded the target therapeutic level. Editas Medicine and Allergan Pharmaceuticals International Limited (Allergan) plan to initiate patient screening in the second half of 2019 for clinical trials to test the efficacy of EDIT-101. They plan to enrol 10-20 patients in the U.S. and Europe. They also have future plans for a similar trial targeted to Usher syndrome and Herpetic Eye Disease.

Clinical trials for ocular therapy are further advanced for certain gene replacement therapies and drug delivery alternatives. Gene replacement using adeno-associated virus (AAV) delivery has been used successfully for the treatment of RPE65, Leber's congenital amaurosis 2 (LCA2), an early onset form of autosomal recessive retinal degeneration caused by mutations in the RPE65 gene. Three separate phase I–II clinical trials were initiated, which yielded promising results after sub retinal administration of AAV2-hRPE65 vectors. Another gene therapy presently at the pre-clinical trial stage, targets wet age-related macular degeneration (wAMD) with an adeno-associated virus vector encoding aflibercept. Aflibercept is a recombinant chimeric protein that targets vascular endothelial growth factor (VEGFA), which plays a key role in the development of wAMD.

Early in 2019, Adverum Biotechnologies reported the drug, known as ADVM-022, to be tolerated in non-human primates with no serious adverse safety-related findings, and that more than one year past a single intravitreal injection, ADVM-022 continued to provide robust aflibercept expression. These initial clinical trials will pave the way for treatment of a number of similar ocular disorders. Indeed, using ocular diseases as a model it is conceivable that soon an array of therapeutics will materialise that will allow safe and efficient correction of a range of genetic defects beyond ocular diseases.

2.14 Alternative models for studying complex diseases

Professor Majlinda Lako, PhD
Professor of Stem Cell Sciences
Newcastle University
Institute of Genetic Medicine and Institute for Ageing
International Centre for Life
Central Parkway
Newcastle upon Tyne

One of the problems with studying Age related macular degeneration (AMD) is that the affected retinal tissue is difficult to obtain, there are no animal models that faithfully mimic the disease and human trials are long and costly. So, Professor Majlinda Lako's team at Newcastle University has created two (stem cell) disease models focusing on age-related macular degeneration (AMD) and Retinitis Pigmentosa (RP).

In relation to AMD, the disease model for patients is designed with the most common genetic risk factors for the disease. Data shows that this model mimics the key features of AMD and can be used to test new therapies and to better understand the pathology of disease and the role of environmental, dietary and lifestyle factors.

Also, new retinitis pigmentosa (RP) models have been created, allowing researchers to design therapeutic interventions (for example gene editing/gene therapy in RP) and test its feasibility/success in a lab model before moving it to the clinic as well as to test new drugs and repurpose current drugs.

The retina is a highly metabolic organ whose function depends on the proper function of a large number of genes assembled together in various combinations through a process called splicing. One of the most common causes of RP is a fault in a group of genes that regulate this process. Despite this defect residing in all cells of the body, the retina is mysteriously the only tissue affected which makes deriving new treatments difficult and so these disease models can unlock some of these mysteries.

Other benefits of using such disease models include applying this knowledge to other organ systems e.g. kidney disease, providing a platform to validate clinical trial strategies and to study complex diseases (such as AMD) and to fully validate the role of other factors (dietary, lifestyle etc) in addition to genetic susceptibility. Also, these disease platforms are relatively inexpensive compared to clinical trials and current drug screening pipelines.

2.15 Understanding the role of the immune system in eye disease

Dr Colin Chu
NIHR Clinical Lecturer
Bristol Eye Hospital and University of Bristol

In early laboratory work, Dr Colin Chu and collaborators at UCL Institute of Ophthalmology discovered that an angiogram dye that has been widely used in hospitals for decades can actually bind to immune cells. This results in them fluorescing so they can then be seen in both the blood and the eye. This is an exciting finding and could increase our understanding of the immune system contribution to many eye diseases by permitting these otherwise invisible cells to be seen in the eyes of living patients. This technique could also possibly identify early relapse of disease and allow for the precise adjustment of the doses of medications until a cell response is seen.

Dr Colin Chu is completing a systematic clinical study of the dye in humans, which has not been performed before. It will identify the correct timings and circumstances in which cells can be seen in a selected range of eye diseases. Blood will also be taken and examined in the laboratory to check if the dye-labelled cells can be seen and check that there are no toxic effects upon them. If these studies are successful, they will lay the foundation for a larger grant which could optimise the dye delivery and analysis methods to bring the technique to international availability.

2.16 Understanding Biology to Develop Novel Therapies or Molecular Therapies for Ocular Scarring

Professor Colin Willoughby
Professor of Molecular Ophthalmology
Institute of Ageing and Chronic Disease
University of Liverpool

In a healthy eye, a constant pressure is maintained by continuously producing fluid (called aqueous humour) while an equal amount of the fluid drains out of the eye through what's known as the trabecular meshwork. However, in glaucoma patients (of whom there are approx. 12.5m worldwide and accounting for 1 in 10 blind registrations in the UK), the trabecular meshwork becomes blocked over time thus increasing pressure in the eye (so called Intraocular Pressure or IOP), resulting in damage to the optic nerve and serious, irreversible sight loss if left untreated.

It has been observed that a protein called TGFβ is increased in the aqueous humour of glaucoma patients and in the most common type of glaucoma, known as 'primary open-angle glaucoma'(POAG), but unfortunately the current pharmacological agents do not target the effects of TGFβ which damages the trabecular meshwork producing raised IOP, therefore leaving the disease in the trabecular meshwork entirely unchecked and the resulting higher IOP may then require further medical or surgical interventions.

There is even worse news – with surgery, the aqueous humour is directed under the lining of the eye (conjunctiva) but as it still contains TGFβ there is a scarring response which can result in failure of the operation to control IOP and stabilise the disease. This scarring response under the conjunctival

involves cells called Tenon fibroblasts and surgeons use potent and toxic anti-cancer drugs to prevent scarring and surgical failure which have significant sight-threatening side effects.

In light of this, Professor Colin Willoughby and his team at Liverpool University have identified small, naturally occurring regulatory genes called microRNAs which target TGFβ and that can be manipulated therapeutically: 'GlaucoMirs'. Therefore, he aims to develop miRNA-based therapeutics (GlaucoMirs) to treat TGFβ induced fibrosis in the trabecular meshwork and in Tenon fibroblasts to improve the treatment of glaucoma medically and surgically. He aims to provide significant insights into the molecular changes that cause glaucoma in the trabecular meshwork and data drawn from computer analysis and genetic sequencing of cells drawn from his cell bank will allow them to develop a new class of disease-modifying therapeutics targeting TGFβ in glaucoma based on miRNA biology.

Excitingly, the implications of this work can transcend glaucoma and miRNA-based therapeutic approaches could be directed to other TGFβ driven ocular scarring: corneal disease and retinal scarring in diabetic eye disease, AMD and following retinal detachment surgery.

2.17 Understanding disease mechanisms with post mortem eye disease models

Dr Marcus Fruttiger
Reader
UCL Institute of Ophthalmology
London

The human eye is one of the few organs where it is virtually impossible to take biopsies, and consequently it is difficult to investigate mechanisms of eye diseases directly. To get around this problem, scientists often use model systems, such as mice and rats. This approach offers very valuable insights into the basic biological processes that can occur, but has the disadvantage that it does not inform us directly about what processes actually do occur in human patients. Consequently, promising looking trials in preclinical models often fail in human patients.

Therefore, a more detailed understanding of human disease mechanisms is a key prerequisite to improve current translational approaches. To address this knowledge gap, we are using human post mortem tissue from eye donors with specific eye diseases and investigate whether current ideas about retinal disease processes can be confirmed. This can provide important guidance for the development of the next generation of therapies that are aimed at curing eye diseases.

2.18 Understanding response, repair and regeneration mechanisms in ocular tissue to improve treatments and patient care

Professor Baljean Dhillon
Professor of Clinical Ophthalmology,
University of Edinburgh
Hon. Consultant Ophthalmology
Princess Alexandra Eye Pavilion

The eye offers a unique window on tissue repair and regeneration. Current work includes molecular diagnostics of the aging lens, limbal stem cell disease and replacement and mechanisms/modelling of inherited and age-related retinal disease. Professor Dhillon and his team have identified potential methods to ameliorate and reverse protein unfolding in the crystalline lens, restore limbal stem cell

function and deliver in vitro readouts in retinal disease for mass drug screening for the prevention and progression of disease.

Their collaborations between chemistry, engineering and physics to image and investigate light-tissue interactions specifically UV-induced damage and oxidative stress will underpin a deeper understanding of how best to detect lens, limbal and retinal tissue response and repair in health and disease. Novel imaging tools based on SPAD sensors, Raman and OCT in development, share synergies with optical imaging research. The capability to directly observe ocular tissues enables Professor Dhillon and his team to usefully apply and interrogate sensor capability in the eye allowing cross-fertilisation between research groups.

The relevance to neurodegenerative diseases is based on the shared origins and parallel pathways between eye and brain, for example MS-related optic nerve inflammation and subsequent atrophy. Optic nerve regeneration requires close integration across different disciplines and research groups in assessing efficacy of regenerative strategies. Cross-disciplinary collaboration is the key to linking and maximising the potential of inflammation and tissue repair research relevant to restoring sight and enhancing patient care.

In summary, Professor Dhillon's intention is to identify more effective and less invasive approaches which might usefully be applied earlier in the disease process. As a result, they will be safer and achieve a better tissue response, improving the likelihood of visual restoration and producing better outcomes for patients.

2.19 Studying gene-gene interaction and gene-environment interaction in support of preventative therapies

Professor Sobha Sivaprasad
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There are no preventive measures for age related macular degeneration. One of the challenges in drug discovery in this area is the heterogeneous nature of AMD. Several genes and environmental risk factors also contribute to the disease. Therefore, in order to study preventive options, it is crucial to recruit a study cohort of people aged 65 years or above and to study the gene-gene interaction and gene-environment interactions and their influence on AMD development and progression over time. This will involve recruiting a large population of Caucasian people aged 65 years or above irrespective of the presence or absence of AMD and studying the above risk factors and correlating them to the macula features using multimodal imaging and visual function tests. They will then need to be followed up 3 years later to study rate of progression of AMD to identify patients that are best suited to study preventive options.

This study will provide the UK with firstly a well characterised cohort of older individuals to study, secondly provide novel information on gene-gene interaction and gene-environment interaction to understand disease mechanisms and thirdly an enriched cohort of patients that can contribute to clinical trials on prevention of AMD.

2.20 Understanding disease mechanisms to improve selection of treatments, identify targets for therapy and increase personalisation of therapies with reference to Uveitis

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University College London (UCL) and Institute of Ophthalmology (IOO)
Consultant Ophthalmologist
Moorfields Eye Hospital, Hammersmith Hospital
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- Understanding disease mechanisms in Uveitis and using different drugs such as those applied to arthritic patients

- Understanding disease mechanisms in uveitis by using Animal models of disease, particularly rodent models. Use of different drugs targeting key cells led to introduction of new and more successful drug treatments

- Understanding mechanisms of disease in different types of uveitis led to identifying various Cell lines derived from ocular fluids from patients with different types of uveitis. Their modulation by different drugs led to the introduction of new therapies for patients based on this understanding

- Understanding how fluid gets into the retina and causes visual loss in patients with uveitis, followed by measuring the permeability of the normal blood retinal barrier and then looked at what inflammatory cytokines disrupt it (using rodents) and looked at effect of cytokines injected into the eye. This has led to knowledge of which were the important cytokines in causing the fluid and visual loss and introduction of novel therapeutic options

- Understanding how to personalise treatment for patients with uveitis by understanding which drugs can modulate their immune system to allow the patient to control the inflammation. This is very new research and will lead to patients receiving personalised immune testing against different drugs

- Understanding pathogenesis of scleritis which was originally thought to be due to innuendo complex disease. Biopsies of lesions in patients with scleritis have led to knowledge of T cell involvement and changed management of this disorder

- Looking at factors that predict disease outcome in patients with uveitis, such as genetic factors and ocular risk factors which have led to more aggressive disease management

- Biopsies of the conjunctiva in different types of severe allergic conjunctivitis have led to a better understanding of the 2 major types which have different disease mechanisms. More successful treatment regimes targeted the key cells in each disorder reducing the incidence of blindness

- In patients undergoing organ transplantation or those with other severe immune mediated diseases, mycophenolate was found to be a very successful drug. As a result, this drug was introduced in pilot studies into patients with immune mediated eye disease where it has been very effective. Similarly, the use of biological in patients with arthritic disorders led to successful pilot studies in patients with eye disease and then their wider instructions to the benefit of many patients

2.21 Complement as a driver of Age-related Macular Degeneration

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Complement is a component of the immune system best known for its ability to attack foreign cells and 'punch holes' in their membrane causing an explosion of cell contents and consequently, cell death. It does this by forming a transmembrane lytic pore called the membrane attack complex, or MAC. The process of complement activation also results in deposition of the activated central complement protein, C3b, on to particulate surfaces such as infectious agents, dead cells and debris. These deposited fragments help to 'flag' the particles for removal by cells of the immune system, this process keeps tissues healthy.

However, a dysregulated complement system can cause a lot of harm, and all the signs point to this in age-related macular degeneration (AMD). In 2005, the complement field was energised by the publication of several genome-wide association studies (GWAS) and candidate gene studies evidencing strong genetic association between a chromosome 1 gene encoding a key complement control protein, factor H (CFH), and risk for AMD. In the following few years, further studies illustrated disease risk associated with other complement genes. These genetic variations, although relatively common in the normal population, were particularly high in the AMD population. Additional data showed that the fatty, retinal deposits, 'drusen', the hallmarks of early AMD, were coated in high levels of C3 fragments and MAC, confirming that complement was active in the retina. Together, these data provided compelling evidence for a role of complement in AMD and suggested that the complement system might actually be doing more harm than good (Anderson et al. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. Prog Retin Eye Res. (2010) 29:95).

Despite the association of gene variants with disease, it was still unclear how complement contributed to development of AMD. Prof Harris and colleagues set out to explore whether the variant proteins arising from these disease-associated genes, changed the way in which the complement system worked. They purified the variant proteins from the plasma of healthy people and teased out the functional differences using highly sensitive laboratory analytical processes. In all cases, the AMD-risk variants of these proteins made the complement system more active, whereas those which lowered risk of AMD generated a less 'vigorous' complement system (Harris et al. The complotype: dictating risk for inflammation and infection. Trends Immunol. (2012) 33:513). In parallel work, others showed that people with the risk variants of these proteins also carried higher levels of activated complement products in their blood ('biomarkers'), strengthening the concept that a highly active complement system was somehow driving the development of AMD.

These data have fed the appetite of academics, small companies and big Pharma alike to develop drugs targeting complement (Morgan & Harris. Complement, a target for therapy in inflammatory and degenerative diseases. Nat Rev Drug Discov. (2015) 14:857). The drug development landscape is bursting with agents progressing through clinical phases and destined for therapy in AMD. Most assets target C3 activation, although some target downstream and prevent MAC formation. The most advanced, lampalizumab, has shown promise in phase 2 by slowing progression of retinal atrophy and is now in phase 3 for geographic atrophy (GA). Interestingly, outcome analysis of patients in the trial indicated that the 'genetic make-up' of their complement system might impact therapeutic success; we eagerly anticipate data from the larger phase 3 trials (CHROMA & SPECTRI) which may provide invaluable insight into disease pathogenesis and treatment outcome.

It seems as though the role of complement in AMD is all ‘wrapped up’, but in reality, there is a long way to go before we truly understand the complex aetiology of this disease. Questions remain, such as:

- The role of the seminal CFH variant found in both CFH and a gene splice product FHL1; it seems to have little impact on activity of the system, we and others speculate that it may play a role in surface localisation and subsequent control.

- The major contribution to disease risk from the non-complement genes, ARMS2/HTRA1 locus (chromosome 10). Are the chromosome 1- and chromosome 10-driven forms of disease distinct? Do these genes dictate the kind of therapy that might be of benefit?

- The systemic or local nature of the disease; controversy remains as to whether therapy should be provided locally in the eye, or systemically. Clearly systemic therapy (particularly oral) would suit a large patient population, particularly if consideration can be given to stopping progression of early disease.

- Our ability to ‘drug’ the complement system; complement is churned out at an enormous level by the liver and other tissues. Developing drugs that can dosed sub-cut or orally at practical levels is a challenge. Is intravitreal therapy the only option?

These questions, and others, are the subject of intense research by academia and drug companies alike. Research is progressing at a fast pace and we anticipate that the pieces of this confounding puzzle will soon come together to give us a clear picture of the pathogenesis of this complex disease.

3.0 Detection, diagnosis and monitoring

The ongoing developments of detection, diagnosis and monitoring of eye disease delivered by the research community continue to highlight the critical role that new technologies, techniques and approaches play in disrupting conventional practice. They not only support improved prognosis, evidence-based management of patients and the development of biomarkers but also help to validate and refine earlier, targeted therapeutic interventions alongside a (soon to be) cheaper and swifter diagnostic regime.

The growth of clinicians' knowledge about the impact of eye disease and the safety and actual effectiveness of treatments is also underpinned by a robust testing, measuring and monitoring regime. Such developments ensure that the momentum is maintained behind creating a more accessible, flexible, responsive eye health and eyecare service that emphasises the need for greater patient self-care and individual responsibility and which can also impact on other areas of health.

3.1 Redesigning perimetry to improve accuracy, precision, and efficiency of the test for glaucoma

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The main focus of research by my group is visual psychophysics, the study of how the visual system processes and behaves in response to visual stimuli, including spots of light, detailed patterns, or natural scenes. In our research, we investigate various regions of the visual pathway, from the eye to the brain, that are responsible for different levels of sight. We do this in order to understand how the functional architecture of these structures enables us to see and perceive everyday scenes, as well as how various attributes of sight are affected in disease.

Armed with an understanding of these mechanisms in health and disease, a substantial translational arm of our research is aimed at developing optimum stimuli for identifying disease from normal eye and brain function in the clinical setting. Damage to the visual field is the primary functional biomarker for glaucoma, the second leading cause of blindness globally, and is screened for by clinicians with perimetry, a clinically-adapted psychophysical technique that uses spots of light varying in brightness to examine the visual pathway. It is well understood that earlier detection, and therefore treatment, of glaucoma are essential for a better visual prognosis. The current clinical method for measuring visual field damage was developed more than 40 years ago, before the pathophysiology of glaucoma was understood. The stimuli (the spots of light that were imported from the predecessor of the test in the 1980s) used in the test are inefficient for detecting the earliest stages of glaucoma and its progression. In fact, computer simulations have shown that it can take many years of repeated measures to identify even moderate rates of deterioration, placing a financial and time burden on the NHS in addition to prolonging identification of true deterioration. There is a timely need to redesign perimetry with 40 years of knowledge and understanding from basic science and clinical studies, in order to improve accuracy, precision, and efficiency of the test. In turn, an optimised test will boost the ability to detect visual loss sooner, treat sooner, and improve prognosis for vision. More accurate and precise tests with lower variability also mean that clinical trials of glaucoma treatments can be shorter.

It is only through rigorous psychophysical research that one can identify the regions of the visual pathway and levels of sight affected in glaucoma and develop an understanding of how, precisely,

these changes can be detected clinically at the earliest opportunity. Our group has made significant headway in recent years in the development and optimization of efficient clinical methods for identifying and monitoring glaucomatous visual field damage. More recently, in collaboration with colleagues at the Cardiff University Brain Research Imaging Centre (CUBRIC), we have been combining psychophysics with high-resolution neuroimaging (functional MRI) to more accurately underpin the regions of the visual pathway responsible for the earliest changes in vision in glaucoma. This will, in turn, enable us to establish a clearer idea of how visual scenes appear to patients and to refine the development of the most accurate clinical test of early visual field damage.

3.2 Organisations partnering to improve detection, diagnosis, treatment and personalised healthcare with large-scale data sets

Helen Khan
Communications Lead,
NIHR Moorfields Biomedical Research Centre
Communications Lead, INSIGHT

INSIGHT: The Health Research Data Hub for Eye Health

Health data research and using large scale data sets – or 'big data' – is becoming an important and growing area of healthcare in the UK and worldwide. Analysing large amounts of data will enable a better understanding of conditions and diseases and subsequently advance diagnostics and treatments. Health Data Research UK (HDRUK) launched seven Health Data Research Hubs in September 2019 as part of a four-year, £37million investment from the Government Industrial Strategy Challenge Fund (ISCF), led by UK Research and Innovation, to create a UK-wide system for the safe and responsible use of health-related data on a large scale.

Sight loss is an ever increasing challenge – the number of people in the UK with sight loss is expected to double to over four million by 2050. Of the seven HDRUK hubs, four of which are disease-centric, the INSIGHT hub is focused on eye disease in order to address this challenge. It will also connect to wider health issues, including diabetes and dementia. INSIGHT will turn routine eye imaging – currently more than 25 million images a year across the whole of the NHS – into an exceptional resource for innovation to improve patient care.

Existing data has been collected from patients at Moorfields Eye Hospital in London and University Hospitals Birmingham (UHB), two of the world's leading centres for eye care, research and education. New data from Moorfields and UHB will be added to the existing data sets on an ongoing basis and other NHS Trusts may wish their data to be made available through the INSIGHT hub in the future. The data is based on individual patient records and includes ophthalmic imaging, electrodiagnosis, visual fields and other clinical data captured in graphical format.

By stewarding access to these anonymised, large-scale data sets, INSIGHT will allow advanced scientific analytics, including artificial intelligence (AI), to develop new insights in disease detection, diagnosis, treatments and personalised healthcare (where treatment can be tailored to an individual based on that person's own health data).

INSIGHT is a collaboration between six partners, each bringing expertise and knowledge to the hub, they are: University Hospitals Birmingham NHS Foundation Trust, Moorfields Eye Hospital NHS Foundation Trust, The University of Birmingham, Roche, Google Health, Action Against AMD (founded by Fight for Sight, Macular Society, Blind Veterans UK, Scottish War Blinded, Royal Blind).

A key HDRUK and INSIGHT ethos is transparency and trust and ultimately patient and public benefit; anyone requesting access to INSIGHT data must demonstrate the benefits that their research

will bring to patients and the NHS. INSIGHT anticipates that those requesting access over time will include universities, research organisations and charities, pharmaceutical companies, technology companies and other organisations.

Involving the public, patients and other stakeholders in deciding how the data made available by INSIGHT is shared and used is central to the hub's plans. The Data Trust Advisory Board (DataTAB) is a key part of this. DataTAB, exists to ensure that the decisions over access to the data are made carefully and most importantly, independently, transparently and fairly. This level of scrutiny aims to ensure that true benefit will be returned to the NHS and therefore patients and the public.

DataTAB members will work together to first create the access criteria against which decisions will be made. The group will then, using these criteria, advise INSIGHT on which cases should be approved for access.

For more information on INSIGHT, visit here or contact us.

3.3 Arclight – less is more

William J Williams
Hon Research Fellow
University of St Andrews
St Andrews
Designer | Optometrist
Arclight Medical

Traditional diagnostic instruments such as ophthalmoscopes or otoscopes are expensive, complex, and heavy. In low income countries few hospital-based health workers have access to these essential devices and almost none at the community level.

Arclight is a low-cost, solar-powered tool. Pocket-sized and easy-to-use – for instant on-the-spot decisions. It can also examine ears, and with a smartphone capture video and images. There is no 'quick fix'. Health workers need appropriate tools together with hands-on training. No hype. No nonsense.

3.4 The potential of machine learning and possible future clinical applications

Professor Sobha Sivaprasad DM, FRCOphth, FRCS
University College London
Consultant
Moorfields Eye Hospital

The heterogeneity of age-related macular degeneration (AMD) is a significant challenge in the field of drug discovery to develop new therapeutic agents in this area. Several genes and environmental risk factors contribute to the disease adding to the complexity of the pathogenesis of this condition. Therefore, deciphering AMD phenotypes using machine learning may be a novel approach in understanding the mechanisms of non-neovascular AMD. In a small study, we recently showed using machine learning that a distinctive change occurs in the outer retina on optical coherence tomography before an eye converts to neovascular AMD. Ability to predict an eye that will convert to neovascular AMD and inform patients accurately about the time to conversion is very useful in our clinical practice. However, explaining the changes observed by the machine remains challenging and future studies need to focus in understanding the observations thrown up by machine learning techniques. We are not ready to take these observations forward to clinic yet.

Recent reports utilising machine learning also confirmed novel structural markers that predict

prognosis in the treatment of neovascular AMD. We have recently focussed on correlating phenotype and genotype using machine learning. As more studies evolve utilising this new area of research, we may be able to develop clinical decision support tools and machine learning may also highlight novel disease mechanisms that will help focus our research in this field.

Despite all the hype on machine learning in Ophthalmology, there is a long way to go before we can translate the findings to our daily practice. Significant resources are required to research in this area before machine learning tools can be utilised to predict development and progression of AMD.

3.5 The importance of accurate measurements to improve personalisation of treatments and management regimes for glaucoma

Prof Ahmed Elsheikh PhD, CEng, MICE
Professor of Biomaterial Mechanics
School of Engineering, University of Liverpool

Accurate measurements of internal eye pressure

Internal eye pressure (intraocular pressure, or IOP) is the only modifiable risk factor for glaucoma, the second most common cause of irreversible blindness, which affects approx. 500,000 people in the UK and 66 million people worldwide. The measurement of IOP is essential for the effective management of glaucoma, determining the amount of IOP-lowering medication and when to intervene surgically to enable a release of internal eye fluid.

Several techniques exist for the measurement of IOP, all of which rely on a simple concept. If a force is applied on the ocular surface (usually the cornea), the resistance of the eye to deformation is dependent on the IOP. While this concept is simple and easy to implement, it ignores the fact that the mechanical resistance of the eye plays an important role with, for example, thicker corneas offering more resistance than thinner corneas, and hence leading to an IOP overestimation.

Considering that the normal IOP range is small (10-21 mmHg), changes in corneal mechanical resistance (due to thickness or stiffness values that are different from average) may lead to either false negatives or false positives in glaucoma risk profiling, or lead to ineffective glaucoma management.

Our new method traces the corneal deformation under the force created by the measurement method, and uses the deformation profile to estimate the effect of corneal mechanical resistance on the IOP measurement. Using this method, we have been able to produce IOP measurements that are much less dependent on variations in corneal properties and hence more suitable for effective glaucoma management.

The new measurements have been assessed experimentally (on human donor eyes) and clinically, and the results have confirmed the accuracy of the IOP measurements. The method is now being extended to produce accurate estimations of the material behaviour of corneal tissue. If successful, the behaviour estimations have the potential to enable customisation of refractive surgeries, corneal implants, contact lenses and other treatment modalities to individual patient's needs.

Continuous monitoring of internal eye pressure

Glaucoma is a progressive disease that leads, if badly managed, to irreversible blindness. The disease, which affects 66m people worldwide, is managed by reducing the eye's internal pressure (intraocular pressure, or IOP) down to the normal levels of 10-21 mmHg.

Current practice relies on measuring IOP over a few minutes every 6 months and using the measurement to develop a management regime that relies either on IOP-lowering medication or surgery to halt glaucoma progression. However, it is known that IOP is dynamic and changes continuously with sleeping and awakening, physical efforts, drinking, etc, and hence a snap-shot measurement over a few minutes may not capture the true IOP effects. For this reason, efforts have been made for many years (>40 years) to continuously measure IOP.

Our new technology has been in development for 10 years and we now have an IOP sensor mounted on a soft contact lens and connected wirelessly to an external device that stores the IOP measurements for later analysis. The technology has been experimentally validated on both animal (porcine) and human donor eyes, and shown to provide accurate measurements of IOP.

We have got MHRA and ethics approvals to test the technology clinically. Two studies have been conducted; a comfort test and a reliability test. The studies, which involved 20 patients confirmed the effectiveness of the device in the long-term IOP measurement. Further work will be needed to develop the technology into a market product and conduct a much wider clinical validation study.

The device could have a significant positive effect in the management of glaucoma patients and prevention of their progression. Currently, about 15% of glaucoma patients lose their eye sight within 15 years of diagnosis, even whilst under treatment. This inadequate management outcome is thought to be caused by the inaccuracies caused by current IOP measurement techniques, and that a continuous measurement method would contribute to improved outcomes.

3.6 Telemedicine or Teleophthalmology

Dawn A. Sim
Director of Telemedicine, Consultant Ophthalmologist
Moorfields Eye Hospital, London

Telemedicine may be defined as the use of advanced communication and technology to deliver and improve healthcare, over the confining parameters of distance and time. It is puzzling that despite being born over five decades ago and described in 2016 by Forbes Magazine as "the new online banking for health", telemedicine has remained in its early infancy within the healthcare environment. Advances in ocular imaging capabilities in conjunction with the ubiquity of internet connectivity surely must pave new paths for the delivery of eye care through teleophthalmology.

The demand for ophthalmic services globally is outstripping supply. Although the number of ophthalmologists in the United Kingdom is rising, it is one of the lowest number per capita in the developed world and only rising at half the rate of the population over age 60. Therefore, our present-day challenge is to maintain the delivery of timely, high quality care in the face of diminishing resources. The impact of this imbalance of demand and supply is evidenced in the recent published figures of 20 patients per month that face severe vision loss whilst waiting to access ophthalmic services.

The resurgence of teleophthalmology has been increased more recently by the introduction of new imaging modalities over the last decade and fuelled by the need to provide additional capacity for unmet demand within the NHS. Proof of concept studies have shown that patients do not require a face to face interaction with a doctor at every hospital visit, and that a safe efficient service can be delivered in a "virtual clinic" pathway.

Furthermore, patients had a shorter "referral to treatment time" (RTT) compared to conventional outpatients clinics, and unnecessary appointments were avoided. In 2018, we published evidence that virtual clinics at Moorfields Eye Hospital reduced the mean referral to appointment time from 18 to 7 weeks. Nevertheless, despite evidence demonstrating a particularly high level of patient satisfaction

with telemedicine compared to conventional clinical care delivery, there remains a relatively poor national uptake of teleophthalmology programs.

The Future of Teleophthalmology

Artificial intelligence (AI) and robotics have been deemed to transform healthcare by doing what humans do but more quickly and at a lower cost. In teleophthalmology this can be applied in two stages; stage one – where information is gathered from the patient in the form of a clinical history and when the eye is imaged; stage two – where this information is analysed and a clinical decision made and communicated.

Stage one lends itself to the use of clinical decision trees, chatbots, machine learning, and automation. Current examples include the widespread use of autorefractors in areas of the world where there is a lack of optometrists, and the advent of chatbots as a symptom screening tool for self-administered triage, designed to improve access to care. Stage two has
been an incredibly popular focus point for research. In 2018, the first deep learning algorithm to classify diabetic retinopathy was approved by the Federal Drug Administration in the United States of America. This was closely followed by the publication of a deep-learning algorithm for OCT retinal images that was able to make referral recommendations for
sight-threatening retinal diseases comparable to expert Ophthalmologists.

Such developments have been a focal point in the recently published NHS 10-year long term plan, which aims to transform services and overcome the imbalance between demand and supply in healthcare. Digital technologies have been described as a critical part to achieve this goal and to provide care in the community where safe and possible.

3.7 Smartphone Eye Camera

Yannis M. Paulus, M.D., F.A.C.S.
University of Michigan
Ann Arbor

RetinaScope is a smartphone-based camera to take photos of the back of the eye (retina). It weighs approximately 310 g and has 3D-printed plastic housing which encloses optics for illuminating and imaging the retina onto the smartphone camera. Deep red (655-nm peak wavelength) light emitting diodes are used for focusing. Polarized bright white illumination is used in conjunction with two polarizing filters to minimize unwanted glare. A display may be magnetically attached to either side of the device to display a fixation target. The RetinaScope communicates with a smartphone application via Bluetooth. It can take in an automated fashion 5 fields of view of the retina totalling approximately a 100-degree montage of the retina.

A clinical trial is being conducted, led by Yannis Paulus, MD (ClinicalTrials.gov Identifier NCT03076697) validating this device in evaluating diabetic retinopathy. The RetinaScope team (including Drs. Tyson Kim, Todd Margolis, Dan Fletcher, and Yannis Paulus) have collaborated with a company Eyenuk to utilize the EyeArt software and perform automatedinterpretation of these photos.

A study of 119 eyes from 69 patients found that RetinaScope combined with EyeArt achieved a slightly lower sensitivity but higher specificity than trained expert graders.

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3.8 The new Visual Fixation System - grabbing attention just when you need it

Simon Berry
Optometrist
Durham

Colin Richards
Manufacturer
Optimec

The Optimec Visual Fixation System (VFS) was developed to allow a clinician to complete clinical measurements when co-operation of the patient is difficult.

The optics of the VFS allow a target displayed on a mobile phone to be placed in direct line of sight of the clinician, allowing a number of clinical observations to be made.

The flexibility of using a mobile phone means that unlimited number of targets can be displayed and can be tailored to the particular needs of the patient. This means that they are more likely to be engaged and relaxed during testing.

It was initially developed to gain a more accurate result when testing the accommodative response. It is the only device capable of measuring accommodative lag on the visual axis, and the only device allowing the clinician to use the MEM and Nott method for assessment.

The VFS is useful as a means to grab a patient's attention. It becomes invaluable in patients where co-operation is difficult and allows the clinician a method of observation when other methods fail. It is useful for young children, patients with a learning disability and patients with dementia.

3.9 Digital technologies to transform care for patients with Age-related Macular Degeneration

Konstantinos Balaskas
Consultant Ophthalmologist
Moorfields Eye Hospital
NHS Foundation Trust

Digital Health technologies are disrupting the way we deliver care to our patients in Ophthalmology by challenging key concepts of who, where and how care is delivered. In the Moorfields Ophthalmic Reading Centre we are researching the optimal clinical work flows for delivering the best service efficiently to the greatest number of patients using digital technologies and Artificial Intelligence decision support tools.

We are currently embarking on a 4-year research project supported by an NIHR Health Technology Assessment grant; the FENETRE study. This is an implementation science project looking at validating a novel model of care for patients with Age-related Macular Degeneration (AMD), the most common cause of blindness in the UK in the adult population. In this study we will demonstrate

the role of digital links between high street opticians and hospital-based eye clinics to enable the safe management of patients with AMD in the community closer to home.

In the context of this project we will develop a transferable training programme for community optometrists undertaking the assessment of patients with AMD and we will thoroughly assess the economic implications of digitally-enabled models of care. We will also explore the role of Artificial Intelligence Diagnostic Support Systems in the management of patients with AMD and assess their performance. We will specifically use the DeepMind algorithm developed through the collaboration between Moorfields Eye Hospital and Google DeepMind. This Artificial Intelligence algorithm is capable of interpreting eye scans (Optical Coherence Tomography) and diagnosing a number of common retinal conditions.

This is the first of a programme of research looking at generating the evidence needed for the meaningful introduction of digital health technologies in Ophthalmology which will have a transformative effect on eye care across the board. The 'Eye Hospital' of the future will look drastically different with the increasing role of 'virtual' clinics, tele-ophthalmology, home-monitoring and Artificial Intelligence Decision support.

3.10 Home monitoring of vision to increase convenience for patients and capacity in secondary care

Dr Ruth Hogg
Senior Lecturer
Centre for Public Health
Queen's University Belfast

Current treatment for wet AMD is a series of monthly injections which reduce the growth of new vessels to limit vision loss. Following treatment, patients attend regular hospital check-ups where clinical staff monitor the macula by taking photographs and doing vision tests, checking whether any follow-up treatment is needed.

Most patients will not require follow-up treatment, but about 30% do. These hospital check-up appointments are important for preventing further loss of vision. However, the check-up appointments put a huge strain on already-stretched resources, and limit the capacity for seeing new patients who, if not seen urgently, are at high risk of losing their vision. They are
also very inconvenient for patients and their friends or family members who may have to take time off work to provide transport to these appointments.

Dr Ruth Hogg, from the Centre of Public Health at Queen's University Belfast and Co-Chief Investigator of the MONARCH study explains: "Injections for AMD have been very successful, with about half of patients retaining vision sufficiently good for driving. However, the burden on the NHS and patients has been considerable due to the need for frequent injections and intensive monitoring throughout the follow-up period. In Belfast, evening and weekend clinics have been added, yet it's still not enough.

The MONARCH study aims to find out whether monitoring vision by patients themselves at home could potentially alleviate some of the burden of AMD on the NHS, as well as be more convenient for patients, without compromising their safety or wellbeing. If home eye tests can detect when treatment is needed, it would mean that patients might only need to attend hospital appointments to have treatment.

Patients participating in the study are provided with three different eye tests for them to do at home, comprising a paper-based booklet of reading tests and two tests ("apps") that run on an iPod-touch. Patients will be asked to do all three tests weekly at home. The results of the tests are sent

automatically via the internet to the Study Management Centre in Bristol. Throughout the study participants will attend their normal hospital check-up appointments and the results of the tests done at these appointments will be compared with the results from the home eye tests.

The MONARCH study is funded by National Institute of Health Research (NIHR) Health Technology Assessment Programme. For more information, please visit:
http://cteu.bris.ac.uk/our-studies/?trialType=Ophthalmology#4007

3.11 Cuttlefish to clinic: blue sea research leads to innovative new technique to assess a key risk factor for Age-related Macular Degeneration (AMD)

Dr Shelby Temple
Co-Founder/Director
Azul Optics Ltd

Research into cuttlefish and octopus by Dr Shelby Temple at the University of Bristol has led to an entirely new way to assess a key risk factor for age-related macular degeneration (AMD). Translation and commercialization of this research led Azul Optics to bring to market the MP-eye device, which enables eye care professionals to run an easy and affordable screening test in under a minute to determine if a patient is at greater risk and should therefore be advised to make simple lifestyle changes to reduce their likelihood of developing AMD later in life.

AMD is a part of the natural process of ageing of the retina, and we will all eventually lose central vision due to AMD if we live long enough, the key is to delay onset past our living years and thereby effectively preventing the disease.

A vast amount of research using molecular, cellular and tissue techniques, small animal and primate work, as well as human epidemiological studies have pointed to key risk factors for AMD being: age; smoking; low macular pigment density; obesity; poor diet; fitness; increased exposure to sunlight (specifically short-wavelength blue light); and genetics.

The challenge with studies of aging is of course that to show causation in humans requires very long-term studies (as long 60 plus years) and due to the multi-factorial nature of many ageing processes the sample size would need to be large and the behaviours of the subjects controlled. For obvious reasons such research in humans is simply not feasible. However, a controlled study in rhesus macaques has recently shown that monkeys that were denied macular pigments in their diet, but which were otherwise treated identically to control monkeys, developed AREDS Stage 3 drusen at half the age (35 human equivalent years of age) compared to controls (65 human equivalent years of age). This research confirms that macular pigments are preventative in AMD. In addition, macular pigment density has been linked to other key AMD risk factors: smoking, obesity, poor diet and sunlight exposure.

It is the blue light-absorbing and antioxidant properties that make macular pigments protective against retinal aging and AMD. However, we can only acquire macular pigments through our diet, and physiology and behaviour can affect the amount of macular pigment present in the retina. The problem is that we cannot tell how much macular pigment we have.

The MP-eye device uses an elegant technique employing Haidinger's brushes to quickly, easily and repeatable assess the density of macular pigment in the macula. For his work in taking this idea from cuttlefish to clinic, Dr Temple was awarded the Biotechnology and Biological Sciences Research Council Innovator of the year award in 2017. Azul Optics is now marketing the MP-eye to optometrists and ophthalmologists in the UK and overseas.

3.12 Preventable vision loss: a global challenge

Moshe Barel
VP Marketing
NovaSight

Nearly 3% of children suffer from lazy eye (amblyopia). Although the condition is treatable, delayed or inaccurate diagnosis and outdated treatment methods often result in partial vision loss.

The gold standard treatment method for amblyopia is patching over the dominant eye, which suffers from low compliance, sub-optimal results and high reoccurrence rate. On top of that, stereoacuity (depth-perception) never develops with monocular treatment.

Recently, digital methods of binocular treatment have begun to emerge, such as iPad games and VR goggles, which aim for higher compliance and stereoacuity development. However, these methods fail to achieve the intended results, as they are difficult to use by young children who are the main target population.

NovaSight had developed CureSight™ – an integrated eye-tracking visual-training system for lazy-eye treatment, intended to replace traditional eye patching. The treatment is carried out using sophisticated, real-time 3D image-processing algorithms, all while the child watches their favourite program in the comfort of their home. While the foveal area (centre of vision) of the dominant eye is blurred according the momentary gaze position, the rest of the image is kept sharp. This way, suppression of the lazy eye is cancelled and visual acuity restored, with the two eyes learning to work as a team as stereoacuity is developed, even in cases of strabismic amblyopia.

The CureSight™ system can monitor the treatment progress of the child in real time, auto adjust the treatment protocol and provide feedback to the care givers and parents through a dedicated mobile application. CureSight™ not only solves the problem of poor compliance with the traditional treatment, but also improves stereoacuity – binocular fusion.

The system is currently undergoing clinical trials. Preliminary results show significant improvement of both visual acuity and stereoacuity in a cohort of 18 children, following 4 weeks of training, with a 90% compliance rate. The CureSight™ system is FDA registered, and NovaSight plans to obtain reimbursement status in the United States during 2021.

Legacy screening methods fall short

Traditional pediatric vision assessment methods are manual, subjective, time consuming and often inaccurate; especially for toddlers who can't always understand examiner instructions or communicate what they're seeing.

There is a large shortage of pediatric ophthalmologists in many countries. For example, in the United States, around 3,000 pediatric ophthalmologists serve a population of 74 million children, while in China there are fewer than 2,000 pediatric ophthalmologists serving 300 million children.

In order to improve the efficiency and accuracy of vision assessment in children, NovaSight has developed EyeSwift® – an automated, objective and easy-to-use eye-tracking based visual screening and diagnostic system. While children watch a series of short videos, EyeSwift® diagnoses numerous vision impairments, providing quantitative analysis results.

NovaSight's innovative technology, which has recently received the CE mark, has attracted the attention of many international industry giants. The company has chosen to partner with one of the world's largest optometry companies, signing a global OEM distribution agreement for the

EyeSwift® system and planning to co-develop a future pipeline of diagnostic products.

About NovaSight:

NovaSight's mission is to bring screening and treatment of common childhood vision impairments into the digital age. Specially designed for the unique needs and attention spans of pediatric patients, our revolutionary eye-tracking based solutions aim to prevent pediatric vision loss through rapid vision screening and innovative vision treatment. NovaSight's management and advisory boards are comprised of experienced executives, researchers and renowned key opinion leaders in the field of ophthalmology.

3.13 Enhancing glaucoma detection with a novel technique to image and track individual retinal cell death

Professor M Francesca Cordeiro PhD MRCP FRCOphth
UCL Professor of Glaucoma & Retinal Neurodegeneration Studies
Hon Consultant Ophthalmologist
Western Eye Hospital
Visiting Professor Imperial College London
UCL Institute of Ophthalmology

The processes of neurodegeneration are implicated in several degenerative diseases of the retina. These include glaucoma, age-related macular degeneration and some inherited retinal disorders.

Professor M Francesca Cordeiro and her Glaucoma and Retinal Neurodegenerative Disease Research Group focuses on mechanisms of neurodegeneration and vision loss, particularly related to the early diagnosis and management of age-related neurodegenerative processes.

The key aims of her group are as follows:

• Identify early markers of cell processes in neurodegenerative disease in the eye – including Glaucoma, Alzheimer's, Parkinson's Diseases

• Establish new methods of early diagnosis and treatment of these diseases – using the eye as a window on to the brain

• Develop non-invasive screening and monitoring of neurodegeneration

• Investigate Neuroprotection and rescue modalities

• Assess novel delivery methods of diagnostic and therapeutic agents – in the eye and in the brain

These are to be achieved using novel non-invasive techniques to assess structural and functional changes in different models of disease and their treatment, with a view to offering quick and effective translation to the clinical arena.

A strong emphasis in Professor Cordeiro's work has been to make use of the strong expertise at UCL to encourage a multidisciplinary approach in her research. She greatly values strong and successful collaborations with a range of experts at UCL, Imperial and externally too.

One particular (first) clinical trial supported by such collaboration is the so-called "detection of apoptosing retinal cells" (DARC) project. It is not only another shining example of the possible translational benefits of eye research but also how painstaking research can greatly improve the

chances of earlier detection of glaucoma (the world's leading cause of irreversible blindness), by spotting individual nerve cell death much earlier than it has been possible hitherto, thus allowing for enhanced diagnosis and an earlier, more refined therapeutic interventions in the disease process to preserve remaining vision.

To underline this point, detecting glaucoma early is vital as symptoms are not always obvious. Although detection has been improving, most patients have lost a third of their vision by the time they are diagnosed because conventional clinical tests cannot detect abnormalities until extensive retinal ganglion cell RGC death and significant vision loss have already occurred.

The "DARC" technique uses a specially developed fluorescent marker which attaches to cell proteins when injected into patients. Sick cells appear as white fluorescent spots during eye examination. The equipment used is similar to that available during routine hospital eye examinations. Researchers hope that eventually it may eventually be possible for opticians to do the tests, enabling even earlier detection of the disease.

Initial clinical trials were carried out on a small number of glaucoma patients and compared with tests on healthy people. The initial clinical trials established the safety of the test for patients.

The test also has potential for early diagnosis of other degenerative neurological conditions, including Parkinson's, Alzheimer's and multiple sclerosis.

3.14 Translation of Ophthalmic Technology to Enhance Patient's Vision

Professor James Wolffsohn
Deputy Executive Dean, Aston University

With a rapidly ageing population, the demands on GP's and hospitals from ocular disease have become overwhelming. Eye disease prevalence increases with age, as with most organs, and innovative treatments, such as for the wet form of age-related macular degeneration, is consuming much more time of our relatively small number of ophthalmologists.

So Professor James Woolfssohn's collaborative and multi-disciplinary team at Aston University is focusing on low cost, portable, objective instrumentation using artificial intelligence to aid in the diagnosis and evidence-based management of patient in primary care. Projects include: advanced, 'intelligent', diagnostic support software; portable, low cost, innovative instrumentation to assess eye health and to refract the eyes.

For example, traditional solutions in the optical industry don't translate to markets where the clinic needs to travel to the client rather than the client to the clinic. Large expensive white instruments are being replaced, allowing the number of referrals to secondary care to be reduced (and to be dealt with more efficiently such as through telemedicine), while improving the vision and visual comfort of patients through advancements in contact lenses and intraocular lenses implanted as part of cataract surgery.

Commercialisation:
Aston University works extensively with industry, largely supported by Innovate UK and the European Regional Development fund (Medical Device Testing and Evaluation Centre MD-TEC, and collaboration between the Queen Elizabeth Hospital, Aston University and Birmingham University enhances British entrepreneurship. The next generation of optometry and biomedical engineering students are enthused through the example of Professor Woolfssohn's own spin-out company "Eyoto" which turns basic research and the aspirations of clinicians into commercial products, made in the UK.

3.15 Providing appropriate eye care for children and adults with learning disabilities

J Margaret Woodhouse
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School of Optometry & Vision Sciences
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People with any form of disability are, of course, entitled to the same standard of healthcare as the general population and it is well known that people with learning disabilities are much more likely to have eye and vision problems than members of the general population. Yet there are many barriers to accessing good eye care, which our research is aiming to break down.

First of all, it's important to establish what sort of problems arise among people with learning disabilities, and how the problems can be best picked up. So, our research team began our work in this field by designing new vision tests that are appropriate for people who cannot cope with a letter chart, or describe their experiences. Our development of a means of measuring focusing led to the discovery that many (in some conditions, most) children and young people with disabilities are unable to focus well on near tasks such as school work. This meant that even when spectacles to correct long or short-sight were prescribed, the young people were left visually impaired for near tasks. Today, many hospital eye clinics are aware of the likelihood of patients struggling to focus, and are taking appropriate steps to measure and correct focusing – but by no means all hospitals. There are still some that are reluctant to accept new ideas.

Our abilities to measure vision in even the youngest or most disabled patients allowed us to establish that people of all ages with Down's syndrome have reduced vision, even when the correct spectacles are worn. This has proved vitally important in schools, where the struggles children had with tasks such as writing on the lines, were being misinterpreted as due to the learning disability; in fact the children can't see faint lines. Now teachers are more aware of the need to make learning materials big and bold, and children are achieving much more at school as a result.

A recent study has concentrated on keratoconus, which is much more common among people with learning disabilities especially Down's syndrome, than among the general population. A new treatment, called collagen cross-linkage therapy, can now prevent progress of the condition but only if applied in the early stage of the disease. Diagnosing keratoconus in its early stage is a challenge, since people with learning disabilities are less likely to complain about poor vision. Our study has allowed us to recommend to optometrists the most efficient tests to allow keratoconus to be picked up early.

Nystagmus is another condition that is much more common in Down's syndrome. A current study, in collaboration with the Research Unit for Nystagmus, is looking at the characteristics of nystagmus among children with and without Down's syndrome. We are all aware that nystagmus forms a visual impairment, and typical children with nystagmus will receive additional support in school. However, it turns out that nystagmus in children with Down's syndrome is often ignored, and parents and teachers are not told that it affects the way children see. Our research is establishing that the condition has the same characteristics in children with and without Down's syndrome, and will allow us to argue that children with learning disabilities need the same support for eye conditions that we expect ordinary children to receive.

There is still a great deal to do, but there are some exciting developments on the horizon, arising from our work. A few years ago, our team carried out a survey of eye care and eye defects among pupils of special schools in Wales. In collaboration with the charity SeeAbility we have repeated the survey in special schools in England. Both studies suggest that around 40% of pupils have never had eye examinations, around half need spectacles but only a quarter of pupils have them. As a direct result of our research, Welsh Government and NHS England are now committed to developing eye care services for special schools. Optometric organisations such as the College of Optometrists is now

including eye care for people with learning disabilities among their priorities, and some local authorities in England support 'enhanced services' which provide funding and training for optometrists to test people with learning disabilities in their area. The situation is set to improve.

3.16 Challenging conventional wisdom to improve sight tests for nystagmus

Professor Jonathan T. Erichsen
Director of Eye Movement Experimental Research Group (EMERG) and Research Unit for Nystagmus (RUN)
Cardiff University

Dr Matt J Dunn
Lecturer
Cardiff (Research Unit for Nystagmus – RUN) University

Dr Lee McIlreavy
Lecturer
Cardiff (Research Unit for Nystagmus – RUN) University

The Research Unit for Nystagmus [RUN] was established in the School of Optometry and Vision Sciences at Cardiff University over 15 years ago. Today, RUN remains the only such centre in Wales carrying our research on infantile nystagmus (IN), and they are recognized as world leaders in investigating the perceptual consequences of IN.

Infantile nystagmus is a continuous oscillation of the eyes that arises shortly after birth and continues for life. Based in their four state-of-the-art laboratories, the research that Professor Jonathan Erichsen and his colleagues are conducting into nystagmus highlights the critical
need for eye tracking technology to provide high quality recordings of the eye movements to look for the characteristic features of the oscillation pattern, deliver an accurate assessment of the impact of current and future treatments, and offer more suitable measurements of the improvement (if at all) in a person's vision.

People with nystagmus generally perceive the world around them as stable, despite the continuous wobble of their eyes. Moreover, the "intensity" of the nystagmus, which can involve both the size and frequency of the eye oscillations, varies considerably in people depending on where they are looking (e.g. being at a minimum in their 'null zone') or on their emotional state (e.g. stress level).

In their quest to determine the underlying cause of infantile nystagmus and help develop treatments for the condition, they need to be able to measure, in real time, the eye movements in a variety of situations. Technological improvements (including large display screens and three-dimensional projection for binocular investigation) now allow them to record accurately
and non-invasively the nystagmus oscillations as well as other eye movements made in response to different visual scenes or stimuli. This enables them to investigate the interaction between moment-to-moment eye movements and visual perception.

Supported by a cohort of over 100 volunteers with infantile nystagmus, Jonathan Erichsen and his colleagues have challenged the conventional wisdom that currently available treatments (involving surgery and/or medication), which slow the nystagmus oscillations, will necessarily result in an improvement in vision. Indeed, they have discovered that visual acuity is largely unaffected by even quite large changes in his or her nystagmus. Whether under stress or using the nystagmus null zone, the result is still the same. It seems that any slowing of the movements is unlikely to produce much improvement in visual acuity. Nonetheless, people with nystagmus do sometimes report that they can "see better" and most will choose to look in a particular direction (i.e. use their null zone), which slows their eye movements, even if this means they need to adopt an unusual head posture. All of this

suggests that their eye movements do affect some aspect of their vision, which is the main focus of their current research efforts.

Most recently, they have investigated whether nystagmus can have an effect on how long it takes to see something. Findings indicate that people with nystagmus do not take longer to mentally process visual information. However, there is evidence that due to the eye movements, people with nystagmus may need to look at things for longer than others to achieve their 'best' level of vision (i.e. their maximum visual acuity). How long it takes to find and/or discriminate objects or even people in different settings may have a profound impact on peoples' everyday lives, so the team are now developing new clinical tests that might better reflect how vision is affected by changes in nystagmus eye movements.

So, bearing in mind that the size and frequency of someone's eye oscillations can vary depending on where they are looking and/or their degree of stress, the standard optometrist's chart, which only tests the smallest letters that can be seen (i.e. visual acuity), is unlikely to be sufficient.

3.17 An unhealthy diet causes small changes in eye cells leading to sight-loss

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Early changes in the retina that lead to irreversible sight-loss

A major challenge in developing effective treatments for complex retinopathies such as age-related macular degeneration (AMD) is an incomplete understanding of early disease pathways that trigger disease. This is reflected by the current lack of effective treatments against dry (geographic atrophy) AMD, whilst the wet (or neovascular) form may be managed with intravitreal VEGF (vascular endothelial growth factor) inhibitors. However, in some wet AMD patients, long-term VEGF inhibition can lead to the death of retinal pigment epithelial (RPE) cells.

Dr Arjuna Ratnayaka's group studies degenerative changes in the aging retina and brain). A major focus is the study of early disease-linked changes associated with cellular and tissue damage so better treatments against AMD can be developed in the future. Recent findings from the Ratnayaka lab has unravelled details of how photoreceptor outer segments (POS) from overlying photoreceptors, which are shed daily to maintain normal vision, are internalised by RPE cells and broken down in the cells' waste disposal system (phagosome and autophagy-lysosomal pathways). With increasing age, this process becomes inefficient, leading to the accumulation of partially degraded POS within lysosomes and related vesicles in RPE cells. Their studies in healthy RPE revealed a considerable degree of flexibility in the way these POS cargos are broken down, perhaps allowing cells to cope with changing conditions in the ageing retina.

Next, they studied whether a high fat diet (typically referred to as a "Western-style" diet) could alter the way POS are degraded by RPE cells. This line of inquiry was instigated by a growing awareness that an unhealthy diet can significantly predispose individuals to disease. A recent report published in the Lancet revealed that a poor diet is responsible for 1/5 deaths globally[1]. Epidemiological studies have shown that a "Mediterranean" diet including fish and nuts can help prevent sight-loss in the same way that unhealthy foods can cause eye disease. Intake of a high fat and cholesterol-rich diet is known to unleash disease-linked pathways including inflammation, oxidative stress and altered membrane trafficking. The group modelled elevated oxidative stress and altered membrane trafficking in RPE cells to study whether these affect the way POS cargos are broken down over time. Their findings revealed that under oxidative stress, outer segments do not spend sufficient time in early

compartments of the phagosome and autophagy-lysosomal pathways. Instead, cargos are rapidly shuttled to terminal-stage lysosomes and autophagy bodies which may be ill equipped to deal with incompletely processed POS. By contrast, when they studied impaired membrane trafficking, POS cargos were observed to be trapped/sequestered in early compartments with only a small proportion reaching lysosomes. Surprisingly, some POS still reached downstream autophagy bodies, suggesting that alternative/compensatory methods of dealing with these important cargos exist in stressed RPE.

The inefficient breakdown of cargos in the phagosome and autophagy-lysosomal pathway is known to result in the accumulation of incompletely degraded POS and generation of lipofuscin and related toxic material in aged and diseased RPE. This is an important process associated with sight-loss in AMD. Their findings reveal new ways in which conditions triggered by an unhealthy diet can affect the build-up of such toxic material inside RPE cells. Furthermore, their data suggest that multiple disease-causing mechanisms in the ageing retina could have contrasting outcomes at cellular level.

Discoveries of this kind provide insights into the complexities underlying AMD and the challenges involved in devising effective treatments against blindness. Interestingly, their studies revealed that not all compartments of the waste disposal pathway were affected by pathogenic conditions of an unhealthy diet. They found unaffected/healthy populations of phagosomes and autophagy-lysosomes, which could be targeted in future treatments to increase POS breakdown and prevent lipofuscin build-up. Their findings highlight the importance of good nutrition to ocular health, and rather than simply viewing cells/tissues in healthy vs. unhealthy terms, to consider complex retinopathies on a spectrum of discrete pathogenic events. This work was published in the journal of Molecular Nutrition & Food Research[2].

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Related links to external sites:
https://www.macularsociety.org/news/poor-nutrition-can-lead-sight-loss-later-life-according-university-study
https://www.southampton.ac.uk/news/2019/03/bad-diet-sight-loss.page

3.18 Correcting mitochondrial decline and improving retinal function – implications for AMD as it reduces inflammation

Professor Glen Jeffery
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There is a growing body of evidence that the pace of ageing is linked to metabolic rate, with high rates associated with faster ageing (Speakman, 2005; Wang et al., 2010). Indeed, the retina is a key example of this as photoreceptors have the greatest energy demand in the body (Linsenmeier and Padnick-Silver, 2000). Experiments with mice have shown that mitochondria decline with age (Kokkinopoulos et al., 2013) and ATP the key source of cellular energy that they produce declines significantly by 3-4 months. More recently, results examining the eyes of old primates have shown

that mitochondrial decline in them is even greater than found in mouse with ATP reduced by more than 70% compared with the 25% found in mice. This is associated with major negative changes in the metabolism of the retina that can result in accumulation of toxic materials. Following these events, chronic inflammation becomes established (Catchpole et al., 2013; Hoh Kam et al., 2013; Xu et al., 2009), and retinal function declines (Kolesnikov et al., 2010; Li et al., 2001). It has been shown that there is a resulting 30% photoreceptor loss in both mouse and man (Cunea and Jeffery, 2007; Cunea et al., 2014; Curcio, 2001)

Supported by this recent body of research evidence, Professor Glen Jeffery and his team are showing that some of these features in the ageing retina can be corrected, based on the principle that specific long wave- lengths of light absorbed by cytochrome c oxidase (Fitzgerald et al., 2013), which is a key element in mitochondrial provision of ATP. These manipulations not only improve mitochondrial function increasing ATP output, but in doing so they also avoid the other negative metabolic changes that occur when mitochondria decline that result in the production of toxic metabolic byproducts.

Perhaps as importantly, Glen Jeffery's laboratory has been able to monitor mitochondrial function in the living eye via reflected light (Kaynezhad et al 2016) and consequently they may be able to identify those in which the function is being undermined at a relatively rapid rate, and as such be vulnerable to disease.

After many years of research in various animal models Professor Jeffery's lab have translated their research successfully into humans. Using long wavelength light they have improved aged vision in those over 40 years. This improvement has been across a wide range of metrics including absolute thresholds, dark adaptation times and also colour contrast measurements. These positive effects come from light exposure for only 3 mins a day using safe energy levels. These data have just been published in the Journal of Gerontology, and are a major step forward in combating ageing and disease using simple technologies that are economic.

https://academic.oup.com/biomedgerontology/advance-article/doi/10.1093/gerona/glaa155/5863431

3.19 The flexibility of OCT and the accommodation of underrepresented groups

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Optical coherent tomography (OCT) has revolutionized ophthalmic practice because we are now able to detect and monitor disease affecting the cornea and retina more objectively.

- Better detection techniques = earlier diagnosis and treatment
- Better monitoring techniques = clearer guidelines about when to intervene or not, based on objective measurements (rather than drawings or photographs)

The best example is how OCT has changed the management of age-related macular degeneration. The decision about when to treat and how often with intravitreal anti-VEGF agents is now almost entirely based on the results of OCT imaging.

The number of applications for OCT is ever expanding so that we can now measure vitreous inflammation, for example, to monitor disease activity in uveitis.

Under-represented groups in previous research using OCT are young children and patients with physical disabilities because standard OCT machines require the subject to sit up at the machine and place their chin on a rest – neonates, young children and physically disabled individuals cannot do this.

Research from Irene Gottlob in Leicester has shown that the retina is still developing in young infants after birth. This was not known before because the technology was not available to image neonates with OCT previously, but now there is an OCT machine (Bioptigen) with a portable imaging probe that makes this possible. Drs Denize Atan and Cathy Williams in Bristol are collaborating with Irene Gottlob to collect further normative data about the normal postnatal development of the retina with funding from Fight for Sight and the same Bioptigen OCT machine. The only other centre in the UK with a Bioptigen machine is Moorfields Eye Hospital.

It is very important to collect normative data so that we can recognize true pathology as opposed to the changes that normally occur during postnatal retinal development. We can then diagnose early onset/congenital retinal diseases, for example, albinism. Albinism can be difficult to diagnose at an early age because the tests that are commonly used rely on some degree of patient cooperation – otherwise the results are not reliable. This means that the tests are often repeated again and again until they give more reliable results when the patient is older. The portable OCT helps to make the diagnosis at a very young age as it is less reliant on patient cooperation and can be performed on subjects who are lying down or unable to sit at a normal OCT machine. This means that new treatment modalities like gene therapy or l-dopa for albinism can be given earlier – even as the retina is continuing to develop – to preserve vision.

There are other advances in imaging technology, currently only available in the research environment, for example, to image individual photoreceptors – rods and cones. This will allow early diagnosis of photoreceptor degeneration before other more invasive tests are performed, e.g. visual electrophysiology, or those that rely on patient cooperation (problematic in young children) and would allow more targeted genetic testing.

3.20 Handheld Oximetric Ophthalmoscope for Enhanced Diagnosis of Retinopathy of Prematurity

Professor Andrew I McNaught
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Retinopathy of prematurity (ROP) is a potentially blinding condition that can lead to retinal detachment and blindness in severely premature and underweight babies. It is associated with abnormal development of retinal blood vessels that may be classified as severity of 'plus disease' from a comparison of images of retinal blood vessels with reference characteristics. Early screening and diagnosis of plus disease and adaptation of treatment according to the severity are effective in reducing the development of ROP and preventing blindness. About 5-8% of premature babies develop ROP in developed countries such as the UK where good treatment for premature babies exists, but the incidence is about 30% in middle-income developing countries such as in Latin America and Asia where more premature babies are surviving, but screening for ROP is not as well developed.

Currently screening involves viewing the retina with an indirect ophthalmoscope whilst physically manipulating the eyeball and recording photographs of the retina using a specialised, but cumbersome and expensive ophthalmic camera called a Retcam (approx. £50k each) that is placed in physical contact with the eye and is stressful for the fragile premature baby and the parents and has to be

repeated regularly during the first few weeks of life. In light of this, a research group at Oxford University, headed by Dr Rebeccah Slater and Mr CK Patel, is investigating how to measure the stress of ROP eye checks and treatment. The group will investigate how to improve on current techniques to make the process less stressful and painful as this is very important for the baby's health and development.

Conventional practice dictates that the retinal photographs are studied by clinicians for abnormal shapes in the retinal veins and arteries indicative of plus disease and treatment of the baby is targeted based on the perceived, subjective development of the disease. Current research is developing computer programmes that promise to more objectively and reliably classify the severity of plus disease and improve the selection of the optimal treatment such as laser therapy or cryotherapy (freezing).

However, Professor McNaught in close collaboration with Professor Andy Harvey and colleagues (who built the ROP focused ophthalmoscope and are now developing the prototype at the Department of Physics and Astronomy, Glasgow University), aim to deliver a device that will improve the diagnosis of the ROP and hence reduce blindness in premature babies in the UK and abroad. This will not only use a new design and exploit low-cost consumer technology to produce a camera for a significantly reduced cost compared to a Retcam but it will accurately distinguish between veins and arteries to enhance automated and objective classification of ROP. It will also be non-contact thus reducing stress to babies and handheld and highly mobile to greatly improve the usability of the instrument.

In the developed and developing worlds where ROP-specialists are seldom found outside major population centres, the features outlined above will reduce the skill level required to record images and this will be highly suited for use in telemedicine for classification of ROP.

3.21 Seeing what they see: Compensating for cortical visual dysfunction in Alzheimer's disease

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"Seeing what they see" is a project which draws together experts in neuropsychology, engineering and social science and individuals living with typical Alzheimer's disease (AD) and atypical AD – namely, the syndrome posterior cortical atrophy (PCA) which primarily affects vision rather than memory. This project is designed to understand and address the issue of dementia-related visual impairment. Some of the broad motivations for the project were that visual impairment in dementia is under-recognised and poorly managed, and most previous research has focussed on people with dementia who also have coincident eyesight loss without addressing impairments of cortical vision ('brain sight') caused directly by conditions such as AD.

This project consists of various strands of work primarily emphasising different disciplines, with the overall aim to develop a better understanding of the nature of visual impairment arising due to AD and PCA, ultimately to develop simple aids and strategies to support everyday abilities. Investigations of dementia-related visual impairment to date have included studying its qualitative and quantitative impact, the significance of the environment, assessment of physical location, activity and eye movement patterns, and detailed exploration of specific visual symptoms and their anatomical basis. The project team have also contributed advances in methodology including the development of new tests for more reliable visual assessment and novel experiments for assessing navigation and object finding. Our initial findings outline which perceptual conditions are optimal for patients with cortical

visual dysfunction to identify simple stimuli, as well as carry out more complex activities such as reading or navigation.

These findings have provided the basis for a computer-based intervention intended to minimise reading problems experienced by individuals with PCA and steps have been taken to address 'appropriate methods of visual assessment', identified as the top priority after consultation with patients, carers, researchers and health professionals. Collaboration has also taken place with the College of Optometrists and a range of optometrists through workshops, conferences and interest groups (e.g. Dementia and Sight Loss interest group).

3.22 Imaging – a powerful illustration of innovation

Julian Jackson
Director
VisionBridge

Patients are quite rightly continuing to ask how eye research can better predict, detect, diagnose and monitor eye disease – and indeed ultimately restore sight. The answers can be found in the fast-moving world of Imaging.

Tremendous innovation is taking place across the wide range of eye research activities but it is clearer than an intraocular lens that the real catalyst which will deliver the maximum potential for positive patient outcomes and most notably and critically influence if not determine the direction of travel for the greatest number of research activities further downstream is Imaging.

Imaging is beginning to make a noticeable impact on positive surgical outcomes by assisting ophthalmic surgeons in better understanding the context in which they are operating, provide greater accuracy in the delivery of treatments and pinpoint the areas of greater or lesser risk prior to invasive surgery – and this is all being achieved with optical coherence tomography (OCT) in support of Robotics.

We are always told that "being forewarned is forearmed" and this is beautifully illustrated in the extraordinary advances in detection – for example, Adaptive Optics (AO) is allowing clinicians to view biomarkers of disease in the form of damaged tissue structures, toxic proteins, inflammation and debris as well as individual cellular abnormalities and dysfunction. Following closely behind, the molecular level will soon be reached thus creating even clearer predictors of impending eye disease by revealing even more detail about for example individual cell metabolisms, cortical remodelling and adaptation to retinal degeneration and even cell death (senescence). And let's not forget the role that Imaging could play in detecting the early onset of Alzheimer's and Parkinson's and indeed in spotting other diseases such as diabetes and diabetic neuropathy, high blood pressure, meningitis, brain tumours and malaria which can all impact on sight if not treated early.

Improved detection can therefore enhance clinicians' ability to predict the likelihood of eye disease and so determine the need for early medical intervention, identify the most appropriate type of treatment if required and assist patients in planning for the future and making more informed lifestyle choices accordingly. Surely, parents of young children could be greatly helped by improved less invasive imaging devices that can spot abnormal microscopic structures in the retina or gauge the density of photoreceptors and indeed older patients would be hugely reassured if there was a sure fire technique for predicting the chance of dry macular degeneration progressing to the wet form?

Imaging can also ride to the rescue in the form of improved monitoring of eye disease too. The secondary sector's ability to cope with the increasing demands and numbers of patients could be greatly enhanced if advanced imaging techniques and equipment were widely adopted by practitioners in the primary sector – indeed, numbers of referrals that currently do not subsequently require an

ophthalmological appointment could be drastically cut and patients with stabilised conditions and in postsurgical phases could be well supported by an upskilled workforce of optometrists.

Peering even further over the horizon, the degrees of predictability drawn from Imaging could be greatly enhanced by an emerging and powerful ally in the form of Artificial Intelligence (AI). If patients are to receive meaningful and timely treatments then human error during image analysis must be minimised, speed of analysis accelerated and indeed correlations and patterns amongst images that perhaps clinicians have not even thought about need to be examined. So, AI in the form of DeepMind's so called "Machine Learning" should be deployed to facilitate in reaching such goals.

As Mr Pearse Keane (*NIHR Clinician Scientist and Honorary Consultant Ophthalmologist, NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology), a strong supporter of VisionBridge, noted:*

"Advances in ocular imaging will be fundamental to all aspects of vision research, and are likely to drive many breakthroughs in eye disease diagnosis and treatment in the next decade. These advances will allow visualisation of every cell type within the eye, from cellular ultrastructure to underlying molecular processes. In parallel, advances in machine learning and artificial intelligence will allow clinicians and scientists to improve patient care and derive new insights into disease pathophysiology. Taken together, new imaging hardware and new artificial intelligence techniques are likely to reinvent the eye examination for the 21st Century."

There is no doubt that the eye which is such an indescribably complex and infinitely adaptable organ is under attack on a daily basis from mutant genes, injury, auto-immune responses, infection, lifestyle choices and the ageing process. So, further and faster developments in the hardware and software within Imaging will constitute the most effective shield against such attacks in both the developing and developed countries but a $1bn injection would help to sustain and secure such exciting progress.

3.23 An innovative testing and monitoring regime yielding results

Professor David Crabb
Professor of Statistics and Vision Research
City University
London

Vision loss from glaucoma occurs when the optic nerve is damaged. In most cases, increased pressure inside the eye (intraocular pressure), is thought to contribute to this damage.

With this in mind, despite the fact that Medication such as "Prostaglandin analogue" eye drops (the most commonly prescribed treatment for glaucoma) to lower raised eye pressure has been used for decades as the main treatment for open angle glaucoma (OAG) to delay progressive vision loss, it had not been proved that this drug had a measurable impact on reducing the risk of further sight loss.

So, David Crabb, co-author and Professor of Statistics and Vision Research at City University London, helped design the innovative testing and monitoring regime used in the trial which epitomized the collaborative clinical working that is so important and which again highlighted glaucoma research in the UK as world leading.

Glaucoma is normally a slow acting disease and observation periods in trials are long. Therefore, David Crabb and his team shortened the trial with the novel use of more frequent testing of patient's vision and the use of precise statistical tests. The trial has set a new benchmark for speeding up novel drug development, reducing costs of trials and increasing the likelihood of bringing new drugs to patients.

The study found that the risk of visual deterioration was over 50% lower in the group treated with daily pressure-lowering eye drops compared to those using placebo drops over 2 years. Importantly, because of the trial design, a significant difference in treatment effects could be seen between the groups after just 12 months.

3.24 How the application of machine learning and artificial intelligence (AI) can assist in the speed and quality of diagnosis

Dr Pearse A Keane
NIHR Clinician Scientitst and Honorary Consultant Ophthalmologist
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A collaborative Research venture is now progressing between Moorfield Hospital's Dr Pearse Keane and Google's DeepMind team led by the co-founder Mustafa Suleyman, aimed at developing ways in which Artificial Intelligence (AI) can be applied to ophthalmology and in particular to the type of imaging of the eye called Optical Coherence Tomography (OCT – an established medical imaging technique that uses light to capture 3-dimensional images).

Undoubtedly, the scanning of patients' eyes using OCT (three-dimensional scans of the retina which is much better at revealing eye disease than traditional retina photography) heralded one of the biggest developments in modern ophthalmology – but unfortunately, the increasing number of false positive referrals received by hospitals like Moorfields will soon be exacerbated by the imminent roll out of OCT devices amongst opticians who may not have the sufficient training to interpret the scans. These scans are quick, easy and safe to acquire, but too many patients are being referred for the wrong reasons, leading to a clogging up of the clinics and the resulting inability of clinicians to treat genuine cases of sight loss (e.g. diabetic retinopathy or wet AMD within an appropriate time scale. This swamping of services could not be happening at a worse time. Ophthalmology is already the second-busiest speciality in the NHS, with more than 9 million outpatient appointments per year.

Therefore, how can the application of machine learning and AI assist in improving the quality and speed of diagnosis thus allowing for earlier and more effective treatment whilst reducing patient numbers and prioritizing those that require urgent treatment first? The answer is that generally, AI is delivering huge improvements on e.g. speech recognition, very good translation, very good image labelling and image recognition. There are much improved machine learning models, access to very large-scale computers and there is increasingly enough training data to help build effective models.

So, with that developmental momentum, the millions of OCT scans held by Moorfields has presented DeepMind with the ideal dataset for DeepMind to apply its research. In a way, DeepMind is replaying all of the scans to the machine learning system in the same way that an expert consultant ophthalmologist might sit in front of their computer and watch scans and case studies over and over again – this is what the DeepMind calls "experience replay". The system being applied to the Moorfields data is "imagining" an abstract form of the disease it looks for such as Diabetic Retinopathy (DR), seeing it in its "mind's eye". This is similar to the technology used for example to look at photographs on Google Photos or Image Search or Facebook or to recognise faces in the photos

Despite The fact that the application of AI in spotting eye diseases is currently very much a research project, there is growing optimism that it will soon be able to "grade" eye scans more effectively and certainly much more quickly and more cheaply than a human. Mass adoption of OCT which is supported by AI within opticians may well be only 3 years away – people will be able to walk into a high-street optician, have an OCT scan and have it graded by an AI system.

However, although machine learning will become an invaluable tool in early diagnosis and the planning of treatment, the advent of AI in handling so many patient data sets will require greater ethical scrutiny and appropriate governance. It is this data that gives machine learning its formidable power, and the NHS is in a unique position to offer huge, well-labelled datasets.

Also, questions such as how patient information which is so key to the use of AI is shared, who gets to use it and who gets to profit from it are questions that could fail to be properly answered in the rush to implement this important new technology. These questions will need to be answered as AI will soon be impacting on healthcare generally – for example, the hospital environment is such an expensive and complex system and clearly the humans working in it are simply overwhelmed by the scale and complexity of managing so many patients who are on so many different pathways and who need so many different tests and interventions. It becomes a massive co-ordination exercise and therefore AI can be applied so tasks in various areas of the hospital could be more efficiently and speedily prioritised to improve patient outcomes and care.

3.25 A collaborative approach to improve visual field tests

Professor Paul H. Artes
Professor of Eye and Vision Sciences
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Plymouth University

Professor Paul Artes and his team in Plymouth focus on creating better visual field tests for patients with advanced glaucoma. These patients often have only a small part of remaining central vision that they use to read, recognize faces, and watch television. Much of the surrounding field of vision is irretrievably damaged, and the important area of "indirect" vision that healthy people use subconsciously to move about is no longer available. Sometimes, small "islands" can remain in the far periphery, and it is important that patients are treated as well as possible to preserve these areas.

Current visual field tests do not measure peripheral vision well enough, and they also do not work well for the most important central areas of vision when there is substantial damage. Most patients with advanced damage find visual field tests difficult and frustrating. The results can vary a great deal between one examination and the next, and this means that clinicians often have little confidence in making decisions of whether the patients' treatment is adequate or not.

Against this background, Professor Artes and his team aim to create tests that are easier to perform for patients and provide more reliable information to eye health professionals. If successful, these new tests will lead to better treatment of individual patients but they will also speed up progress with comparing drugs and surgical techniques. Ultimately, they will improve understanding of how eye diseases and their treatments affect patients' "real-world" visual function – their ability to move through a busy environment, climb stairs or drive a car.

His approach to this field of "clinical vision research" is to break down individual challenges into smaller pieces and try to find solutions accordingly and then translate the specific problem into the language spoken within other disciplines such as vision science, mathematics, or computer science. Step two is to translate the challenge into a practical clinical application that can be used by eye doctors in the consulting room, for example a new vision test or a computer programme that helps doctors to make better sense of data from existing tests. However sometimes he will work with basic scientists from his field or from other disciplines to understand the underlying problem, formulate the right research question and design the experiments required to solve it.

Paul is a founding member of the "Open Perimetry Initiative", a group of scientists, engineers, and doctors who collaborate on making high-end commercial equipment accessible for scientific

studies, and it is notable that his groups' work on improving visual field tests relies on close collaboration with industrial partners such as instrument manufacturers.

This group freely share tools and expertise, and this has tremendously accelerated progress in terms of translating new scientific knowledge into prototype clinical tests. In turn, instrument companies are beginning to benefit from a much wider network of scientists for research and development than was available in the past – a development that will lead to more rapid advances in clinical tools and, ultimately, clinical care.

Bearing in mind the many unsolved problems in eye care and the new potential solutions which are becoming increasingly available through advances in basic science laboratories, Paul Artes is passionate about the education and training of new scientists (PhD students and postdoctoral research fellows) to ensure that his fields of research continue to make sense of these findings and bridge the gap between bench and bedside.

3.26 The importance and translational benefits of improving the accuracy of diagnostic tests

Dr Tony Redmond
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Cardiff University

Damage to the visual field is the primary functional biomarker for glaucoma, the second leading cause of blindness globally, and is screened for by clinicians with perimetry, a clinically-adapted psychophysical technique that uses spots of light varying in brightness to probe the visual pathway. It is well understood that earlier detection followed by appropriate treatment, of glaucoma are essential for a better visual prognosis. However, current clinical methods for measuring visual field damage are inefficient for detecting the earliest stages of glaucoma and its progression, and more appropriate stimuli are urgently needed to improve the diagnostic accuracy of perimetry. It is only through rigorous psychophysical research that regions of the visual pathway and levels of sight affected in glaucoma can be identified and then develop an understanding of how precisely these changes can be detected clinically at the earliest opportunity.

With this in mind, by studying how the visual system processes and behaves in response to visual stimuli, including spots of light, detailed patterns, or natural scenes, Dr Tony Redmond and his team who have made significant progress in the development and optimization of efficient clinical tests for glaucoma, continue to probe various regions of the visual pathway, from the eye to the brain, that are responsible for different levels of sight. This area of "visual psychophysics" helps them better understand how the functional architecture of these structures enables us to see and perceive everyday scenes, as well as how various attributes of sight are affected in disease.

So, armed with an understanding of these mechanisms in health and disease, a substantial translational arm of Tony Redmond's research is aimed at developing optimum stimuli for identifying disease from normal eye and brain function in the clinical setting.

More recently, in collaboration with colleagues at the Cardiff University Brain Research Imaging Centre (CUBRIC), psychophysics has been combined with high-resolution neuroimaging (functional MRI) to more accurately underpin the regions of the visual pathway responsible for the earliest changes in vision in glaucoma. As a result, this will enable them to establish a clearer idea of how visual scenes appear to patients and to refine the development of the most accurate clinical test of early visual field damage.

3.27 A new way of detecting and monitoring eye disease

Professor David Crabb
Professor of Statistics and Vision Research
City University
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Eye movements are a continuous and ever-present part of vision. When we look around our eyes generate saccadic eye movements (extremely fast voluntary movement of the eyes, allowing them to accurately refix on an object in the visual field), interspersed by periods of time where the eyes are stable (fixations). Scan paths reveal the sequence of fixations and saccades. Scan path data, collected during the time a person is engaged in watching a film could give an individual 'eye movement fingerprint' akin to the level of data that might be found in a genetic profile.

So, Professor David Crabb and his team at City University have devised a "proof of principle" project to prove the concept that there is a signature or 'fingerprint' in people's scan paths and to accumulate evidence to show that patients with age-related visual disease have different eye movements compared to visually healthy people. Prof Crabb has already collected scan paths from 100 elderly people and will develop statistical methods to analyse these complex eye movement data. This will determine if the concept of monitoring eye movements in people while watching a film could reveal data that could be a biomarker for eye disease.This 'proof of principle' work could lead to 'Eyecatcher' potentially becoming a new way of detecting and monitoring eye disease.

4.0 Treatments

Eye research constantly questions the efficacy of standard treatment approaches as it remains clear that not all treatments suit every patient and indeed there is always an imperative to create treatments which are better targeted, less invasive, longer lasting and require less applications in the fight to prevent further sight loss, stabilise conditions and ultimately restore sight. Work is also ongoing to treat patients without the current unpleasant side effects and surgical shortcomings.

The breadth and depth of eye research continues to grow in the treatment arena, reflected in the research into stem cell and gene therapies, drug treatments and drug delivery, pharmacogenetics and personalised medicine, light, x-ray and other non-invasive therapies, antibodies, neuro-protection, the innovation behind surgical instruments and techniques that are safer, faster, more accurate and less invasive.

4.1 Synthetic microbicidal peptides: A novel therapy for the management of corneal blindness

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The cornea, a dome-shaped transparent window of the eye, is essential for clear vision. Corneal infection, also referred to as microbial keratitis, is the leading cause of sight loss worldwide. Prevalence of microbial keratitis and pathogen involved varies geographically and is dependent on various risk factors.

Ocular trauma and extended contact lens use are the major risk factors of corneal infection. Bacteria, fungi and yeast are frequently isolated from the corneal surface of patients with microbial keratitis. Often patients presenting with bacterial and fungal keratitis show severe pathology and pose extreme challenges to the clinicians due to the lack of effective therapeutics. The constant rise of pathogens resistant to conventional antibiotics and poor penetration of available anti-fungal agents have further increased the prevalence of corneal blindness. *Acanthamoeba spp.* and Herpes simplex virus are the other common pathogens known to cause corneal infection worldwide with their presentation often confused with fungal keratitis leading to delayed treatment and loss of vision.

For the past 5 years, my team has been rigorously working on the development of alternative microbicidal therapeutics for the treatment of corneal infections. Based on our previous discoveries of the antimicrobial peptides from the corneal surface of patients with microbial keratitis, we developed a novel class of synthetic microbicidal peptides (SMPs) through structure-function relationship approaches. This research was supported by generous funding from the Fight for Sight charity and other council organisations, namely EPSRC and MRC. Currently, we are investigating the safety, efficacy and pharmacokinetics of these novel SMPs utilising the preclinical animal models of corneal wound-healing and corneal infection, respectively. Our key collaborators are world renown molecular microbiologists, parasite biologist, medicinal chemists, and ophthalmologists based within the UK, US, and Singapore.

We are always looking out for collaborators for cross-disciplinary and multi-disciplinary advancement of our novel therapy for the treatment of other bodily infections.

Investment and commercial collaborators are also sought for taking our library of pathogen specific SMPs for testing into human-based clinical trials.

4.2 The development of novel oculosubarachnoid glaucoma shunt devices (OGDs)

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Glaucoma remains a leading cause of blindness. The need for daily medication usage, repeated laser, and multiple surgical interventions means it is one of the eye diseases which puts most strain on healthcare systems and significantly impacts patient quality of life.

Despite half a century of innovation, trabeculectomy with Mitomycin C and tube-shunt device implantation remain our most effective means of treating glaucoma. Unfortunately, despite our best efforts at optimisation, subconjunctival fluid drainage is still associated with a high rate of complications and failure.

Oculosubarachnoid shunting, being pioneered by Dr McClunan and LIQID Medical, is a novel method for treating glaucoma. Oculosubarachnoid shunting creates a fluid shunt communication between the eye and the retrolaminar subarachnoid space. This has four potential benefits over traditional subconjunctival fluid drainage:

1. Draining aqueous to the subarachnoid space **does not create a bleb**. The presence of a bleb poses a lifelong risk of complications, including a 1.3% per patient-year risk of blebitis and endophthalmitis. Blebs require ongoing follow-up and management which cause quality of life loss and ongoing costs for patients and healthcare systems.
2. The fluid in the subarachnoid space is controlled by robust mechanisms to a pressure averaging 12 mm Hg — the holy grail pressure for preventing progression in glaucoma. This means that by "piggy backing" ocular pressure to subarachnoid pressure, it should be possible to ensure **predictable, optimal and self-regulating IOP control**.
3. Fluid within the subarachnoid space has a chemical composition identical to aqueous fluid for all intents and purposes. The space is therefore naturally designed to accommodate such fluid. On the contrary, the subconjunctival space inherently reacts to aqueous with fibrosis and scarring. This means that shunting aqueous to the subarachnoid space does not require the use of Mitomycin C and is less likely to cause fibrosis and filtration failure. Subsequently, oculosubarachnoid shunting could be the first **long-term solution for highly effective glaucoma control**.
4. Translaminar pressure has been shown to be directly correlated to glaucoma progression. By creating a shunt communication between the eye and the subarachnoid space, **translaminar pressure is nullified**. Current literature suggests that this holds the key to eliminating the progression of glaucoma.

These characteristics mean oculosubarachnoid glaucoma shunt devices (OGDs) have the potential to dwarf the clinical performance of the current gold standard. LIQID Medical is developing two forms of OGDs, the OptiShunt and iPortVR, which leverage this novel concept from both an ab-externo and ab-interno implantation technique. The iPortVR is also the first glaucoma device designed for implantation during vitreoretinal surgery.

The Glaucoma treatment by OculoSubarachnoid Shunt Insertion Pilot (GOSSIP1) study, is an early feasibility study assessing the safety and feasibility of oculosubarachnoid shunting using a proof of concept device, the OptiShunt Version1.

The GOSSIP1 study is being conducted in a sample of 15 patients with severe end stage glaucoma at Groote Schuur Hospital, a premier academic hospital in Cape Town, South Africa. Study results over a period of six months for patients recruited to date are demonstrating that oculosubarachnoid shunting is safe and highly effective at lowering IOP. IOP was reduced from baseline of 41 mm Hg by 73% to 11 mm Hg at 3 months and by 62% to 15 mm Hg at 6 months. This demonstrates a 1.5-2 times higher IOP lowering effect at 3 and 6 months, when compared to IOP lowering following tube-shunt implantation in a similar group of patients. Complication rates were similar in both groups and no adverse events occurred in the GOSSIP1 study, which investigators identified as being related to the novel implantation technique, or the oculosubarachnoid shunting mechanism of action.

Buoyed by these early study results, LIQID Medical is actively pushing OptiShunt design optimisation, ongoing development of the iPortVR, and multicentre clinical trials in pursuit of creating the most cost saving, clinically effective and quality of life improving glaucoma devices available.

4.3 SAVIR-Therapy for vision restoration - Vision recovery and reactivation of "silent" neurons

Professor Bernhard Sabel
University of Magdeburg, Germany

Vision loss is caused by different diseases that damage nerve tissue in the retina or brain. But unfortunately doctors and patients have no way to improve vision again because traditional thinking teaches that cell death occurs and the resulting damage is "irreversible". No solution and no place to go to improve vision again. All one could hope for is delaying or halting further vision loss.
But there is light at the end of the tunnel.

Of course, cells which are dead are "irreversibly" gone, yet research by Prof. Sabel and his team at the University of Magdeburg/Germany shows that loss of vision is in part due to inactivation, not death, of neurons. In fact, many nerve cells are not dead but only functionally inactive because of hypometabolism – the "silent survivors" can be reactivated by innovative techniques which re-energizes them by way of enhanced blood flow in the eye and brain.

Based on this new scientific understanding, new therapy options have emerged. SAVIR, a pioneer in "awakening" silent neurons, now offers such a solution to restore vision, even long after the damage was done. With its all-inclusive, holistic "one-stop-shop" package of diagnostics and therapeutics interventions, SAVIR complements and does not replace standard ophthalmological therapy. When ophthalmology is done, SAVIR begins.

What is SAVIR Therapy?
SAVIR stands for "**Sa**bel **Vi**sion **R**estoration", a menu of different methods to help improve vision in patients with vision loss. SAVIR offers a holistic program with diagnosis and treatment that does not end with the eye, but also considers the person behind the eye: patients´state of the brain, vascular system, mental state, and lifestyle. SAVIR is a comprehensive program combining innovative technologies for vision restoration in combination with relaxation and psychological/lifestyle counselling. SAVIR's alternating brain microcurrent stimulation (ACS) is the "backbone" of the therapy with proven efficacy as shown in controlled clinical trials and confirmed independently by other scientists.

What is alternating micro-current stimulation (ACS) and why does it work?
ACS is a non-invasive method to stimulate the eye and brain. Because it acts on a fundamental cellular level of improving blood flow and brain signal processing. Therefore, it is effective in different diseases of the optic nerve, retina, and brain: The therapy is performed with certified,

devices which deliver tiny microcurrents to the eyes and forehead, 30-60 min. daily for 10 days. ACS enhances vascular blood flow (which gives "silenced" nerve cells more energy, i.e. glucose and oxygen, and it enhances the synchronization of brain activity to improve and strengthen neural processing of "residual vision". The ACS treatment is embedded in a menu of additional procedures which enhance its efficacy and longevity of the treatment effects including relaxation techniques (meditation, eye yoga) and psychological /lifestyle counselling, all of which are critical to optimize individual recovery rates.

At SAVIR patients are not only treated medically, but they also learn how to improve their quality of life by adapting to – and coping with – their vision loss and fear. This holistic approach of SAVIR therapy is unique, with no other place like it.

Which diseases can be treated and how soon does one have to start?

As the treatment affects very fundamental cellular processes (increasing the cells energy state), SAVIR is effective in many different diseases: glaucoma, optic nerve damage (optic neuropathy), macular degeneration, diabetic retinopathy, amblyopia, brain lesions due to stroke and brain trauma, and even "unexplained" causes of vision loss.

As SAVIR activates "silent" neurons which have survived in an inactive state for months or years, therapy is effective independent of age, duration of the vision loss, or its level of severity. SAVIR strengthens those visual capacities which were neglected – or even actively suppressed – by the eye and brain. However, SAVIR cannot help blind patients that have no subjective vision at all.

What is the scientific evidence?
The holistic SAVIR-approach is based on 30 years of research by Prof. Sabel and his team at the University of Magdeburg. Being an expert in medical psychology, Prof. Sabel has a unique and broad view to look beyond the "eye problem" of low vision and has published over 200 scientific studies in reputable scientific journals. To find the right therapy, he has collaborated around the world with key scientists from different disciplines (USA, China, Italy, Sweden, Poland etc), jointly conducting experiments and clinical trials to test different approaches. His fundamental proposal of brain plasticity and visual restoration has been independently confirmed by others.

How much improvement can be expected?
The experience with more than 1,000 patients shows reliable and stable results:
Measurable treatment effects are on average as follows:

- 24% larger visual field size
- 60% reduction of impaired visual field sector
- 84% of patients have subjective improvements
- But 1/5 patients show little or no change
- Note: return to normal vision is not expected

Subjective improvements include:

- Enlargement of field of vision
- Less "foggy" vision ("dirty glasses"), less glare.
- Faster reaction time and better reading ability
- Recognizing stairs and feeling safer when walking on uneven ground
- improved far vision and better fixation
- Improved acuity, i.e. more clarity to see details of faces and objects
- 94+% of patients are satisfied with SAVIR, even those where vision did not improve.

Adverse effects are benign: not a single serious adverse event (SAEs) was observed and milder adverse events (AEs) are very rare (<5% of cases). They include slight (temporary) headaches, fluctuations in foggy vision, dizziness, or blood pressure fluctuations. An acceleration of vision decline never occurred.

If you refuse to accept the widely accepted but depressing prediction "blind stays blind", then SAVIR is the right partners for you. Where others give up, SAVIR takes over.

For further information please follow these video links:

Technique presentation: https://www.youtube.com/watch?v=g8p3mWsLvAI

Patient testimonial: https://www.youtube.com/watch?v=62HrqVfCKPw&t=148s

Overview science lecture of holistic ophthalmology:
https://www.youtube.com/watch?v=6p_RUsSo_04&t=1807s

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4.4 Research towards a revolutionary drug delivery mechanism for AMD treatment and prevention strategies

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Age-related macular degeneration (AMD) is a leading cause of vision loss in Europe and the US. About 1 in 50 people aged 50 or over have some form of AMD, increasing to nearly 1 in 10 for

people aged 85 or over. Usually vision loss is gradual and happens over a period of years, but sometimes vision loss can be rapid, happening over several weeks. The macular region is a part of the retina where the most detailed images are formed. Its loss makes activities such as reading, driving and recognising faces very difficult. In the UK 600,000 people are estimated to have advanced AMD and 70,000 new cases are diagnosed annually.

The current recommended therapy for neovascular AMD consists of monthly intravitreal injections of anti-VEGF antibodies for a minimum of 5 years. It is a rapid outpatient procedure, and for most patients it is an effective therapy. However, it has significant side effects, including uveitis, retinal detachment, and raised intraocular pressure.

With 400,000 procedures being performed annually within the UK, there is a *de facto* rationing of therapy based on the cost of drugs and the availability of ophthalmologists to perform the injections, leading to wide variations in the proportion of eligible patients offered therapy even in adjoining clinical commissioning groups. Additionally, the process of attending clinics for injections is unpleasant for patients, with treatment centres reporting between a third and half of patients failing to complete the course.

There is therefore an unmet, clear need for topical applications that can be applied by the patient themselves anywhere. However, the eye poses significant barriers to drug delivery as the structures of the eye act as barriers to the penetration of drugs.

In our research we have investigated the use of biogenic polyamines as a membrane-penetrating drug

delivery agents (MPPAs) that can deliver drugs to the retina when applied to the cornea as eye-drops. Using both a membrane translocation model and an ex-vivo porcine eye model, we have demonstrated that they are able to translocate and deliver significantly higher concentrations of drug molecules than existing technology built on polyarginine cell-penetrating peptides (CPP) which are currently in development. We have also shown that both large (150 kDa), and small proteins (2.9 kDa) used in anti-VEGF therapy can be successfully transported using these MPPAs.

Our research into the structure and function of the MPPAs has additionally shown that we can rationally select MPPAs to deliver molecules of varying charges and hydrophobicities. This raises the possibility that we may also be able to deliver molecules that have either preventative or therapeutic benefit to the retina, but are currently impractical to deliver invasively, such as carotenoids to the macular region, or glucose to the RPE in retinitis pigmentosa.

This research has the potential to make treatment safer and more convenient for patients and less costly for the NHS as eye drops can be administered by the patient themselves when and where they choose to.

4.5 Intraocular Magnifying Lenses for Advanced Macular Disease – Current Status

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Background

Data from the United Kingdom, show that 600,000 individuals in the UK have age-related macular degeneration (AMD). Approximately one third have a degree of bilateral visual impairment that impinges on their ability to undertake tasks which a normally sighted peer would consider fundamental to comfortable and effective daily living. Individuals with hereditary central macular dystrophies are similarly affected and in this group loss of central vision can have an impact on ability to work leading to financial difficulties and loss of self-esteem. AMD can be either wet (neovascular) or atrophic (geographic atrophy) both of which cause loss of vision. Over the past decade anti-VEGF therapies have made a significant impact on reduction of visual loss in wet AMD, however no therapy exists for the atrophic (dry) form of the disease. In addition, a substantial proportion of patients with wet AMD still become visually impaired either because of late diagnosis or lack of effect of current treatments. The only treatment option for these individuals is the enhancement of vision through the use of external low vision aids. Optical Low Vision Aids (LVAs) can be successfully used by some vision impaired individuals however practical limitations include a requirement for good hand-eye coordination. In addition, optical limitations include field of view restrictions and aberrations which vary according to mode of use and magnification power which makes these devices unpopular.

A novel concept is the use of **"implantable intraocular magnifying telescopes or lenses"** to enhance vision. The prospect of being able to implant a magnifying device/lens, in selected suitable patients, provides a convenient, effective and cosmetically attractive option. These devices are not in routine use in the NHS as there is a lack of evidence regarding their effectiveness. Intraocular magnifying devices were reviewed by the National Institute for Health & Care Excellence (NICE) in 2008 (IPG272). The appraisal concluded that these devices should be used under "Special

Arrangements". A further planned NICE appraisal review in 2011 was abandoned due to lack of further evidence.

Implantable Magnifying Devices

Nine implantable magnification devices Centrasight" (IMT) implantable miniature telescope (VisionCare Ophthalmics), IOL-VIP System (Veni-Vedi); the Lipshitz macular implant, the sulcus-implanted Lipshitz macular implant, the LMI-SI, (Optolight Vision Technologies); Fresnel Prism IOL; iolAMD, EyeMax Mono IOL (LEH Pharma) and the Scharioth Macular Lens (SML) are currently available but none are available on the NHS. These devices work by magnify the image projected on the retina and/or deviate the image away from the central scotoma (blindspot). Most designs are based on Galilean telescopic principles, consisting of two lenses with high positive and negative power, respectively. Recent publicity has resulted in considerable patient interest in the use of intraocular magnifying technologies which are complimentary to other therapies. Details of the different device options are shown below.

- The "Centrasight" (IMT) implantable miniature telescope device produces excellent magnification 2.5-fold magnification however, there is significant reduction in peripheral field in the implanted eye. In addition, the implant is large requiring a wide surgical incision, a lengthy recovery time and potentially increases risk of damage to the corneal endothelium. A newer model which is implanted through a smaller incision is currently being investigated.
- The IOL-VIP is a 2-lens system that is easier to implant however again concerns exist regarding long-term safety in terms of corneal damage. Also, as the magnification potential is low 1.3-fold magnification the visual benefits are more modest.
- The OriLens offers a 2.5-fold magnification and is based on "Cassegrain" telescopic principles which has facilitated the design of a telescope with several advantages. These include reduced device thickness: 1.25mm versus 4mm (Centrasight) which allows reduction wound size, shorter recovery time and less reduction of visual field. As the OriLens device is suitable for patients who have already had cataract surgery, this offers the potential of treating more individuals.
- Fresnel Prism IOL is an in-the-bag IOL designed to deviate the image from the diseased to healthy retina.
- The iolAMD is a double-implant system with the high plus-power lens is implanted in the sulcus. The high plus-power IOL has a hyper-aspheric-optic that is slightly de-centred which is reported to deviate image unto a less affected part of the macula. The lenses provide a 1.2-fold magnification.
- EyeMax Mono IOL (wide-angle IOL) is a novel monofocal IOL with a 3-fold magnification. The lens is designed to extend macular vision, the EyeMax Mono's lens optics are optimized to provide enhanced images across all areas of the macula extending 10° from the foveal centre.
- Scharioth Macular Lens (SML) – this is detailed below.

None of the devices have been studied in randomised controlled trials, and apart from the Centresight device, a paucity of information exists to support the efficacy of these devices. All of the available technologies have advantages and disadvantages.

The Scharioth Macular Lens (SML) is the focus of a current Clinical Trial in our unit. The MAG-VUE Trial which is funded by the Macular Diseases Society UK, is designed to test the SML intraocular magnifying lens to assess if this would be helpful and safe in patients with poor vision due to advanced macular disease due to either age-related macular degeneration (AMD) or inherited retinal diseases (IRD). The SML is suitable for both phakic and pseudophakic eyes, is an inexpensive and relatively simple device, is easily implantable and offers potential for treating more individuals due to the low cost.

The Scharioth Macular Lens (SML; A45SML, Medicontur Ltd) is a new CE marked, sulcus fixated add-on one-piece foldable intraocular hydrophilic acrylic lens. It is designed to increase near acuity in

patients with stable macular disease. The overall diameter of the lens, which has 4 symmetrical haptics, is 13mm. The central +10D portion of the lens (1.5mm in diameter) provides 2-fold magnification for near vision. The periphery of the lens is optically neutral and is designed to leave distance acuity undisturbed. This is hugely advantageous as patients using other implantable magnifying devices with higher magnification, report having trouble with binocularity for distance which impacts on their ability to mobilise safely. With the SML binocularity is only reduced for near vision tasks at a reading distance of 15 cms.

The device is inserted through a 2.2 mm corneal incision in front of a standard IOL (piggy- back), at the time of cataract surgery or later as a secondary procedure. The learning curve for experienced cataract surgeons is short and recovery for the patient swift. The cost of the device is low.

Conclusion

Intraocular magnifying devices have now been available for some time with numerous models available and yet widespread usage is still not available. This is testament to the fact that although the concept is good, the application is fraught with difficulties. However it is important that we do not give up as the need is great and ever increasing.

The cost of caring for a visually impaired individual was estimated by the HTA Group in Birmingham in 2003, to be £6455 in the first year and £6295 in subsequent years. Data provided by a US survey carried out n 800 individuals through the Macular Degeneration Partnership reported that the direct cost in the US of low vision devices ranged between $281 to $1589 per individual. However, the survey also identified that the indirect costs associated with care provision ranged from $225 to $47,085, depending on the level of visual acuity of the individual. Therefore, the possibility of identifying a magnifying intraocular lens that is easy to implant, easy to use and affordable for large numbers of patients with stable advanced macular disease thus providing a degree of vision rehabilitation would be pivotal.

4.6 New research findings in corneal biology from Newcastle team that are driving innovative treatments for blindness

Professor Che Connon
Professor of Tissue Engineering
Newcastle University

Professor Connon's research team seeks to engineer functional replacement and temporary 'bridge' tissues using a modular approach while also developing model systems to study physiological and pathophysiological corneal tissue formation.

Recent Highlights

Prof Connon was the first to demonstrate 3D printing the cornea. In a proof of concept publication (most downloaded article in Exp Eye Res) his team shows the incredible potential of 3D bio-printing the corneal stroma. This was achieved by combining collagen with alginate to form a printable hydrogel containing human corneal stromal cells. They then used 3D coordinates taken from a patient's own cornea to 3D bio-print an exact geometric replica containing donor cells that were shown to remain viable through this process. They are now looking to develop this technology further and create a process for the rapid production of transplantable corneal stromal tissue to treat the growing numbers of corneal blind across the world with no access to donor tissues via a startup company 3D Bio-Tissues Ltd.

Early 2019, Prof Connon's Team published a landmark study (Nat Comms 2019) showing how the mechanical environment at the corneal limbus is responsible for maintaining corneal epithelial

homeostasis. Specifically, they were the first to show that limbal stem cells require a soft environment in order to thrive and that loss of stem cells following chemical burn can be treated not by a stem cell transplant but by simply restoring the correct level of tissue compliance – chemical burns cause a pathological stiffening of the limbal tissue affecting stem cell function. They are now looking to bring this novel treatment to the clinic, called biomechanical modulation therapy, it has the potential to treat and restore the sight to millions of people around the world.

Background

Che Connon obtained his PhD in Biophysics from the Open University Oxford Research Unit in 2000, during which time (under the supervision of Professor Keith Meek) he investigated corneal wound healing and transparency. He subsequently obtained a JSPS post-doctoral fellowship to work with Professor Shigeru Kinoshita in Kyoto, Japan for two years studying corneal stem cell transplantation. Upon his return to the UK he was awarded a Royal Society Fellowship to investigate the use of biomaterials in stem cell therapies. He obtained his first permanent position in 2007 at University of Reading, School of Pharmacy and since 2014 he has held the position of Professor of Tissue Engineering at Newcastle University.

4.7 Glaucoma Care in the Blink of an Eye

Marina de Moses
Founder and CEO of EuMuse and Compass in Philanthropy
Advisory roles for medical and healthcare startups
in EU, Israel and China

Large-scale changes driven by tech innovation are only as valuable as their impact on individual people’s lives. Worldwide there are 70 million glaucoma patients and only 220,000 ophthalmologists to treat them. BELKIN Laser’s vision is to revolutionize accessibility to glaucoma care by offering a very simple one-second laser therapy, which can be applied by any ophthalmologist as a first-line treatment of choice, all over the world. BELKIN Laser, with its automated one-second glaucoma laser treatment, will enable the limited number of ophthalmologists to treat many more patients.

BELKIN’s innovative technology is applicable for the prevalent Open Angle Glaucoma (OAG) (~50M), and in addition it will pioneer treatment for Angle Closure Glaucoma (ACG) (~20M), which is most common among Asian populations and is one of the leading causes for irreversible blindness globally.

BELKIN Laser, a MedTech startup company, is developing the novel automated Direct Selective Laser Trabeculoplasty (DSLT) device. Recipient of the prestigious European Horizon 2020 grant of €2.5M – the biggest EU Research and Innovation program ever – BELKIN Laser, the leader of the GLAUrious consortium, has started its First in Human clinical trial during the World Glaucoma Week in March 2018. This was the first time that 100 green laser beams were delivered automatically, within a second, to the sclera around the limbus of a human eye. This is made possible by an advanced image acquisition algorithm which locates the treatment zone and locks-in the eye-tracker. This treatment doesn’t involve contact with the eye, it’s painless and requires a negligible learning curve. Initial follow-up of the first patients treated with the novel automated one-second glaucoma laser device shows positive results and a good safety profile.

BELKIN Laser, founded in 2013, is named after its founder and medical director, Professor Michael Belkin, a serial entrepreneur and the inventor of the “Ex-Press” glaucoma shunt, which was acquired by Alcon in 2009. The company is a graduate of RAD BioMed Accelerator as a part of the Incubator Program at the Israel Innovation Authority.

In December 2018, Daria Lemann Blumenthal, CEO, presented at the prestigious China-Israel Innovation and Entrepreneurship Contest, and won the first prize. The contest was organized by Chinese ministry of science and technology and the Israel Innovation Authority. BELKIN Laser has also won the first place at the Startup competition of the Israeli Academia Showcase 2016, as well as at the Business Opportunities in Israel Lasers and Electro optics (BOLEO) Competition 2016. It was elected finalist in Clearly Vision 2016, London-Hong Kong, Innovation Prize Paris 2017, and project of choice by Wharton Business School, USA in 2017. After a successful round A, amounting the total fundraising to $6.6M, with investors including Singapore-headquartered ZIG Ventures, China's Rimonci Capital and private investors, BELKIN Laser is now launching round B with a goal to raise $9M.

There are well over 1,400 life-science and healthcare companies in Israel whose innovations have the potential to bring great benefits to the world healthcare arena and patient population. Innovation in this field thrives at the meeting point of scientific expertise, entrepreneurial vision, and scale-enabling technological solutions. BELKIN Laser does provide a mechanism that explores and applies innovation through a prism of scientific, social and economic filters. The humane, social and economic consequences of its success are incalculable.

4.8 Partner Diagnostics and Therapeutics for genetic eye disease

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World-leading ophthalmology research at Ulster University specialises in the discovery of specific mutations in genes linked to inherited eye disease. In collaboration with industrial partner Avellino Labs USA, Tara and her team are developing genetic testing for a number of inherited eye diseases including but not limited to a range of Corneal Dystrophies alongside a relative genetic risk test for Keratoconus. If an individual harbours certain mutations, this can influence the response to environmental stimuli, medical intervention or ocular injury.

For example, numerous studies have shown patients receiving elective refractive surgery, who carry a mutation in TGFBI, display a post-operative accelerated deposition of mutant protein and develop symptoms of Corneal Dystrophy, which otherwise may not have developed for decades. Avellino Labs USA provides a genetic test for TGFBI gene mutations, which allows candidates considering corrective laser eye surgery to be advised on the risk of adverse corneal dystrophy related pathology post surgery. To date, Avellino has tested almost 800,000 individuals worldwide and prevented over 1,000 people from having a potentially blinding reaction post laser eye surgery.

Whilst the diagnostic provision for TGFBI mutations is well established, our efforts must now extend to complex diseases that require a greater appreciation of not only genetic variants, but non-genetic regulatory influence that contributes to disease. For example, the genetic testing for Keratoconus is more complex in nature and increasingly challenging.

In terms of developing novel treatments for genetic disease of the eye, the eye itself offers distinct benefits in the field of genome engineering. A high proportion of genetic ocular diseases are monogenic with the causative gene elucidated in many cases. In addition, the eye offers unique anatomical and physiological qualities that make it amenable to treatment; it is easily accessible, has a small surface area and is propped to hold an immune-privileged status making ocular diseases an ideal system in which to develop for CRISPR/Cas9 gene therapy.

The team's continual drive and passion to understand genetic variants associated with monogenic disease, for which a single gene is accountable, has demonstrated new and novel treatment options. Their ability to modify the genome using molecular surgery has emerged as a promising therapy for inherited disease, many of which would otherwise have no effective treatment. The team were the first in the world to show CRISPR/Cas9 gene editing in vivo for corneal dystrophy, demonstrating knock out of the mutant allele. In the era of personalised medicine, by knowing the DNA sequence of an individual and detecting the mistakes which relate to disease, pre-screening of all family members allows a bespoke gene therapy to be designed and administered prior to disease symptoms developing.

The advancements in genome engineering have accelerated the prospect of personalised medicine as a therapeutic option

Recently, Editas Medicine published results detailing the development of EDIT-101, a CRISPR engineered treatment for Leber congenital amaurosis (LCA). EDIT-101 is targeted to delete or invert a mutation within CEP290, which causes a miss-splicing of the transcribed mRNA. In vitro experiments in human cells and retinal explants were able to restore functional CEP290 expression. It has been reported that in mice and non-human primates subretinal delivery of EDIT-101 was well tolerated, and sustained CEP290 editing in photoreceptor cells was achieved that met or exceeded the target therapeutic level. Editas Medicine and Allergan Pharmaceuticals International Limited (Allergan) plan to initiate patient screening in the second half of 2019 for clinical trials to test the efficacy of EDIT-101. They plan to enrol 10-20 patients in the U.S. and Europe. They also have future plans for a similar trial targeted to Usher syndrome and Herpetic Eye Disease.

Clinical trials for ocular therapy are further advanced for certain gene replacement therapies and drug delivery alternatives. Gene replacement using adeno-associated virus (AAV) delivery has been used successfully for the treatment of RPE65, Leber's congenital amaurosis 2 (LCA2), an early onset form of autosomal recessive retinal degeneration caused by mutations in the RPE65 gene. Three separate phase I–II clinical trials were initiated, which yielded promising results after sub retinal administration of AAV2-hRPE65 vectors. Another gene therapy presently at the pre-clinical trial stage, targets wet age-related macular degeneration (wAMD) with an adeno-associated virus vector encoding aflibercept.

Aflibercept is a recombinant chimeric protein that targets vascular endothelial growth factor (VEGFA), which plays a key role in the development of wAMD. Early in 2019, Adverum Biotechnologies reported the drug, known as ADVM-022 to be tolerated in non-human primates with no serious adverse safety-related findings, and that more than one year past a single intravitreal injection, ADVM-022 continued to provide robust aflibercept expression. These initial clinical trials will pave the way for treatment of a number of similar ocular disorders. Indeed, using ocular diseases as a model it is conceivable that soon an array of therapeutics will materialise that will allow safe and efficient correction of a range of genetic defects beyond ocular diseases.

4.9 Novel ways to deliver immunotherapies in drop form for Age-related Macular Degeneration

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University of Birmingham, Edgbaston, Birmingham

Dr Sofia Theodoropoulou and Dr Lisa Hill from the University of Bristol and the Institutes of Clinical Sciences at the University of Birmingham, respectively, are working towards the development of drop-based immunotherapies to treat Age-related macular degeneration (AMD).

The development of effective and safe therapies that can be delivered in 'drop' form, is a major priority for patients with AMD. Unfortunately, many of the commonest causes of AMD, are caused by damage to the structures at the back of the eye, tissues that cannot be reached by standard eye-drops. Currently, such treatment needs to be delivered either directly into the eye (intravitreal injection) or to the whole body (by tablet or injection/infusion) which expose the patient to risks that would be avoided if an effective 'drop' therapy could be developed.

Dr Sofia Theodoropoulou and her team in Bristol have a programme of research dedicated to developing highly targeted molecules to control the inflammatory process that underlie AMD pathologies. Dr Hill and her team in Birmingham bring expertise in retinal diseases and in a novel drug delivery system which can deliver drugs to the retina in 'drop' form, including those drugs which have previously required an injection (such as the anti-VEGF therapies for AMD).

Research, funded by Fight for Sight, is currently underway for the formulation of these exciting new immunotherapies for AMD. We are hopeful that this project will lead to effective and safe drop-based therapies for AMD.

4.10 Circadian Therapeutics – Tackling the problem of circadian rhythm disruption

Professor Russell Foster CBE, FRSB, FMedSci, FRS
Director, Sleep & Circadian Neuroscience Institute (SCNi)
Head, Nuffield Laboratory of Ophthalmology
Fellow, Brasenose College, Oxford
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We all generate an internal representation of the 24-hour day, referred to as our "body clock" or circadian rhythms. These rhythms are essential for fine-tuning every aspect of our physiology and behaviour to the varied and predictable demands associated with the day/night and wake/sleep cycles. Body temperature, cardiovascular function, hormone production, mood, alertness and just about anything you can measure shows a 24h change, rising and falling in anticipation of physiological need. These endogenous circadian rhythms are not exactly 24 hours, and in humans usually run a little longer than 24h. As a result, to be of any adaptive value, they need to be synchronised (entrained) to the astronomical day by external daily time cues, and the changes in light intensity at dawn and dusk provides the
most important environmental time signal for entrainment.

In humans, these rhythms are centrally controlled by the suprachiasmatic nuclei (SCN) or "master clock", located at the base of the hypothalamus. The SCN consists of about 50,000 coupled clock cells all capable of generating their own circadian rhythm using an internal molecular clock. The molecular clockwork of the SCN cells are then entrained by specialised photoreceptors within the eye. These recently discovered photoreceptors are quite different from the rods and cones of the retina that provide us with our sense of vision. Remarkably, a small number of photosensitive retinal ganglion cells (pRGCs) are directly light sensitive and utilise the blue light-sensitive photopigment melanopsin. As a result, it is important to appreciate that the eye not only provides us with our sense of space – by generating a visual image, but also provides us with our sense of time – by regulating the molecular clockwork within the SCN. In addition to the SCN, individual cells throughout the body can also generate their own circadian rhythms. This network of clock cells is in-turn coordinated by the SCN, and time physiology throughout the tissues and organ systems of the body.

Circadian rhythms can be disrupted very easily. Societal disruption arising from 24/7 and night shift working patterns, the intrusion of social media, or even the excessive use of caffeinated drinks can all act to shorten and disrupt circadian patterns of sleep. In addition, multiple health problems are associated with circadian rhythm disruption, including mental illness, neurodegenerative disease, normal aging and serious eye disease. Profound eye damage and eye loss can make us both space and time blind. Collectively such circadian disruption can have both short and long-term effects. Acute short-term impacts include; impulsivity and loss of empathy, memory impairment, loss of attention, mood instability, reduced cognition and an impact on creativity and the ability to process information. Chronic long-term disruption includes: depression, anxiety, cardiovascular disease, immune suppression, cancer, metabolic abnormalities including Type 2 Diabetes. Thus the consequences of circadian rhythm disruption are far more serious than feeling tired at an inappropriate time!

In response to this increasing and often neglected problem, Circadian Therapeutics was founded in 2016 as a spin-out from Oxford University.

Our aims are to build upon the fundamental research we have undertaken to understand the molecular control of circadian rhythms. This has led to the establishment of a therapeutic pipeline to develop new evidence-based therapeutics to treat serious circadian rhythm disruption across the health spectrum. A major success has been our discovery of drugs that mimic the effects of light on the circadian clockwork. Several classes of compound have now been isolated and tested in cellular assays and mouse models, which we have shown, act upon the same entrainment pathways as the pRGCs. The pre-clinical studies are now complete and we aim to undertake the "first in human trials" during 2019. Once these have been completed, and working closely with Blind Veterans UK, we will work with the profoundly blind to restore a sense of time to these time-blind individuals. The results from this first clinical trial in the blind will then inform how well others react across diverse areas of health where circadian rhythm disruption is endemic.

4.11 Development of anti-fibrotic treatments for Primary Open angle glaucoma

Dr Lisa Hill, PhD
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Edgbaston, Birmingham

Mr Imran Masood FRCOphth
Consultant Ophthalmologist/Glaucoma Specialist
Birmingham Midland Eye Centre
and the Birmingham Institute for Glaucoma Research

The development of safe and effective therapies to treat fibrosis is a major priority for patients with glaucoma. This ocular disease is characterised by elevated eye pressure (IOP), resulting from ineffective drainage of the aqueous humour. This, in part, is caused by the blockage of the aqueous humour outflow due to increased extracellular matrix deposition in the trabecular meshwork (TM). Over time the increased pressure can damage structures in the eye resulting in vision loss.

The lack of safe and effective anti-fibrotic treatments presents an important clinical challenge. It is therefore important to identify novel targets for drug development.

Drs Hill and Masood are working closely to develop novel anti-scarring treatments. One particular compound, which has shown promise in other scarring diseases, is called Decorin. In preclinical models, Decorin is able to reduce the levels of scar deposition within the TM and hence restore the normal outflow of fluid from the eye, which leads to restoration of IOP to normal levels and

protection of the retina. Being able to directly modulate the disease process is critical for developing new treatments for glaucoma. Further to laboratory studies, Drs Hill and Masood are currently investigating the anti-fibrotic effects of Decorin in tissue taken from glaucoma patients during surgery.

Currently, there are no treatments which target the underlying scarring pathology so developing an anti-scarring therapy for glaucoma would be game changing for patients, not only in developed countries, but for also in developing countries, where access to surgical interventions are limited.

4.12 The need to move from rehabilitation to effective treatment strategies for rare eye diseases

Professor Marcela Votruba
Professor of Ophthalmology
Consultant Ophthalmologist & Head of Cardiff School of Vision Sciences
Cardiff University

Inherited mitochondrial eye diseases are rare diseases.
Some startling facts:

1 in 17 people, or 7% of the population, will be affected by a rare disease at some point in their lives. This equates to approximately 3.5 million people in the UK. 80% of rare diseases have a genetic component. There are over 6000 rare diseases but only 126 rare disease medicines in Europe. Progress for patients with rare diseases is slow.

One group of rare diseases that affect the eye are mitochondrial diseases. One main reason for vision loss in these conditions is optic atrophy or optic neuropathy, including Leber's hereditary optic neuropathy and dominant optic atrophy.

Mitochondrial optic neuropathies affect an estimated 1 in 10,000 individuals, especially among children and young adults. The pathological hallmark is the preferential loss of retinal ganglion cells (RGCs) within the inner retina, which results in progressive optic nerve dysfunction and the onset of visual symptoms. The past 25 years has seen tremendous progress in our understanding of the molecular genetic basis of this group of disorders, providing at the same time invaluable insight into the shared disease pathways that precipitate retinal ganglion cell (RGC) loss. The devastating visual loss, which is almost always irreversible, lacks effective treatments and management is currently largely supportive aimed at visual and occupational rehabilitation.

Significant resources will need to be invested in an effort to develop effective treatment strategies aimed at rescuing RGCs. There are promising avenues of research, including gene therapy and novel therapeutic molecules. However, the fast tracking of translational breakthroughs for inherited optic neuropathies will not be possible without continuing funding and collaboration between academics, clinicians and the commercial sector.

4.13 Improving the treatment of retinal diseases through new injectable polymer technologies

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Steve Rannard
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Retinal detachment can result in the development of sight-threatening conditions such as proliferative vitreoretinopathy (PVR) and proliferative diabetic retinopathy (PDR), where fibrosis, or scar tissue, develops at the back of the eye. Silicone oil tamponades are used to replace the vitreous and exclude liquid from the site of damage. They are often used in patients at high risk of these secondary conditions to reduce the likelihood of scar tissue development. There has been no improvement, however, in primary success rates for many years. Combining silicone oils with adjunctive drug treatments that could reduce the scarring has been studied but, to date, no clinically proven medical intervention has been reported. This is possibly because the drug loading is too low or the therapeutic window is too short.

A multidisciplinary research team lead by Victoria Kearns and Steve Rannard has developed two different technologies to achieve controlled, extended release of drugs from silicone oils. These technologies allow more drug to be loaded into the oils and extend the time over which drug can be released from silicone oils to several weeks, even when drug loading is relatively low. These oils are not toxic to relevant cells in our laboratory studies, are stable at room temperature over extended periods, and can be sterilised using commercial protocols. The team are now working in collaboration with an industrial partner to develop the technology so it can be incorporated into existing, commercially-used tamponade agents.

Treatment for many other sight-threatening conditions, such as diabetic retinopathy and wet age-related macular degeneration, requires delivery of drugs to the vitreous cavity of the eye over many years. The most effective route for drug delivery to the vitreous cavity is by intravitreal injection. This creates a significant financial burden to the NHS (a cost of £155
million per annum, approximately 1% of the total NHS prescribing expenditure) and impacts negatively on patients, who have to attend clinic appointments and endure an uncomfortable procedure on a regular basis. There are certain patient groups for whom this is even more challenging, particularly the elderly, those in rural areas and those with dementia, for whom the prevalence of sight loss is higher than the general population. Repeated injection also carries the risk of sight-threatening complications, including retinal detachment and infection.

Nanomedicines are made of particles hundreds of times smaller than the width of a human hair. They have huge potential to treat a number of chronic, sight-threatening eye diseases. Nanomedicines could improve the action of drugs that are already used to treat diseases of the back of the eye, but also

provide a way of delivering drugs that have poor solubility in standard formulations. A team lead by Victoria Kearns and Tom McDonald has previously developed technology to make nanocomposites that can sustain drug release for over 100 days and that can gel when injected into vitreous. The rate of drug release can be tuned by changing the composition of the hydrogel. They are now working to extend the drug release time and optimise the formulation so that forms a gel when it is injected into the eye. The advantages of this over existing devices are that this technology could be tailored in terms of the drug and dosing, and that higher doses will be possible due to the use of nanoparticles.

4.14 Combating corneal infections with innovative agents

Harminder S Dua
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Chair and Professor of Ophthalmology
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Corneal infection is a major cause of blindness worldwide and its prevention is a key health priority as stated by the World Health Organisation. Emergence of antibiotic resistant organisms has made treatment with currently available antibiotics difficult with increasing risk of eye infection related blindness. It is estimated (WHO) that 98% of the world's corneal blindness of 5 million cases is due to infections. Investment in newer antibiotic is very limited and no new antibiotic has been introduced to treat eye infections for almost two decades. Moreover, antimicrobial resistance is currently costing 700,000 lives a year and the death tolls are expected to climb to 10 million per year by 2050 costing the global economy as much as 100 trillion US dollars.

Antimicrobial peptides (AMPs) are naturally occurring molecules produced by cells in the body that offer the first line of defence against infections. The research group in the Department of Ophthalmology at the Queens Medical Centre, University of Nottingham were the first to demonstrate AMPs in the eye and have profiled and characterised a range of AMPs, some of which have a huge potential to combat infections in the right combination, dose and duration of exposure. The group has further established a means of identifying key sequences or components of different AMPs that kill bacteria and are able to assemble these key components of different AMPs into one molecule that can exhibit several times greater kill power than that of each of the individual components. Moreover, the side effects of high doses of AMPs on the cells of the body can also be considerably reduced by the use of such hybridised molecules.

Funding to support this research and partnership with industry to carry this approach to development of a new and radically different means of combating infections is being sought.

4.15 Reversing Type 2 Diabetes Proved to be Possible

Dr Elizabeth Wilkinson
Consultant Ophthalmologist
Clinical Lead
North and East Devon Diabetic Screening Programme

During the National Diabetic Eye Screening Conference in London I was lucky enough to listen to the inspiring Professor Roy Taylor talking about his DiRECT study. There has been a huge buzz in the media about this low-calorie diet for reversing Type 2 diabetes with programmes recently on the BBC and, the inevitable, spin off in the Daily Mail. So, it was brilliant to hear directly from Roy as he told us why he thought a low-calorie diet might work and how he went about it. He is refreshingly, and enthusiastically a supporter of the idea that diabetes is not inexorably progressive. In fact, he has proved that you can reverse it AND the risk of complications.

His study, information for professionals and the public is at: https://www.ncl.ac.uk/magres/research/diabetes/reversal/#publicinformation.

I strongly urge you to have a look. I believe we may be at a turning point in diabetes care where we no longer monitor for progression but aim for regression.

4.16 Latest developments in sight-saving corneal therapies

Keith Meek PhD, DSc, F.Inst.P., FRMS, FARVO
Professor and Chair of Structural Biophysics Research Group
College of Biomedical and Life Sciences
School of Optometry and Vision Sciences
Cardiff

All clinical treatments are underpinned by basic scientific research, sometimes retrospectively, but mostly by forward planning and development, and the UK has historically been at the forefront of such efforts.

Indeed, the Structural Biophysics Group at Cardiff University led by Professor Keith Meek highlights the benefits of high levels of specialisation and multi-disciplinary working in determining positive clinical outcomes for patients.

Patients at high risk of corneal blindness face the twin challenges of possible corneal rejection following a corneal transplant and the worldwide shortage of donated corneas.

So, notwithstanding the ongoing stem cell research which is providing some hope (although currently only really viable in developed nations as cell expansion costs that meet regulatory requirements are too high), it is important to drive towards the removal of the reliance on donor corneal transplantation.

Specific research initiatives are focusing on developing and successfully testing cell-free, pro-regeneration implants comprising genetically produced human collagen (collagen is a hard, insoluble and fibrous protein that makes up one-third of the protein in the human body) as safe, reliable alternatives to human donor transplants in a range of high-risk corneal transplantation patients. In collaboration with groups in Sweden, USA, Ukraine, India and Canada, the Cardiff group have carried out a small clinical trial in six patients with little or no vision and at high risk of rejection of donor tissue. Three of the six patients showed significant vision improvement and the rest were sufficiently stabilised to allow follow-on surgery to restore vision.

This was the first step to demonstrating that cell-free implants are potentially safe, efficacious options for treating high-risk patients. A completely synthetic collagen mimetic (a material imitating collagen) has also been developed to treat corneal diseases. Quality control studies of this mimetic have been carried out and clinical trials are planned. Successful testing of these implants in a simple organ system like the cornea will in future allow for the extension to more complex applications such as skin and cardiac regeneration.

The structural and biophysical basic science carried out in the Structural Biophysics Group has also been applied to "Corneal crosslinking", which is now widely used to treat progressive keratoconus and other conditions. However, the conventional treatment is uncomfortable, and takes over 30 minutes, leaving patients vulnerable to infection. Quicker, pain-free methods have been developed in Cardiff in collaboration with Professor David O'Brart, and are currently being refined. One of these, the St Thomas'/Cardiff iontophoresis protocol, has undergone a successful clinical trial at St. Thomas' Hospital and, with some improvements suggested by their most recent research, should translate into clinical practice within a few years.

4.17 Advancing visualisation in vitreoretinal surgery with light-field imaging

Dr Christos Bergeles
Senior Lecturer
Department of Surgical and Interventional Engineering
School of Biomedical Engineering and Imaging Sciences
King's College
London

Vitreoretinal surgery (VRS), i.e. the manipulation of submillimetre structures on the retinal surface, takes place under high-magnification stereo microscopy. This limits the maximally attainable depth-of-field, and requires constant manual adjustment of microscope focus with every eye motion. Additionally, high magnification combined with stereo viewing hinders depth perception, forcing surgeons to rely on complementary cues, such as shadows, to understand the proximity of their tools to the sensitive retina.

To improve depth perception and eliminate the need to manually refocus in VRS, we are investigating retinal imaging via a plenoptic sensor. The plenoptic sensor, also called light-field sensor, is a standard photodetector array with a matrix of micro-lenses in front of it. The micro-lenses can be considered as a packed array of micro-cameras, each of which captures unique but overlapping micro-images. The parallax and disparity between the micro-images allow 3D reconstruction of the scene, and the super-resolving and computational refocusing of the final image and video stream. Images captured via the plenoptic sensor, will be computationally processed for focusing, and will be relayed to a 3D display. By incorporating the plenoptic sensor, 3D in-focus video streams will be acquired intra-operatively.

Our designs are being considered for a patent application, while we are currently working on engineering our system and evaluating it on human volunteers.

4.18 Cell therapy for cure of corneal blindness

Madhavan Rajan
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The result of the first human clinical trial on corneal endothelial cell therapy was published in March 2018 from Japan. Although this is a promising start, cultivation methods for corneal endothelium, storage and delivery strategies require careful attention before it could be safely translated to human studies.

Our research group had recently established an in vitro human
corneal model of bullous keratopathy to investigate treatment strategies for corneal cell therapy. We had previously reported on our cell cultivation protocol and have successfully demonstrated the formation of the endothelial monolayer in human corneas devoid of Descemet's membrane with functional recovery of normal corneal thickness in a randomised trial.

In continuing our efforts, the current proposal focusses on developing a clinically meaningful methodology to translate laboratory results to human clinical trials in the cure of corneal blindness.

4.19 Improving Surgical Dexterity and Speed

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The benefits that Robotics are bringing to Healthcare are self-evident. From efficient and rapid delivery of food and medicine from one hospital wing to another, to supporting the work of nurses and physicians in patient rehabilitation, and assisting in surgery by providing increased dexterity, robotics are becoming a key pillar of efficient and effective healthcare services.

Following their increased uptake in the domains of rehabilitation, laparoscopic or keyhole surgery (which ensures less time in hospital and faster recovery times) and orthopaedics (prevention/treatment of skeletal and associated muscle/bone disorders), robotics is starting to find applications in eye surgery, fulfilling the unique needs of this niche area of healthcare.

Two main research branches can be identified in robotics for eye surgery. For example:

Firstly, robotics aim to speed up and simplify existing operations of high volume such as cataract surgery, corneal sculpting and transplantation where various procedures can be supported by snake like robotic instrumentation in the front (anterior) of the eye. Also, in the back (posterior) of the eye, robots aim to improve the precision of epiretinal membrane peeling and increase the safety of the procedure by providing auditory, visual, and haptic (touch) feedback to the surgeon when risks are identified.

Secondly, research is being conducted to create systems that surpass the surgeon's capabilities towards enabling currently impossible interventions. Most notably, researchers are investigating the delivery of stem cells, genes, and small drug molecules to specific retinal layers. Therefore, with those new systems, it will be possible to reach and affect every part of the retinal surface, from the photoreceptors to the retinal pigment epithelium and choroid.

However, despite the increasing success of robots in improving speed, safety and the minimally invasive nature of existing surgical procedures, they all need to achieve very high levels of precision, meeting the minimum requirement of suppressing/removing the natural hand tremor, especially if subretinal interventions are to be considered. Also, As the forces applied in eye surgery are sometimes below the threshold of human perception, the recording and amplification of haptic information is vitally important, thereby keeping the clinician in the loop and in control of the robot.

Close collaboration between engineers and clinicians is ensuring that robots continue to be developed which are clinically relevant and allow for co-manipulation and full hands on control by the clinician. In time, robotic tools and systems will become an integral and indispensable part of the operating theatre.

4.20 Testing novel therapies

Professor Andrew Lotery
Professor of Ophthalmology
Director Clinical Neurosciences Research Group
University of Southampton

Unfortunately, COVID19 has delayed clinical trials. As we start to restart our clinical trials. Gene therapy trials for single gene disorders will continue. This includes studies for choroideremia and retinitis pigmentosa. Complement drug therapies continue to be evaluated for age related macular degeneration with some promising therapies moving to phase 3 clinical trials. Drug therapies for Stargardt's disease are also being tested. Artificial intelligence is being used to develop better screening of retinal images to help triage patients The results of these various trials will become available in the next few years.

4.21 Bioengineering – the ability to rethink models of treatment and care.

Development of a less invasive therapy for Keratoconus with potentially radical effects on the delivery of patient care

Professor Rachel Williams
Professor of Ophthalmic Bioengineering
Department of Eye and Vision Science
University of Liverpool

Professor Colin Willoughby
Professor of Molecular Ophthalmology
Institute of Ageing and Chronic Disease
University of Liverpool

Keratoconus is a progressive corneal thinning disorder that is a significant health burden in teenagers and work-age adults. Increasingly, a therapeutic procedure called "collagen cross-linking" using ultraviolet A (UVA) irradiation combined with the photosensitiser riboflavin has been used as a treatment for keratoconus to stiffen the cornea.

Current cross-linking requires exposure to UVA radiation which is toxic to the cornea and may result in long term damage. In light of this risk keratoconus patients must have a minimal corneal thickness or this treatment is not applicable and no other therapy can be used to stabilise their condition and thus they may eventually require a corneal transplant. There is also a need to remove the corneal epithelium to facilitate diffusion of riboflavin throughout the corneal stroma causing significant discomfort for the patient and an increased infection risk.

So, Professor Rachel Williams and Professor Colin Willoughby in the Department of Eye and Vision Science at The University of Liverpool in partnership with the Aravind Eye Care System in Madurai (India) have developed an alternative therapeutic approach to conventional corneal cross-linking for keratoconus.

They have created a novel chemical cross-linker to cause corneal cross-linking without the need to remove the epithelium or the use of UVA irradiation therefore avoiding the need to withhold treatment on the basis of thickness. The novel chemical cross-linker has been extensively tested in the laboratory and been shown to increase the stiffness of ex vivo pig cornea by 85% and this increase in mechanical properties was related to chemical changes in the tissue. Also, her team has shown there is no cytotoxicity (for example arising from mechanical or chemical trauma or abuse of toxic eye drops) to corneal epithelial and endothelial cell in culture.

This treatment can be administered as a simple eye drop removing the need for specialised equipment in a hospital setting – indeed, the less invasive nature of this therapy, the resulting reduced risk of collateral damage and the fact that it can be administered away from a hospital setting might have a major impact on the clinical treatment of these patients.

Novel ways of fighting infection, delivering drugs and post-operative therapies

Rachel Williams
Professor of Ophthalmic Bioengineering
Department of Eye and Vision Science
University of Liverpool

Professor Stephen Kaye
Professor of Ophthalmology
Lead for the Corneal Service
The Royal Liverpool University Hospital

The cornea is the clear window at the front of the eye. Following surgery or various treatments to the cornea a bandage contact lens (BCL) will frequently be used to protect the cornea and increase comfort for the patient. To reduce the risk of infection antibiotics will also normally be administered. We have developed a novel hydrogel with a high water content, excellent transparency and that has mechanical properties similar to existing hydrogel contact lenses. The specific advantage of this new hydrogel is that it is naturally antimicrobial unlike any of the existing contact lens materials and there is certainly potential for its use as an antimicrobial bandage contact lens post-surgery or intervention, such as corneal crosslinking. It could also increase comfort and reduce infection for patients.

The effective treatment of corneal infection relies on frequent application of antibiotic drops; routinely every 5-15 minutes for the first 48 hours, then 2-6 hourly over 1-2 weeks. Therefore, to circumvent such a drug delivery regime, Rachel Williams and her team have been developing BCLs that deliver therapeutic doses of antimicrobial drugs in a sustained and controlled manner which would provide a more effective treatment strategy and could augment conventional treatments. They have demonstrated that model antibiotics and model fungal can be incorporated into the new hydrogels and have antimicrobial properties in vitro.

Another example where the use of a contact lens material with intrinsic antimicrobial properties could greatly reduce the risk of infection by specifically inhibiting surface colonisation of the lens and subsequent microbial biofilm formation, is best seen in the fight against "Microbial keratitis" (MK). This is one of the commonest conditions affecting the cornea, accounting for 5% of cases of blindness worldwide. Contact lenses worn for vision are associated with a six-fold increase in MK.

Longer term, the potential of the new hydrogel material could be optimised as a daily disposable contact lens.

These materials are being developed in the Department of Eye and Vision Science at The University of Liverpool in collaboration with SpheriTech Ltd.

4.22 Model eyes that enhance the safety and efficacy of surgical training

Mr John Ferris
Consultant Ophthalmologist
Gloucestershire Royal Hospital
Stroud General Hospital
Cheltenham General Hospital

Surgical opportunities for trainees are continually being reduced as a result of shorter training programmes, fewer surgical opportunities on operating lists which are filled to capacity and a greater emphasis on improving the safety of surgical training. This is a far cry from the long training programmes, virtually unlimited access to surgical cases and a "see one do one teach one" attitude that prevailed years ago.

Against this backdrop, The Simulated Ocular Surgery (SOS) model eyes have been refined over a 15-year period by Phillips Studios, using a variety of materials that accurately replicate the look and more importantly the feel of real ocular tissues. They come complete with conjunctiva, Tenons capsule, extraocular muscles, including superior and inferior oblique's and a sclera that handles just like a human eye. The cataract models have a life like capsule, nuclei of varying densities and a posterior chamber that can be filled with a vitreous like material. The retinal eyes can be used to perform vitrectomies, have retinal tears and membranes that can be peeled. Furthermore, the model heads have noses and eyebrows that will hamper surgical manoeuvres just as they do in real life.

There are over 20 types of model eyes, each one being custom made to faithfully replicate the simulation of a particular operation. In the field of glaucoma surgery there are eyes designed for practicing trabeculectomy (surgical partial removal of eye's drainage system to reduce internal ocular pressure), Ahmed and Baerveldt valve surgery and for the insertion of a wide range of Micro-Invasive Glaucoma Surgery (MIGS) devices. All of these procedures can be practiced outside of the operating theatre, using bench-top microscopes. It is also possible to practice managing uncommon surgical complications, much in the same way as pilots practice dealing with mechanical failures and other untoward events.

The use of the SOS system has now been integrated into training in the UK and is becoming more widespread in the US. Recently Orbis, the flying eye hospital charity, has incorporated the system into their training programmes in Indonesia, China and South America. These simulation techniques can be seen on the Simulated Ocular Surgery website.

There is no doubt that sustained deliberate practice speeds up the learning curve, enabling trainees to reach a high level of competence before they perform live surgery for the first time. This results in a more comfortable learning experience and a more rapid progression to becoming an adept adaptable surgeon, whilst also making surgical training safer for patients. Another byproduct of this enhanced training program is that operations are performed in a more timely fashion, so improving theatre throughput and enabling more cases to be performed on each operating list.

4.23 Gene therapy – prevention therapy supported by early diagnosis

Julian Jackson
Director
VisionBridge

Many inherited eye diseases are caused by a small variation or mutation in a single gene – the equivalent to a misspelling in an instruction manual. So, designed to rewrite this so-called manual, gene therapy can deliver billions of healthy genes to replace a defective gene via an injection of a tiny drop of liquid underneath or near the retina. The new genes are carried to the target cells by specially designed viruses.

Innovative research around gene therapy to achieve improvements in visual health is ongoing in a range of top laboratories and hospitals across the UK. For example, studies into rare conditions such as choroideremia which causes progressive vision loss leading ultimately to complete blindness, have led researchers at Oxford University to conclude that the effects of gene therapy are potentially permanent and could therefore provide a single-treatment cure for many types of inherited blindness. These include retinitis pigmentosa which affects young people and age-related macular degeneration (AMD).

There has been a lot of justifiable excitement about the potential of gene therapy, but there are calls from the research community not to overhype the results as it may be decades before these treatments become widely available.

Gene therapy also highlights the importance of early diagnosis followed by early preventative medical interventions, because as eye diseases progress in their severity, they become increasingly hard to treat with gene therapy. One leading researcher believes this is one reason why only half the patients in one early clinical trial benefited. So, the ultimate aim of gene therapy specialists will probably be to correct faulty genes before disease starts, before patients are aware that anything is wrong. To put this into context, currently there are tens of thousands of children in the UK who have eye conditions for which there is no effective treatment. Genetic eye screening may also provide a model for other branches of medicine, enabling millions of patients to bypass the trauma of inherited blindness.

4.24 Stem cell therapy for retinal degeneration

Dr. Anthony Vugler
Lecturer in Retinal Neurobilogy
UCL Institute of Ophthalmology
London

Various sources of retinal stem cells are currently being investigated for their capacity to slow the progression of vision loss in degenerative retinal disease. Two major strategies are being pursued: 1. Cell replacement, 2. Preservation of retinal cells using neuroprotective factors.

For conditions such as Retinitis Pigmentosa (RP), where photoreceptors called rods degenerate followed by cones, cell replacement is being attempted using retinal progenitor cells derived from pluripotent human stem cells (human embryonic stem cells). These cells have shown the ability to integrate into the retina and restore function in animal models of advanced rod (photoreceptor responsible for peripheral vision and seeing in dim light)-/cone (photoreceptor responsible for seeing detail and colour) dystrophy.

The second and alternative approach seeks to slow the rate of rod / cone death by transplanting retinal cell types which produce neuroprotective substances, such as neurotrophic factors and anti-oxidants. As these cells do not need to respond to light and drive neural circuits within the retina, it is preferable that they are either encapsulated in the vitreous cavity of the eye, or, if they are to be delivered directly to the retina, that they integrate in a manner that does not interfere with signal transmission through existing circuitry. As such, glial support type cells (surrounding neurones and providing support and insulation), which lack neural activity, are well suited to the task. Indeed, these cells are capable of integrating into retinal circuitry in a way, which does not degrade normal vision. They can also preserve vision in animals with outer retinal degeneration and are currently being trialled in patients with RP.

In addition to outer retinal degeneration, stem cell derived neuroprotection is also being tested in animal models of glaucoma, with a view to preserving retinal ganglion cell survival / function in patients.

4.25 Operating microscope with integrated OCT helping to refine surgical procedures in gene therapy

Julian Jackson
Director
VisionBridge

Following the successful world's first Phase I gene therapy trial for choroideremia, Professor Robert MacLaren and his team at Oxford University and the Oxford Eye Hospital at the John Radcliffe Hospital have started a Phase II trial enrolling 30 patients.

In this trial Professor MacLaren is using an operating microscope with integrated optical coherence tomography (OCT) that will refine the surgery that is integral to the gene replacement therapy. The purchase of this vital piece of equipment called OPMI Lumera 700 Rescan is thanks to a number of funders including: National Eye Research Centre, The Tommy Salisbury Choroideremia Fund, Choroideremia Research Foundation USA, Hospital Saturday Fund, Fight for Sight and benefactors of the MacLaren Group. The project has been funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council (MRC) and NIHR partnership.

Choroideremia is an incurable genetic condition affecting approximately 50,000 men worldwide. It is caused by a genetic fault in the REP-1 gene and gene therapy is being trialled to replace the faulty gene with a healthy one. The intraoperative OCT microscope enables surgeons to track changes in the retinal anatomy in real time and thereby permit safe and precise delivery of the gene therapy with the ultimate goal of improved vision for patients.

Professor Robert MacLaren, said: "On behalf of the Clinical Ophthalmology Research Group at the University of Oxford I would like to thank all its generous benefactors for assisting us in raising funds for an OCT operating microscope for the Oxford Eye Hospital. The equipment is being used in exciting new gene therapies for the treatment of patients suffering from incurable eye conditions. By using the OCT operating microscope, it allows for better and safer outcomes for patients due to more refined surgery using the microscope."

If successful this trial can be translated to other conditions such as retinitis pigmentosa (RP) which affects 1 in 4,000 people in the UK.

4.26 Gene therapy options for AMD

Dr. Simon Clark
Centre for Ophthalmology & Vision Sciences
Faculty of Medicine and Human Sciences
University of Manchester

When compared to other therapy options, such as traditional drug-based treatments, gene therapy is best suited at the early stages of disease, preferably prior to major physical changes. This can be achieved given the genetic nature of AMD and well developed algorithms that take into account a patient's genes, diet, age and smoking to predict their level of risk. Other methods are best suited to later stage disease, such as stem cell therapies, that seek to replace the RPE cells already lost because of disease progression.

"Given the localised nature of AMD, gene therapy represents a very real opportunity to deliver therapeutic potential right in the part of the eye we here it is needed. Altering the way the retinal pigment epithelium (RPE) cells contribute to inflammation, lipid synthesis and blood vessel growth means a patient would have a therapy constantly maintained in their eye. This may be delivered by a single sub retinal injection, removing the need for monthly eye clinic appointments currently endured by patients receiving anti-VEGF.

While the anti-VEGF era has seen a tremendous advance in our approach to AMD, the window of opportunity for initiating this therapy is very short. In some senses, anti-VEGF therapy is palliative medicine. Patients are observed until they have the most advanced form of AMD before injecting an eye with drugs that actually fail to target the underlying disease process. Significant tissue damage and visual loss may have already taken place and, further, some patients respond poorly to these treatments.

A note about VEGF: VEGF, or Vascular endothelial growth factor for those in the know, is a small protein that promotes blood vessel growth. Given that excessive blood vessel growth is a major

feature of wet AMD it is perhaps not surprising that therapies directed against VEGF were quickly employed. Anti-VEGF is an antibody that perturbs VEGF function, thus stopping blood vessel growth when applied directly to the site of disease. One problem, however, is the transient nature of this treatment and explains why patients are constantly needing injections to keep up the levels of anti-VEGF, or face the consequences of the blood vessels growing again. Herein lies the greatest criticism of anti-VEGF treatments, that it only slows down, or stops the final stages of the disease, and does nothing to address the underlying problem or prevent it in the first place."

Furthermore, with a new delivery method come new opportunities for therapies and treatment may no longer be the preserve of the wet form of AMD.

However, we still have no treatments in routine use for geographic atrophy, which is thought to affect over 8 million people worldwide. We need to understand that dry AMD is a multi-faceted disease, which can only be cured if treated in its very early stages and indeed linked to the underlying disease process and a patient's specific genotype.

4.27 MicroPulse laser for drusen removal

Professor Victor Chong
Head of Department
Oxford Eye Hospital

"Drusen" is the name given to small yellow deposits in the retina, which is often described as the first signs of AMD. They sit between the vascular supply of the retina (choroid) and the light sensitive photoreceptors for vision. Increase number and volume of drusen increases the risk of significant visual loss and common symptoms include difficulty with reading and adapting to changes in light.

The concept of using laser to remove drusen is not new as it has been used since the 1990's. However, traditional laser causes scarring and can lead to conversion to wet AMD. Unfortunately, the current "rejuvenation laser" 2RT laser is also understood to cause scarring albeit much reduced compared to previous procedures. So, another laser is in use by a growing number of consultant ophthalmologists, the "MicroPulse" laser, which is used extensively in diabetic patients and patients with serious central retinopathy for many years. The MicroPulse laser delivers the laser energy in short pulses, and the treatment parameters have been tested in diabetic patients for over 10 years leading to the biological benefit without any scarring. The assumption is that drusen removal will have short term benefit in improving nutrient supply for the photoreceptors, but the long-term benefits remain unclear.

4.28 Alternative treatment for glaucoma to circumvent shortfalls in drugs and surgery

Dr Colin Chu
NIHR Clinical Lecturer
the Bristol Eye Hospital
and University of Bristol
working with Professor Andrew Dick

Glaucoma is the leading cause of irreversible visual loss worldwide and an estimated 12.5 million people worldwide will be completely blind from the disease by 2020. Clinical trials have shown that reducing the pressure in the eye can prevent loss of vision from the commonest forms of glaucoma. Treatment using eye drops has been available for many years, but they are expensive, have side-effects, need lifelong use and often don't reduce the pressure enough. Surgery is effective, but requires highly trained surgeons, is potentially high risk, has a relatively long recovery period and can fail over time.

So, more effective treatments are needed, particularly for use in the developing world where these same limitations are prohibitive and one such example is Dr Colin Chu and his team's work at Bristol University in gene therapy using engineered viruses to re-programme cells of the eye. This has been shown to be safe in recent clinical trials and explores the use of the same viruses to infect cells of the ciliary body, the part of the eye responsible for continually producing aqueous humour – the fluid that maintains the pressure of the eye.

Using human ciliary bodies donated for research from the Bristol Eye Bank, Dr Colin Chu will programme the virus to deliver components of a system called CRISPR. This can cause genes to be accurately disrupted to stop them from making their encoded proteins. At this stage, genes known to be critical to aqueous humour production will be targeted. In theory this approach as a treatment could allow lifelong reduction in eye pressure following a single injection.

4.29 Repurposing a drug

Professor John KG Dart
Consultant Ophthalmologist
Hon. Professor
University College London

Scarring conjunctivitis is a major cause of chronic pain and sight loss. The conjunctiva is the membrane that lines the eyelid and covers the eye. In health, it helps lubricate and protect the eye, but in conditions such as ocular mucous membrane pemphigoid (ocular pemphigoid), severe eye allergy, Stevens-Johnson syndrome and trachoma, the associated inflammation triggers rapid pathological scarring, which often persists after the inflammation has gone, destroying the protective functions of the conjunctiva.

Currently, standard treatment for both mucous membrane pemphigoid and its ocular form is to suppress the immune system. This controls inflammation when it works, but there are unpleasant side effects and it has little effect on scarring. Approximately 1 in 5 people with the ocular form go blind.

Therefore, the aim of Professor John Dart's research project at UCL Institute of Ophthalmology in collaboration with Moorfields Eye Hospital and Duke University School of Medicine was to identify potential therapeutic target molecules and provide a test bed for treatment. So, the enzyme ALDH1 was identified as critical for one step in the process of turning vitamin A into retinoic acid – a key protein in immunity, inflammation and scarring.

The chosen therapeutic drug Disulfiram is a drug that's licensed for treating alcohol abuse. It works by blocking ALDH activity, including ALDH2, which processes alcohol. Laboratory tests have demonstrated that inhibiting ALDH1 activity with disulfiram effectively reduces inflammation and prevents scarring *in vivo,* and significantly reduces the signs of scarring *in vitro,* in human ocular pemphigoid fibroblasts.

It may be that this approach will be more effective at scar prevention when there is active inflammation, but John Dart and his team have confirmed that this is an important proof-of-concept that currently untreatable scarring conjunctivitis may respond to eye drops or other topical application of a drug that can be repurposed.

4.30 Translational research for blinding surface diseases of the eye – including the cornea

Professor Julie Daniels
UCL Institute of Ophthalmology

Mr Sajjad Ahmad
Moorfields Eye Hospital
and UCL Institute of Ophthalmology

Diseases of the surface of the eye (including the cornea) result in both painful and blinding eye disease. As per World Health Organisation statistics, corneal disease is one of the most common causes of blindness globally. The main focus of clinical need driven basic science research in this area include:

- **Development of cell therapies for corneal tissue replacement:** As a result of our ability to grow stem cells of different layers of the cornea in the laboratory, targeted replacement of abnormal corneal cells has become possible. One such therapy is limbal stem cell therapy for blinding corneal surface disease and this has traversed the translational and regulatory pathway to successful clinical trials and is under-going NICE evaluation. This process has paved the way for developing cell therapies for other layers of the cornea and indeed for other tissues of the eye. One such approach is the development of stem cell-populated biomimetic collagen tissue equivalents, known as "RAFT", that is anticipated will enter clinical trials in the near future.

- **Understanding the biological processes resulting in corneal diseases:** In order to prevent the need for corneal replacement therapies, understanding the causes and contributors of corneal diseases are important. There are several examples of research within this field that have led to successful clinical applications. One such example is the use of cross-linking therapy to strengthen the cornea in keratoconus, a common corneal disease affecting young patients, and this has reduced the need for corneal transplantation and subsequent life-long monitoring.

- **Biomarkers for corneal diseases and their severity:** We are studying patients and their biological samples (blood and tissues) with rare blinding corneal diseases such as the genetic disease of aniridia related keratopathy and the drug toxicity induced Stevens-Johnson syndrome. We have large cohorts of patients with these diseases and we are seeking ways in which we can identify biological features (or biomarkers) that result in some patients having more severe corneal disease. By identifying these biomarkers early on in the disease process, we can provide closer monitoring and personalised treatments for such patients.

Although corneal diseases often result in eye pain and account for a significant proportion of blindness both nationally and globally, research in this field is poorly funded. The impact of clinically relevant corneal research is significant to patients, society and indeed to medical research as a whole. One such area of translational research is the development of a corneal cell therapy for chemical eye burns. This is the first stem cell therapy in any disease to be approved by the European Medicines Agency.

4.31 Nutrition that enhances vision in patients with retinal disease

Professor John Nolan
Waterford, Ireland

The macular carotenoids lutein (L), zeaxanthin (Z) and meso-zeaxanthin (MZ) selectively accumulate in the central retina (macula lutea), where they are collectively referred to as macular pigment

(MP) (1; 2). The anatomic (central and prereceptorial location), biochemical (antioxidant and anti-inflammatory) and optical (short-wavelength [blue] light-filtering) properties of the macular carotenoids make these ideal candidates to enhance vision and protect against age-related macular degeneration (AMD). The light absorbance spectrum of MP peaks at 460nm and therefore this optical filter has the capacity to absorb/filter high energy short-wavelength (blue) light before it reaches the photoreceptors (the cells of vision) (3). This light-filtering process minimises" chromatic aberration") de-focused light) and light scatter, contributing to an improvement in visual function.

Indeed, this has been confirmed by Professor Nolan's group via the ERC-funded (starter grant; 281096) CREST study (4). Also, MP's constituent carotenoids are powerful antioxidants and are believed to reduce oxidative stress at the retina (5; 6). Our recent clinical trials in patients with early AMD have shown that optimising MP in patients with early AMD greatly improves visual function in these patients, (7) and other work from Moorfields London has demonstrated the importance of enriching MP in patients with other forms of retinal disease (e.g. diabetic retinopathy). (8)

It is important to point out that, although Professor Nolan and his team value the importance of optimising nutrition using standard dietary methods, the scientific studies conducted to date show that supplementation is required to achieve optimal tissue concentrations of the macular carotenoids. It is Professor Nolan's view that humans are deficient in certain carotenoids and that this is in part due to intensive farming of foods for human consumption, resulting in carotenoid-deficient food. To this point, a typical European diet, contains only circa 1.5 mg/day of the macular carotenoids, whereas, it has been shown that at least 10mg/day of these carotenoids are required to achieve optimal tissue concentrations.

Antioxidants are man-made or natural substances that may prevent or delay some types of cell damage. Antioxidants are found in many foods, including fruits and vegetables. They are also available as dietary supplements. Examples of antioxidants include Beta-carotene, Lutein, Lycopene, Selenium, Vitamin E.

Carotenoids: Any of a class of yellow to red pigments found especially in plants, algae, and photosynthetic bacteria. They have a wealth of health benefits, from giving us vitamin A to providing our bodies with antioxidants.

4.32 Pharmacogenetics: facts, estimate of potential and benefits of implementation in ophthalmology

Dr Pirro Hysi
Senior Lecturer in Ophthalmology
King's College

Most of the adult population in industrialized countries takes prescribed medication. Taking the USA as an example (it benefits from better statistics drawn from a larger market with socio-economic similarities with the UK and are currently the only statistics available), as much as 80% of adult Americans take at least one and almost 30% is prescribed five or more different medication at any given time.

Adverse Drug Reactions (ADR), defined as a harmful, unintended or more generally undesired response to medication, are common, of which 700,000 cases are annually reported in the US each year, resulting in 120,000 episodes of hospitalization and they are the 6th leading cause of death in the US.

There is also a large variation in medication efficacy, most of which is genetically driven. As much as 95% of the population carries at least one variant which would cause a clinically important variation in drug response, which could be prevented if the genotypes were known prior to medication intake

("actionable variants"). Pharmacogenomic drug labelling is available for approximately 160 currently marketed drugs, none of which is used in ophthalmology, although there are multiple ongoing clinical trials on the efficacy of ranibizumab for age-related macular degeneration (AMD). Pharmacogenomics, as an important component of personalized medicine is becoming more popular in recent years, with multiple initiatives generously funded by taxpayers under way in the United States and many smaller initiatives, mostly at the inception stage in the United Kingdom. Drug response variability is strongly genetic in 1/6 of the drugs.

Not all the drugs will show variability, in other words the same predictable response in all patients will be recorded. However, when this response is variable, heritability tends to be high. Put simply, if the drug response varies, this is largely genetic in most cases.

Identifying determinants of the efficacy of the drug in individual patients can save considerable time, reducing the strain of very busy practices and shortening waiting times by cutting the number of visits that the current "trial and error" approaches entail. For example, the only treatment for glaucoma to date consists in medication that lowers internal eye pressure (IOP), of which two classes are particularly popular: is β-adrenergic agonists and in the last decade Prostaglandin Analogs (PGA). However, as many as 28% of treated patients do not respond to β-blockers (timolol) and 18% fail to respond to PGA (latanoprost) and an unknown number of patients somewhere between a full response (IOP reduction by at least 30%) and no response at all.

In the absence of adequate funding for eye research, most studies of response to IOP lowering treatments are carried out in small samples, with limited power. Yet, despite these limitations, studies show that perhaps as much as 80% of the variability of response to latanoprost may be determined by known DNA polymorphisms (unpublished studies, Hysi and Hammond, KCL Department of Ophthalmology). More work is needed to further evaluate the exact heritability of response to IOP-lowering medication and to identify the main DNA variants responsible for it.

In other areas of medicine, these approaches have been particularly fruitful. The hope is that pharmacogenetically guided treatment will become a reality for most classes of drugs as is currently the case for many cancer (for example olaparib) and cardiovascular (for example warfarin and clopidogrel) drugs.

4.33 Surgical innovation – providing effective alternative treatments for glaucoma

Mr Keith Barton
Consultant Ophthalmic Surgeon
Glaucoma Service
Moorfields Eye Hospital
London

Glaucoma is the commonest cause of irreversible visual loss in the world. While the prevalence is low at around 1 in 1000 at age 40 in white Europeans, it increases dramatically with age to approximately 1 in 20 in their 80's. Treatment is lifelong and usually involves the long-term use of medication (eyedrops) to lower the intraocular pressure (IOP). These can cause a multitude of local side effects, from redness of the eyes to irritation and even allergy. More than 50% of patients with glaucoma require 2 or more different drugs to control the condition. The greater the number of drugs used, the greater the risk of intolerance due to local side effects.

With this in mind, surgery has always offered the potential to achieve better intraocular pressure control than medical therapy as proven in past randomised trials. For example, the most commonly used IOP-lowering procedure called "trabeculectomy", has been shown in randomised clinical trials to be more effective than medical therapy and yet only approximately 2.5% of glaucoma patients have

surgery each year. A lack of predictability and the risk of morbidity associated with the surgery have limited the popularity of this procedure, with most patients preferring to persist with mediations.

This situation may be about to change. After 2 decades of unprecedented innovation in the medical treatment of glaucoma, there are no new classes of pharmaceutical agents on the horizon, patients are less tolerant of the side effects of medication and have greater expectations than before. Coinciding with this change in expectations, a new class of glaucoma surgical procedures has evolved, such as the "iStent", a 1 mm long titanium snorkel that can be quickly inserted into the drainage channels of the eye to reduce outflow channel resistance. Also, so called "minimally-invasive" or "micro-invasive glaucoma surgery "(MIGS) is promising to open up the possibility of a surgical solution for glaucoma to a much wider population compared to the previous trabeculectomy procedure. However, while many of the newer devices are only modestly effective in comparison with traditional surgery, they are, as the name suggests, truly minimally invasive and can be offered at the same time as cataract surgery to a wide population of glaucoma patients undergoing cataract surgery with almost no extra risk in return for the possibility of reducing or even eliminating the burden of medication.

Other devices now commercially available include the "Cypass MicroStent" which drains aqueous humour from the anterior chamber into a space behind the retina known as the supra-choroidal space and the Xen Gel Implant, a 6mm long hollow collagen noodle with an internal diameter of only 45 microns that drains aqueous humour from the anterior chamber to subconjunctival space. Other devices in development include the Hydrus, a nitinol Schlemm's canal scaffold and the MicroShunt which drains, like the Xen, to the subconjunctival space. In addition, outside the MIGS category of devices there have been a multitude of surgical innovations including MicroPulse diode laser cyclophotocoagulation, high frequency focused ultrasound cycloablation, ab interno canaloplasty and gonioscopy assisted trans-luminal trabeculotomy.

The current boom in the commercialisation of MIGS and associated surgical procedures has cast a spotlight on glaucoma surgical innovation that appears only to be growing. It is likely that the next evolutionary steps will be in two directions. Firstly, the development and commercialisation of long-acting drug-emitting implants which can be injected into the eye or placed into either the lacrimal ducts or conjunctival sacs to provide medication for durations of one month or longer. Secondly, the development of intraocular pressure sensors that can be placed inside the eye at the time of cataract surgery and provide long-term continuous telemetric eye pressure measurements that are more accurate and more informative than current IOP-measuring methods.

In summary, the benefits of improved treatments for patients are obvious but the benefits to NHS England of evolving surgical procedures and devices are also clear to see. For example, the reduction of patients' long term dependence on drugs, the minimising of disruptive side-effects of drugs, the introduction of minimally invasive surgery and long term emitting therapeutic implants and the opportunity to provide cataract removal in conjunction with glaucoma surgery are all strong illustrations of how repeat visits for treatment can be reduced, overall costs of drug treatments might be minimised, patient flow and surgery time-efficiency can be vastly improved and patients' quality of life may be enhanced over the longer term.

4.34 The path from scientific research to a marketed medicine

Dr. Heather Giles
Chief Scientific Officer
Vapogenix

Scientific discovery forms the basis for virtually every new medicine. Many new medicines can result from the discovery of one new molecular target and a key function of scientific research is to understand the role of that target, in health and disease. This process takes several years. For example, the molecule "VEGF" was discovered in 1983, and in the following decade researchers gradually

pieced together its role in physiological processes and identified diseases where blocking VEGF action could result in therapeutic utility, including for (Wet) macular degeneration. This is the point where the challenge of making a medicine begins. (Note: Vascular endothelial growth factor or VEGF is a signal protein produced by cells that stimulates new blood vessel growth. Overexpression of VEGF can cause vascular disease in the retina and other parts of the body.)

The science of drug discovery starts with making molecules that block, or activate the target, and show efficacy in animal models of disease. The molecule must also be 'druggable' – meaning that it can reach the target organ, exert the desired effect, does not cause undesirable effects in cells or animal models, and has the potential to be made in large quantities. This identification of a 'drug candidate' suitable to test in humans can typically take 5-10 years. The failure rate is extremely high, and less than 1 in 100 projects reach the clinical drug development stage.

The goal of drug development is not only to demonstrate clinical efficacy but also to show that the benefit to the patient outweighs the risks. This requires three development functions to be conducted in parallel: manufacturing, non-clinical safety, and clinical studies. A common misconception is that the development process is 'cookie-cutter" but nothing could be further from the truth, as unique scientific challenges occur throughout. For example, effective drug delivery continues to be particularly challenging for topical ophthalmic drugs.

During clinical development, patient safety is paramount, therefore every aspect of the process is heavily regulated, mostly by internationally accepted guidelines. Early studies are in healthy volunteers, and then in small groups of patients. The goal is to identify a safe dose, potential side-effects and, of course, an indication of efficacy (Phase 1 and 2). Phase 3 'pivotal' studies must provide statistically significant evidence of efficacy and long-term (at least 1 year) safety data. Generally, several thousand patients must have been treated prior to marketing authorisation. For example, in 2016 the FDA approved Lifitegrast for use in dry eye disease. As a result of the small number of patients with this disease, approval was granted following clinical studies in about 1400 patients. However, the regulatory path was not without challenge and prior to final approval, an additional clinical efficacy study was required involving more than 700 patients at 42 clinical study sites. Additionally, more rigorous manufacturing controls had to be implemented.

It takes 7-10 years for a drug candidate to reach the market, with a 1:10 success rate. Even after this, there are final hurdles to overcome before a drug can be prescribed for a patient in the NHS, such as a positive pharmaco-economic evaluation by NICE.

Robert J. Lefkowitz, NL, once said that the basic unit of time for science is the decade. A VEGF inhibitor to treat macular degeneration reached the market in 2006, more than 23 years after the discovery of VEGF. The impact of this drug on reducing sight loss demonstrates that a long-term funding of basic and translational ophthalmology research results in successful new treatments.

4.35 Glaucoma: Translating Science into Solutions

Professor Sir Peng Tee Khaw
PhD FRCP FRCS FRCOphth FRCPath FRSBiol
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Professor of Glaucoma Studies and Wound Healing
Institute of Ophthalmology, Faculty of Brain Sciences
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The 10:10:10 challenge and re-energising the optic nerve

Glaucoma is the leading cause of irreversible blindness in the world, currently affecting over 60 million people worldwide, and estimated to rise to 76 million by 2020 and nearly 112 million by 2040

(Tham, 2014). It is one of the most common neuropathies in the world. In the UK, the risk for glaucoma is predicted to increase to almost 10% in people over 75 and approximately 10% of UK blindness registrations are attributed to glaucoma (NICE, 2009).

The management of the disease, however, is challenging. Unlike an available one-off treatment for cataracts, the treatment of glaucoma is less straightforward. Eye drops are often considered impractical, costly and burdensome with patients sometimes struggling to adhere to their treatment. In the 2012 James Lind ‘Sight Loss and Vision Priority Setting Partnership’ report, glaucoma was identified as one of the 12 categories of sight-loss conditions around which patients and clinicians had unanswered questions. The highest ranked priority questions in glaucoma were “What are the most effective treatments for glaucoma and how can treatment be improved?”

Surgery is usually considered for glaucoma when medicines do not sufficiently lower eye pressure, but it is specialised surgery and, like other forms of surgery, can be associated with risk of further complications. In many parts of the world, it is the most practical treatment. Scarring during healing, for example, is the most common cause of failure of surgical procedures that treat glaucoma. As Professor Sir Peng Tee Khaw, Director of the NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology comments: “Our ability to control wound healing and scarring is the most important event which determines whether or not surgery succeeds.”

The Moorfields Safer Surgery System which has evolved from our iterative research, first introduced more than a decade ago, has improved the outcomes and consistency of glaucoma surgery throughout the world. The system, designed to be easily implemented, has evolved over the years to reflect new clinical research, and it requires the minimum equipment. There remains, nonetheless, room for significant improvement. Says Sir Peng: *“The system still requires a lot of training and it is not 100%reliable as it is so reliant on the surgeon’s skill. It is also time consuming. We need a procedure that can be carried out very quickly.”*

Fast, reliable and effective

Sir Peng’s ambitious goal for the future is what he has termed the ‘10:10:10 challenge.’ The challenge is to achieve 10 mmHg (millimetres of mercury) for 10 years and performed within a 10-minute procedure. More specifically, its objectives include:

- 10-minute rapid, reliable, relatively simple, safe single surgical procedure using a device/drug under topical/local anaesthesia with minimal hypotony (soft eye) or other significant complications

- 10 mm of Hg pressure in the eye, achieved with minimal diurnal (day/night) or postural (lying/standing pressure) variation in virtually all patients

- 10 years or more duration of effect

“We have evidence that getting the eye pressure down to 10 mmHg stops the disease in more than 95% of patients for five to 10 years,” explains Sir Peng. “If you can get it working for 10 years, then it will probably work well for life. Furthermore, if you can do the operation in 10 minutes, then you can do it in the developing world. It would potentially revolutionise the treatment of glaucoma globally.”

“It is the only real answer for glaucoma in the developing world. If we want to really make an impact, then we have to have a one-off treatment that works really well.”

While Sir Peng acknowledges that this is indeed very ambitious, he is also certain that it is achievable. "Two areas must, however, be addressed first," he stresses. "Firstly, we need a micro device to control drainage very precisely during surgery, and secondly, we need to control how the eye heals following surgery or it just heals up the drainage hole created." *"We are now working on new micro flow devices and anti-scarring agents in our attempt to achieve 10:10:10 and we'll be moving forward to try to achieve this target within the next few years."*

In parallel with this research, Sir Peng and his colleague Professor Astrid Limb are looking at ways to improve or 're-energise' optic nerve function. They had discovered some special stem cells, named the 'Moorfields Institute of Ophthalmology cells', and isolated them from donor human eye. In one study, they found that these stem cells restored some vision in rats that had had damage, similar to that from glaucoma, to their retinal ganglion cells and their long nerves (Singhai, 2012). These stem cells induced a partial functional recovery of the Retinal Ganglion Cells (RGCs) / axons of the eye, the layer of cells necessary to carry signals from the light sensing photoreceptors of the eye to the brain.

Although the authors point out that the present study did not address the re-growth of the optic nerve, the results suggest that it may be possible to improve the function of RGCs enough to achieve significant clinical improvement in humans. Further research is certainly required, but these findings show the exciting evidence of recovery of visual function by transplantation of RGCs.

"It is vital that we look at pressure too as there is no point in making advances in stem cell transplantation if raised pressure will just kill the nerve again," explains Sir Peng.

"We have improved glaucoma treatment significantly over the years, but 10:10:10 is really the biggest step. I think we can get close to achieving 10:10:10 within a decade".

4.36 The potential of stem cell therapy in retinal disease

Julian Jackson
Director
VisionBridge

Stem cells have the potential to save the sight of hundreds of thousands of people with age-related macular degeneration (AMD), the UK's most common form of vision impairment. AMD causes central vision loss, making it hard to drive or read. The macula lies in the centre of the retina where incoming rays of light are focused.

So, there is justifiable and growing excitement around the so called London Project launched in 2007 and the ongoing stem cell research and clinical trial led by Professor Pete Coffey at Moorfields Eye Hospital and the UCL Institute of Ophthalmology, who are running an experimental stem cell treatment on ten patients, supported by a stem cell specialist Professor Harry Moore, now co-director of Sheffield's Centre for Stem Cell Biology. His team developed the stem cell line Shef-1 for the London trial. Shef-1 is derived from one-week-old embryos comprising about 100 cells. Such cells have the potential to develop into any type of cell in the body. Adding different growth factors induces cells to develop into different cell types. Developing Shef-1 took many years and involved extensive safety monitoring.

If successful, the technique could be available on the NHS within two-and-a-half years. The procedure, which has attracted the support of medical giant Pfizer, is carried out under local anaesthetic. It involves taking a single embryonic stem cell and growing it into a 6mm patch of 100,000 retinal pigment cells. That patch is then rolled into a thin tube, which is injected through a tiny slit in the eye. Once unfurled, it is placed behind the retina where scientists hope it will replace the faulty cells. The first step has been carried out on the wet form of the condition when a patient

bleeds at the back of the eye. But scientists are confident it could also be used for the more common dry AMD, which affects over 85 per cent of British sufferers.

The key point here is that these cells have been derived from the patients themselves. Pete Coffey will be using four genetic switches on a piece of skin thus creating the "beginning cell" that made each patient. The use of the patient's cells has meant that their DNA could also be studied at the same time, potentially allowing for a personalised diagnosis of their condition as well as an individualised treatment.

Following the second stage, which is being funded through a £3m donation from the Michael Uren Foundation, regulatory approval for general patient use will be sought. As long as Pete Coffey and his team can show that there is good safety and good visual outcomes, then they can approach government and ask if they can go through a new advanced therapeutic route, which will allow that therapy to go quickly into the NHS. If these therapeutics are proven to work, they could save the NHS millions of pounds simply because the restoration of sight (to whatever degree) could provide independence and mobility to many thousands of patients again.

4.37 Protecting and regenerating the optic nerve in glaucoma with gene and stem cell therapies

Professor Keith Martin
Professor of Ophthalmology
University of Cambridge
Honorary Consultant Ophthalmologist
Cambridge University Hospitals
NHS Foundation Trust

Glaucoma affects over 60 million people worldwide. Blindness occurs through damage to the optic nerve, which transmits visual information from the eye to the brain. Reducing the eye pressure medically or surgically is currently the only treatment that can slow the progression of glaucoma, although visual deterioration continues despite treatment in many patients. There is an urgent need for new treatments that can prevent blindness in the most severely affected glaucoma patients, and restore some useful vision to those who have lost their sight due to the disease.

Keith Martin is a clinician scientist glaucoma specialist based at the John van Geest Centre for Brain Repair in Cambridge where he is working to develop new treatments for degenerative eye diseases, using stem cells, gene therapy and other approaches to regenerate the injured optic nerve. He works in an environment where he is constantly interacting with researchers working on other neurodegenerative conditions such as Parkinson's disease and Alzheimer's disease as well as other researchers working at the forefront of axonal degeneration research, spinal cord repair and remyelination. They share many interests and technologies as well as ideas in their joint quest to improve the lives of our patients. The ultimate aim of his work is to reduce the terrible burden of blindness caused by optic nerve diseases in the future.

A current focus of the Martin lab is modulating neurotrophic factor signalling pathways to improve neuronal survival. It has been shown that brain-derived neurotrophic factor (BDNF) delivery to the retina is reduced in animal models of glaucoma and that retinal delivery of BDNF by gene therapy can improve retinal ganglion cell (RGC) survival in experimental glaucoma, at least transiently. Work in the Martin lab has shown that human, mouse and rat cells can be targeted to produce BDNF and TrkB proteins simultaneously and that in animal models of optic nerve injury, treatment with both proteins is more protective than either given alone. Importantly, the use of gene therapy does not appear to have a negative impact on retinal health and the beneficial effects can be seen for long periods after a single treatment. A current major focus for the lab is to move a gene therapy strategy based on this work through to early stage clinical trials.

Another major focus for the Martin lab is developing strategies to enhance optic nerve regeneration after injury. Damage to the optic nerve is often accompanied by an inflammatory response and formation of a scar. Components of this scar include proteins called chondroitin sulphate proteoglycans (CSPGs). CSPGs may promote or inhibit nerve growth based on the pattern of sulphur atoms attached to chains on the protein. The lab is currently working to modify the levels of inhibitory CSPG at the injury site and enhance RGC axon regeneration. By reducing the inhibition caused by CSPGs and combining with other strategies to stimulate RGC to regenerate, they aim to enhance optic nerve regrowth after injury for the benefit of patients in the future.

4.38 A drug delivery platform that empowers patients and reduces costs and pressures in the NHS

Dr Felicity de Cogan
Research Fellow
University of Birmingham
Institute of Microbiology and Infection

As has already been highlighted in this report, intraocular injections of anti-VEGF therapies to treat wet AMD are well established in the clinic. While the anti-VEGF therapies are effective at arresting the symptoms of wet AMD in a large number of patients, the delivery mechanism (intravitreal injections) have a risk of significant side-effects, such as infection, retinal tears/detachment, and poor patient compliance. The procedure also requires a sterile environment and trained ophthalmic staff to carry out each injection, which puts a huge strain on ophthalmology services in the NHS and abroad. With an increasing ageing population, the burden of treatment for wet AMD will only rise.

To target this problem the de Cogan group at the University of Birmingham has developed a cell penetrating peptide (CPP) as a platform technology for ocular drug delivery. The peptide is mixed with the current anti-VEGF therapeutics ranibizumab and bevacizumab and applied topically as an eye drop. Animal studies demonstrated that after 6 minutes the therapeutic load is detectable in the anterior chamber and after 30 minutes in the posterior segment. The therapeutic once delivered to the posterior segment of the eye clears over 24 hours, suggesting a daily eye drop regimen. The CPP does not hinder the efficacy of the anti-VEGF. Animal models of choroidal neovascularisation showed the same anatomic outcomes whether the anti-VEGF is delivered by CPP or by intravitreal injection. This demonstrates great promise for translation into the clinic, as it will allow the current clinic stockpile of anti-VEGF therapeutics to be used while reducing the side-effects associated with the intravitreal injection-based delivery method.

The simplicity of this technology allows it to act as a broader platform to deliver a range of ocular therapeutics, in addition to anti-VEGF therapies. Research with collaborators at the University of Birmingham and Queens University Belfast has demonstrated the ability of the CPP to deliver a range of different therapeutics from anti-VEGF antibodies and proteins to siRNA and short sequence peptides. The CPP can be simply mixed with the appropriate drug and applied topically as an eye drop. This means that the potential of this technology is not limited solely to AMD but can be used to treat other posterior segment diseases such as diabetic maculopathy and macula oedema. Ongoing work in the field of glaucoma has also shown its potential for delivery to the anterior chamber to allow the treatment of glaucoma.

The aim of this research is to drive drug delivery in ophthalmology forward to a point where injection-free ophthalmology treatments can be reached. This has the double goal of empowering patients and assisting them to take control of their own treatment while simultaneously reducing the financial burden for the NHS and other healthcare providers. It also raises the possibility of the care of these patients transferring from hospitals to primary care. While significant progress has been made on this and other technologies in the field of ophthalmology, translation to the clinic will not arrive

without funding to bridge the gap between bench and bedside. Significant resources are needed to develop academic ideas through clinical translation to change these treatment regimens.

5.0 Rehabilitation

Healthcare professionals cannot solely rely on the efficacy of a range of treatments to improve clinical outcomes for patients. Support is at hand to help them assess and even diagnose patients' conditions as well as plan, explain and deliver appropriate treatments with the help of the orthoptic community backed by evidential research.

There is also an impetus within the research community to challenge accepted rehabilitation practices and to focus on initiatives that can measurably deliver results. Technologies that enhance functional vision or deliver so called "artificial sight" in the form of intraocular and retinal implants as well as various tele-health devices to support treatment regimes and positive lifestyle choices and low vision aids to support everyday tasks, are very illustrative of the innovation driving the eye research community.

5.1 Understanding user requirements to build better Low Vision Aids

Dr Sandra Starke, MSc PhD
Aston University

Low Vision rehabilitation still inhabits a somewhat neglected space in eye- and vision research, as much scientific and funding effort is focused on prevention and cure. However, for the 360,000 people who are registered as blind or partially sighted and many more living with sight loss in the UK alone, making the most of their residual vision and improving access to everyday activities is an absolute priority. With no cure or prevention on the near horizon for common conditions such as AMD, research in the area of rehabilitation and management of sight loss is therefore urgently needed.

The last decade has seen exceptional progress in technology that can leverage residual vision, alongside other solutions such as the sonar cane or improved text-to-speech. Miniature cameras, computers and other technology are now enabling new Low Vision Aids (LVAs) that are small, wearable and offer more functionality and broader application than conventional options such as desktop magnifiers. Over the last years, we have seen some early solutions come to market. Yet the question remains: what exactly should be built?

As part of a collaborative InnovateUK project, we had the opportunity to look at this question scientifically. We developed the first study of its kind to find out what people living with sight loss need in a "perfect" Low Vision Aid – by making them pretend they had one! This approach is called 'pretotyping' (not prototyping), where it is possible to find out about product use without having to build a functional prototype. In a nutshell, we gave 32 visually impaired volunteers spectacles equipped with a video camera (SunnyCam Sport). We asked participants to pretend that this was the "perfect" sight aid and to record and narrate for one week all situations in which they would use it. This was followed by a de-brief interview.

The study gave us an incredibly rich insight into the everyday reality of sight loss and requirements for LVAs, allowing to explore functional, psychological and design factors. We quantified characteristics of the recorded scenes using computational image analysis and categorization, exploring many aspects relevant to design input requirements relevant for future LVAs: viewing distances, object size, scene characteristics and much more. We also explored captured use cases in great detail and discussed participants' views of current LVAs and their experience with the SunnyCam pretotype device.

Results will be published as a two-part series, with the first paper due to be published in the Journal of Vision this month and the second paper currently under review. Both papers will be available Open Access.

Inquiries about the study can be sent to s.starke@aston.ac.uk.

Read paper: 'Everyday visual demands of people with low vision: A mixed methods real-life recording study.'

5.2 Voxmate - a blind-first, gesture-based app for Android

Gleb Zevkov
Founder
info@voxmate.com

Voxmate is an intuitive, gesture-based, Android app that flattens the smartphone learning curve for people dealing with sight loss. By primarily using one-finger swipes: up, down, left and right, you can navigate to an article, a radio station, play games, or scan printed text. Most users figure out how to use Voxmate in under 10 minutes.

The groundwork for the app was laid after a founders' family member lost their eyesight. The team discovered that re-learning using a smartphone with Talkback or VoiceOver can be extremely difficult for the elderly, while simultaneously being cut off from news and means of communication adds insult to injury. They then decided to make something that would "just make sense", and be easy to use from day one.

Voxmate is designed from the ground up to never rely on displaying anything on screen, instead focusing on a great audio experience. This "blind-first" approach can be contrasted with a regular screen reader – while screen readers make existing software usable, Voxmate is making truly accessible software from scratch. In an ironic table-turning twist, Voxmate's blind and visually impaired users become comfortable with the app more quickly than the sighted, who instinctively freeze while searching for visual cues on a blank screen.

The app does not have a standard visual interface, which means there are no buttons to press or screens to scroll. Voxmate's main navigational metaphor is a rolodex, with cards you can "visit". Started by throwing out the book on traditional user-interfaces, Voxmate aims to find better, more natural solutions for games, audio, video and text consumption. By creating a brand new audio-only user experience design language, Voxmate presents a uniform experience across many conceptually dissimilar services.

Voxmate already offers many such services, called voxlets. To date there are voxlets for news, podcasts, audiobooks, radio, a diler, several games, OCR, the weather, and the list of them is growing rapidly. Each voxlet is carefully constructed to deliver important information with natural language, while at the same time getting to the content you care about is always just a few gestures away. Voxlets are delivered with seamless updates over the internet, so that you always have the latest version.

Another new aspect of Voxmate is the ability to configure it remotely through a web portal. The app can be managed by the user using a PC or, if preferred, it can be configured by a loved one, a caregiver or an assistive technology specialist. The portal not only allows changing general settings, such as speed with which information is presented, but to also configure individual voxlets. Adding credentials for audiobook services, or social media accounts; adding and rearranging radio stations – can all be done through the portal. The changes made in the portal sync automatically with the app, and are instantly applied.

In conclusion, Voxmate is an upcoming ecosystem with a modern approach, deep focus on user experience and limitless potential to help people with sight loss to quickly find their bearings. While initially intended as a tool to ease people into using screen readers, Voxmate is finding its footing as an independent alternative that is welcomed by more tech savvy users who understand its long term promise.

Voxmate is coming out in 2020 on Google Play, and is already available for trial. If you would like to test Voxmate as a medical, or assistive technology professional, then reach out to us at info@voxmate.com. For more information, and to register for updates visit https://voxmate.com.

5.3 Colour tents – reducing clutter and over-stimulation leading to improvements in visual awareness and attention

Suzanne Little,(Special Needs Consultant)
Professor Gordon Dutton

Colour tents are a valuable resource for children with multiple disabilities and cerebral visual impairment (CVI).

Tents provide a space which cuts out overstimulation from noise and visual clutter.

Children with complex needs may "switch off" from connection with their immediate environment because of sensory overload, or become distressed as they become overwhelmed by stimuli.

Being inside a tent has helped many children with severe brain injury to make use of their visual awareness and attention, often for the first time. Their vision appears to be "switched on" because the colour tent has enabled their brain to connect to the experience, by taking away the overload of surrounding information

The question you may well be asking is "Why should a child who appears to have no vision, starts to look around for the first time when surrounded by a tent?". This means that the child must have had some vision all along, but couldn't use it when surrounded by clutter.

It has been known since the early 1900s that injury to the part of the brain just above the ears, the posterior parietal lobes, causes inability to see and give attention to more than one or two things at once, often with inaccurate reach, when using vision to guide the movement. In children with severe cerebral palsy their posterior parietal lobes that map their visual surroundings, are commonly damaged. So it's not too difficult to come up with the underlying cause. The posterior parietal lobes have been injured. This condition is called Balint syndrome.

While inside the tent the child has time to engage with their vision at their own pace. The adult can observe from outside without interaction, and record changes, such as improvement of posture, calmness, and vision responses.

The tent provides the opportunity for a 'one thing at a time' visual experience which the child can relate to. This also relates to the nature of what we say and how we say it. Much of our language is verbal, and of course relates to our experience. But what if we use our normal language to teach children who can only be aware of one thing at once? The language used makes no sense to them, and so they cannot learn from it.

So for everyone who responds to tent therapy, for them to start to understand language, the words used need to be simple, at first singular, while simply labelling what they experience as they

experience it. For even the most profoundly affected, learning from the meaning of what others say can start to take place for the very first time using this method!

Ali has quadriplegic cerebral palsy and severe CVI. She showed an immediate visual awareness and attentional response to being surrounded by colour tent for the very first time when she was 8 years old. She later followed a routine of regular tent time as part of her education programme. As she entered the tent her name was used as well as the word ‘ orange’. After 20 minutes she was taken out of the tent and the word ‘more’ was introduced, and Ali was returned to the tent for a few minutes linking the action with the word. After repeating this activity for a few months Ali responded with a consistent vocalisation as she came to understand the word ‘more’ in context, because the tent had become a motivating sensory experience.

Until the use of the tent Ali had only responded to light and dark. She often became distressed in noisy or cluttered environments and would self harm. Her response to entering and being in the tent became one of calmness and one of gaining visual awareness.

Ali could not reach out and she was unable to move her eyes to any specific targets, after tent work sessions over a period of two years, Ali began to locate and fix on movement of lights in the tent, enabling observation of her visual field preference.

Prior to the use of the tent 11 year old Tom kept his head down most of the day. Tent sessions motivated him to lift his head, increasing his visual awareness and attention. This led Tom to improve his posture by holding his head up and he began to use his vision in a range of different settings.

Many teachers and parents who have adopted tent work, have reported that the tent has brought about a remarkable transformation, bringing about greater attention, as well as better engagement and understanding for children with severe CVI. The potential for the use of these tents is considerable and the dissemination of this knowledge would allow many more children to benefit.

We are building up case study evidence and with the CVI society, we are helping to plan a feasibility study with Great Ormond Street Hospital in the foreseeable future, into using tents to help at risk babies.

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5.4 Right Hear technology – turning public and private spaces into accessible environments for the visually impaired

Idan Meir
Co-founder, CEO

RightHear is a mobile-based orientation solution that allows people who are blind or visually impaired to be more independent in public spaces. The free app on Android and iPhone describes the spatial orientation in 9 different languages and has over 1,000 locations worldwide. At present, most of the locations are currently in Israel, where the development of the system and company is headquartered.

There are a few features and capabilities that set RightHear apart from the accessible indoor navigation landscape. One of them is the integration of many different 3rd parties apps like Be My Eyes, Cash Reader, Uber, Lyft, and more. The developers are planning to add even more integrations in the app in 2020 but they are currently not revealing precisely what apps.

The RightHear solution also has a very powerful feature that allows the user to record audible notes which are location-based. These audible augmented reality capabilities, bring a new layer of customization experience for the user so if one wants to pin on the map a certain landmark on one's daily routine – now it is possible, and privately.

As regards privacy, RightHear is amongst the very few apps that do not require any sort of registration or authentication when installing it. RightHear does not collect users' data and maintains a very high level of user privacy.

The business model behind RightHear's activity is based on charging businesses, institutions, and other organizations for turning their spaces into more accessible environments. With the new reality of social distancing, it seems like the need for providing independent and private experience in public spaces has just increased.

While some of the RightHear partners like McDonald's Israel are doing it because of ethical and branding reasons, there are also markets with regulations that support this effort as well.

The installation of RightHear in a public space is relatively simple and quick and according to the RightHear team, they had over 100 locations that turned into accessible environments 100% remotely. With this in mind, the scale of the RightHear solution is planning to make another big leap as the founders of RightHear describes it thanks to new technologies currently under development with the team.

One of the unique projects that RightHear has done in the past year was turning Eben Gavirol Street, which is one of the main streets in Tel Aviv, Israel into an audible street.

Watch the video here.https://www.youtube.com/watch?v=JJUvSgqgfhg&t=39s

RightHear installed over 100 beacons on this street and also utilized GPS capabilities to provide an independent experience for the blind, visually impaired users as well as for the tourist that are touring in this busy street.

The app is available for free on iOS in this
link: https://apps.apple.com/us/app/righthear/id1061791840

And on Android in this link: https://play.google.com/store/apps/details?id=com.righthear

For inquiries and more information, contact: support@right-hear.com or go to www.right-hear.com

5.5 The Owlett - A camera to help the visually impaired around the house

Billy Wood
Founder

The Owlett is an upcoming device designed to help the blind and visually impaired around their house. It is a small hand held camera that can take a picture of something placed in front of it, then after a few seconds come back with a full description. It works using a cloud AI algorithm that can quickly annotate an image and is seamless from the user's perspective. It's designed for everyday household tasks such as identifying who a letter is addressed to, giving a description of objects around your house, or identifying what's in a packet before you open it.

The problem that it seeks to solve is that of the visually impaired being cut off from the people and things around them. According to RNIB data, 4 in 10 blind and partially sighted feel this way, and as there are 360 thousand blind people in the UK this issue affects a large portion of the population. Positive testimonies have been gathered from an assistive technology expert with the RSBC and an optometrist specialist at Moorfields eye hospital who have confirmed that this could have a serious positive impact on the populations they work with.

In order to meet the needs of the technically inexperienced and those with tighter budgets it is designed to be easier to use and cheaper than the closest competing products which either rely on a smart phone or require expensive hardware.

Development on the Owlett started in 2017 and is ongoing. So far a number of trials have been completed in order to gain feedback with another planned in the near future. This has been invaluable, and has ensured that our design will meet the customers requirements when it's released.

Feedback and trialing help was provided by a number of charities and organisations for the blind, including Blind Veterans UK, the RNIB, and Blind aid.

To sign up for official updates or to be part of the upcoming trial, go to: http://theowlett.com/

5.6 The Ocutrx Oculenz headset – see around your blind spot, ignore your scotoma, improve your quality of life!

Victoria McArtor, MFA
Ocutrx Vision Technologies, LLC.
Irvine California

Ocutrx Vision Technologies, a California-based technology start-up, is developing an augmented reality headset to treat the devastating effects of Advanced Macular Degeneration (AMD). The Oculenz™ AR headset utilizes patented, state-of-the-art technology and will soon allow users to see around their blind spot, ignore their central scotoma, and drastically improve their quality of life.

How it works:

Visual field test:

Upon first use, the user will put the Oculenz headset on their head similar to wearing a pair of glasses. The screen will prompt them to take a visual field test which is presented on the lens. The Oculenz visual field test is two-fold, measuring the patient's absolute and relative scotomas through both

ARITA Static and ARDIPA Dynamic tests. The augmented reality Interactive Thresholding Algorithms (or, the Random Dot Association Test) displays concentric circles on the headset. The patient uses an external toggle to click when they see images. If a circle is displayed and the patient does not click, then the software creates a digital edge of their defect, essentially "mapping" their scotoma. Secondly, the Augmented Reality Dynamic Interactive Perimetry Algorithms (or, the center-out shooting star), requires patients to click when they see streaking lights, which identifies an assumed center of the macula. This creates a further digital edge of the defect area.

The Oculenz visual field test takes approximately 5 minutes per eye and produces a unique image of the patient's scotoma, called the "scotoma marker." The scotoma marker is stored in the central processing unit of the headset. The patient can re-take the visual field test as often as they like so that their unique scotoma matches the scotoma marker. Ocutrx recommends patients take the test no less than once a week; no more than once per day.

Scotoma marker:

After the visual field test is completed and the scotoma marker is stored, the patient is ready to use their Oculenz headset. While the patient goes about their daily tasks, the headset's 4K front-facing cameras receive images from the outside world. Then, Oculenz's patented eye-tracking technology continuously follows the patient's eye-gaze while pixel-manipulation technology alters images from the outside world around the patient's scotoma. With no recognizable lag time (approx. 5 milliseconds), the Oculenz moves real-world images around the area of the bind spot and projects an augmented image onto the lens. This allows patients to complete housework and lawn work, compose emails, read the newspaper, and distinguish faces in meetings and among family members, without noticing their scotoma.

HIPAA-Secured Patient Portal:

Once the patient completes the visual field test, the data from the test will be automatically uploaded into Ocutrx's HIPAA-secured "patient portal." This new database will make it possible for doctors to better analyze data regarding the growth of a patient's scotoma and will help track trends of the disease. This means better service to individual patients and improvements in our overall education and understanding regarding the progressive nature of AMD.

Results of recent patient study:

In a recent single-arm crossover study of subjects with AMD, trial patients took a visual field test while wearing the Oculenz headset, which mapped the area of their scotoma. These results were compared to a Fundus Autofluorescence photo of each eye taken prior to the testing to ensure accuracy. Reading performance was evaluated using the logMAR chart, per eye, both before and after wearing the Oculenz AR headset.

The study showed Oculenz AR glasses significantly improved patient's ability to read small letters and print at near and far viewing distances when compared to their own standard near correction (or no correction). Best corrected visual acuity improved from 20/200 to 20/63; 4-5 lines more on the logMAR chart. Zero patients in the study could read without Oculenz; all 25 patients were able to ready 30-point type, and eleven patients were able to read 12-point type. When given a Familiar Faces Recognition Test, all patients were able to discern faces of loved ones that were previously unrecognizable prior to Oculenz.

Problems with current low-vision enhancement tools:

In Ocutrx's opinion, current vision enhancement tools utilize VR (virtual reality) technology, which completely replaces (and shuts out) the real world. These devices are not desired by the medical or

low-vision community and are reported to cause vertigo sensation, myopia progression, and limit the user's mobility as they cannot be used outside or while walking around. Most importantly for AMD patients, these devices only magnify the real-world image, they do not move the image outside of the patient's blind spot.

Current AR headsets are too heavy for low-vision users, have too limited a field-of-view, and their image is low resolution, making it hazardous to complete tasks such as yard work or chopping vegetables. Most importantly, these devices utilize waveguide technology, which works by transmitting images via fiberoptic cables from the computer in the back of the headset to the front lens. Users have reported putting towels on the back of the headset to block the heat from the processing unit. In many cases, the fiberoptic cables will pinch, causing dispersion of colors called chromatic aberration. To date, Hololens has shut down their production line due to chromatic aberration issues.

Ocutrx Vision Technologies has listened to the criticisms and recommendations from users regarding these AR and VR devices and has addressed these hinderances, resulting in a myriad of unique features.

Features of Oculenz:

- Lightweight (>200 grams, weighs less than a cell phone)
- Highest Resolution in the industry (60 pixels per degree)
- Widest Field-of-view of 110°
- Dynamic Opacity can transition lens from AR to VR
- HD imaging
- Embedded SLAM and OCR technology
- Patented Pixel Manipulation for AMD
- Patented Eye-Tracking technology
- Mini-HDMI and USB-C connectors
- Cellular, BlueTooth® BTLE® and WiFi wireless connectivity
- Sound connectivity with hearing-aids or through bone conduction
- Noise cancelling microphones for indoor or outdoor use

Conclusion:

While the Oculenz does not remove the scotoma, by moving text and images outside of the geographical area of the scotoma to adjacent good sighted areas of the retina, the person can see all images, providing a "perceived de-emphasis" of the scotoma. Dr. Hugo Quiroz-Mercado, M.D., a member of Ocutrx's International Medical Advisory Board and Ophthalmologist in Mexico City recently said, "so far, technology has failed the medical community. Oculenz is the tool we've been waiting for." Ocutrx Vision Technologies plans to have commercialized Oculenz headsets by Q4 2020 and will be available through low-vision centers.

5.7 Falcon Autofocus bioptic - Supporting visual needs while interfering the least with habitual behaviour

Henry Green
Chief, Advanced Low Vision Section, Hefner VA Healthcare System, Salisbury, NC
Co-founder, President, Ocutech, Inc., Professor and Director (retired), Low Vision Service, UNC Department of Ophthalmology, Chapel Hill, NC

The goal in developing sight enhancing technology is to best support the user's visual activity needs while interfering the least with their normal, habitual behavior. The more natural the

device's functioning, and the less the user needs to engage with the device, the more effective and efficient the user will be.

Ocutech's new **Falcon Autofocus bioptic** has been designed to address the challenges inherent in conventional telescopic vision enhancing devices. Bioptics are miniature telescopes usually mounted toward the top of the eyeglass frame so as to not interfere withthe user's regular line of sight. This allows the user to conveniently switch their view between the regular eyeglass lens (carrier) and the telescopic view with just a slight downward head tilt. Bioptics are a convenient way to magnify objects at normal working distances. They are most frequently prescribed to support distance and midrange visual activities for individuals with best-corrected visual acuity in the 20/70 to 20/300 range.

Bioptic telescopes need to be refocused when the user looks at different distances, requiring the user to continually manipulate the device. This is especially relevant with the shallower depths of field encountered at closer distances and with higher magnification power devices. The benefit of the Falcon Autofocus is that the image is in focus immediately at virtually any distance. No manipulation of the device is required. All the user has to do is look at the object of interest, making the Falcon's user experience as close as possible to natural vision. And, as an additional benefit, as the user moves closer to an object, the image size will increase clearlyand seamlessly, providing a helpful zoom effect.

When an individual needs to look at a fixed near distance for an extended period of time (i.e.: the computer screen)one might assume that there would be no benefit from an autofocusing device. However, since the telescope's depth of field is most shallow at near distances, even a slight postural change could be sufficient to blur the image. As a result the user would be forced to maintain a fixed posture to maintain image focus resulting in fatigue, lowered efficiency, and ultimately undermining the device's long-term acceptance. As a result, autofocusing for activities at near distances can provide a more natural visual experience, lessening the user's physical demands, lessening fatigue and increasing their performance.

When viewing objects solely beyond 20 feet (6m) (for bioptic driving perhaps), most optical telescopes used by the visually impaired will be at infinity focus. No additional focusing for viewing beyond that distance would be required. So, if the sole goal of the device is to support vision at 20 feet or further, an autofocusing device would offer no additional benefit. However, if the device is intended to also be used for a range of other distances, an autofocusing device may still be acompelling option.

WHEN: Autofocusing bioptics are ideal for individuals needing enhanced vision at multiple viewing distances, for those with hands-free needs such as playing music orusing the computer keyboard, and for mid-range and tabletop activities. They have been found effective for individuals with dexterity challenges and for those with mild to moderate cognitive deficits, where their ability to manipulate a manual focus device is undermined.

When traveling on public transit or at the airport, individuals will benefit greatly from the ability to see any object of interest at a glance. This visual necessity becomes less burdensome when the focus is automaticand hands-free. The classroom requires distance, intermediate, and near visual tasks all day long, as such, students can benefit tremendously from the convenience of an autofocusing device, and they are usually eager and quick adopters of such technology.

The emotional benefit of seeing a loved one's face and expressions cannot be overstated. As mentioned in the introduction, a growing body of research demonstrates that the lack of distance vision can undermine socialization, can lead to feelings of isolation, and ultimately to depression and cognitive decline in seniors. Efforts to support distance seeing for the visually impaired should go beyond specific task-related activities to also consider their emotional and social well-being.

HOW: When prescribing any device, we must consider how it will be used. If intended primarily for distance-seeing, positioning the Falcon in the ‘bioptic position’ is usually the most practical option, as it will not interfere with vision through the carrier lenses for walking and othernon-visually demanding activities. Individuals who intend to use it mostly for near or midrange, or in more sedentary distance activities, will likely find the straight-ahead ‘full diameter position’ to be more comfortable such as when viewing TV, movies, the computer screen or tabletop. The Falcon can be positioned at the top of the frame (bioptic position) using Ocutech’s K or U frames, or in the straight-ahead position (full diameter) using the Ocutech Sleek frame.

The Falcon instructional videos and fitting guides will take you step-by-step through the fitting process. Designed to be easy to use, you’ll soon find just how convenient it is to demonstrate, fit and prescribe the Falcon Autofocus bioptic.

5.8 NuEyes Technologies - a leader in head worn assistive technology devices

Mark Greget
CEO and Founder

NuEyes Technologies is a leader in head worn assistive technology devices. Their inclusive digital ecosystem is offered on the NuEyes e2, e2+, Pro, and Pro2. All devices deliver best in class display and camera technology to provide the clearest picture when magnifying objects at great distances. With their patented, easy to use software you can also utilize augmented reality contrast overlays, optical character recognition, as well as simply controlling the Pro and Pro2 with voice commands. All products come standard with a new Telemedicine platform to connect you with your doctor from anywhere in the world. Specific to the e2 and e2+ you can stream movies and television and enjoy a full digital ecosystem featuring a web browser, as well as virtual reality platform to meeting up with friends or continue education classes. Whether you have macular degeneration, glaucoma, diabetic retinopathy, retinitis pigmentosa, or any other visual impairment, NuEyes offers a multitude of head worn devices to fit your visual needs!

Links:
https://www.youtube.com/watch?v=9FCRDE_iY0s&t=106s
https://www.youtube.com/watch?v=c5q4ClNL2VU
https://www.youtube.com/watch?v=tgkIf_wbUNk
https://www.youtube.com/watch?v=-LlTe3zeLo0

website: www.NuEyes.com

5.9 Empowering Visually Impaired people - NaviLens

D. Javier Pita Lozano
CEO NAVILENS PROJECT CORP.

NaviLens is a new universal digital signage that helps visually impaired people to orient themselves autonomously indoors and obtain accessible information contextualized to a place only with the use of their camera mobile device.

It is based on a code similar to a QR, but much more advanced, that allows it to be read at a great distance (12 times greater than QR code), in movement and without focusing or previously knowing the place where it is located.

NaviLens has been developed by Neosistec and University of Alicante after 8 years working jointly in the search for a code that might support the improvement in the quality of life for the visually impaired. (https://youtu.be/YGPuTIHP-Oo).

How does Navilens help users?
When the phone camera detects a Navilens code, it notifies the user and directs him to the code with accuracy through a system of voice instructions and sounds. (it is capable of setting with high precision the distance and direction to the desired position, the two variables that enable reliable orientation).
In addition, Navilens provide the user with accesible information about the element, asset or place signed (https://youtu.be/nOQaFtaQCvE)
Navilens is a scalable technology with a low and sustainable cost. To make any space accessible with NaviLens Technology is as easy as to add the NaviLens codes to the current signage. The maintenance is equivalent to the usual signage for sighted people. It makes any space accessible, so that people with visual impairment can move completely independently and on equal terms, without requiring the installation of expensive electronic devices.

NaviLens is a system that is perfectly adapted to multi-modal stations and means of transport, (Metro, Bus, Train, Tram), helping people with visually impairement to reach the stop or to guide themselves in a station and to obtain accesible information such us arrival/departure times, service isuues, subscription to alerts and notifications, etc.
The speed of reading the code allows it to be read on the move and used in vehicles such as buses or trains so that the user can confirm that this is the bus or train they want to take, as well as knowing precisely where the access or exit door is. of the same. It also allows real-time information on the status of lifts or the most accessible routes for people with reduced mobility.
Tram of City of Murcia: https://youtu.be/cq3VI0vUtO0.

In addition, NaviLens is a very helpful system in environments such as museums, public buildings, theaters, educational and commercial centers. It offers accesible and contextualized information about the rooms, pieces and works of interest, hours, etc….Archaeological Museum of Murcia: https://youtu.be/cmYKOrtnOz4
NaviLens is a technology that is present in many spaces around the world with great success: New York Subway, Los Angeles Subway, Barcelona Subway and Buses, Alicante Buses, Donostia Bus Station, Murcia Archaeological Museum , Pedralbes Museum of Barcelona, Madrid Cruz Roja, etc.

PERSONAL USE TAGS
Users who wish to use NaviLens technology to signal their closest surroundings and their personal use items can do so by downloading the "Kit NaviLens for personal use". It is a package of free labels that the user manages with his mobile device. Download link:

https://cloud.navilens.com/sample/

NAVILENS FREE KITS
NaviLens has launched two free marker kits: NaviLens school Kit and NaviLens Asociations Kit. These are two standard kits that mark the most common spaces of schools and associations.

Download link: https://free.navilens.com/

You can download Navilens app here: www.navilens.com/n/

TECHNICAL FEATURES OF NAVILENS
Distance *reading capacity:* ***12 times further*** *than QR and barcodes (A4: 12 meters)*
Ultra-fast reading capacity*: 1/30 second*
Wide-angled *reading up to* ***160º***
Reading *in all light conditions* ***(dark & bright)***

***Multiple Reading**: 200+ codes per frame*
***High density** (codification & space)*
***Accuracy in** distance information (centimeters)*
***CRC** Protection*
***No focusing required**. Not time-consuming for users*
Patented Technology

5.10 Improving quality of life and health outcomes through increased interdisciplinary competency and health literacy of vision and vision rehabilitation

Professor Helle K Falkenberg
National Centre for Optics, Vision and Eye health
Department of Optometry, Radiography and Lighting Design
Faculty of Health- and Social Sciences
University of South-Eastern Norway (USN)

Vision changes due to normal ageing or visual impairments (VI) affect the ability to perform everyday tasks, quality of life and health. Arranging for older people to work and age healthily for as long as possible may result in both improved quality of life and significant social economic effects. Most age-related vision loss can be improved by appropriate prescription glasses and lighting. Still, many adults are unnecessarily visually impaired because of uncorrected vision, reducing activities such as reading or driving. Research from USN has shown that the awareness and health literacy, of how lighting affects vision and abilities to perform everyday activities, is low among healthy older persons. Further, that improved lighting can lead to improved quality of life, and improved lighting can be achieved with a basic lighting control system. Poor lighting and vision have also been linked to increased ocular symptoms and reduced reading performance, particularly during computer work. Kongsberg based researchers have shown that direct glare exposure during computer work affects trapezius blood flow and development of eye symptoms, and is associated with neck pain, reduced concentration and increased psychological stress. Further research is necessary to increase interdisciplinary competence and health literacy of lighting and vision ergonomics to improve quality of life and participation at home and work for older adults and people with vision loss.

Vision impairment due to age-related eye or systemic diseases (e.g. age-related macular degeneration, glaucoma, diabetes, hypertension or stroke) may be permanent, less amenable to correction with glasses, and need specialist or municipal health care treatment and/or vision rehabilitation. VI is associated with an increase in falls, reduced outcomes of rehabilitation, quality of life and additional mental distress. Coping with the consequences of vision loss is complex and difficult, especially after a lifetime as a sighted person. Symptoms of VI are difficult to understand, and ageing further exacerbates vision loss as other senses (e.g. hearing) also deteriorate.

Our ongoing interview studies with patient experiences of living with vision loss, confirm that vision rehabilitation should not only include visual aids to magnify the image, but also include vision rehabilitation and increased health literacy of coping living with their vision loss. Those with VI must therefore be identified as patients needing vision rehabilitation, relevant advice, and in addition, they may benefit from visual training.

Development of new knowledge in complex areas often requires multifaceted and creative research, combined with extensive interdisciplinary cooperation not only within and between health services and municipalities, but also involving other care and welfare services. In addition, future studies need to include the individual person and their families perspectives.

Falkenberg and her collaborators' research therefore focuses on increasing competence and health literacy to improve vision and quality of life for people, through an interdisciplinary knowledge translation framework.

NorVIS –Norwegian Vision in Stroke network

Vision impairments are common after brain diseases, and the leading cause of brain disease is stroke. VI affects more than 60% of survivors, in addition to other sequela after stroke. In Norway, >30 000 stroke survivors live with the consequences of VI after stroke, and this is estimated to increase

with the ageing population. The National guidelines states that vision function should be assessed after stroke. Despite this, impaired vision is one of the most commonly overlooked and under-treated conditions following stroke. This is mainly due to lack of awareness, competence and interdisciplinary knowledge translation across services, disciplines and sectors. Falkenberg and her group have shown that symptoms of VI also often are "invisible" to the individual, causing further delayed visual assessment, treatment and/or rehabilitation. The knowledge created from the persons own experiences are invaluable to understand how future vision care pathways must be organized.

The Norwegian Vision in Stroke (NorVIS) network lead by Professor Falkenberg aims to facilitate implementation of vision research and structured vision assessment in interdisciplinary stroke care services to meet the future needs of improving outcomes after stroke.

The most common VI include visual field loss, eye movement disorders, reduced central vision and perceptual deficits such as neglect. Regardless of severity, much can be done to improve VI through vision rehabilitation and improved health literacy. Research confirms that assessing visual functions will raise self-awareness and that compensatory training is useful for vision outcomes and the overall rehabilitation process. Better care for the individual and their relatives will promote work participation and community integration. Thus, failing to identify VI after stroke can have a severe negative impact on the patient's coping, further recovery and ability to perform meaningful activities. Falkenberg hopes NorVIS will attract attention to this neglected complex area and improve awareness and health literacy of the importance of vision for better stroke and brain health outcomes, and quality of life.

Falkenberg et al., (2020) "Invisible" visual impairments. A qualitative study of stroke survivors' experience of vision symptoms, health services and impact of visual impairments 10.1186/s12913-020-05176-8

https://prosjektbanken.forskningsradet.no/#/project/NFR/299074

5.11 Towards a Cortical Visual Neuroprosthesis for the Blind: CORTIVIS Approach

Eduardo Fernández
University Miguel Hernández and CIBER-BBN (Spain)

Loss of vision affects millions of people worldwide and poses extraordinary challenges to individuals in our society that rely heavily on sight. Although in recent years the techniques of molecular genetics have led to a rapid identification of a great number of genes involved in visual diseases, and there are significant advancements in the development of different approaches for artificial vision, at present there is no effective treatment for many patients who are visually handicapped as a result of degeneration or damage to the inner layers of the retina, the optic nerve or the visual pathways.

Therefore, there are compelling reasons to pursue the development of a cortical visual prosthesis that bypasses the damaged visual pathways and be able to restore a limited but functional vision in these profoundly blind patients.
Even if only a crude representation of the surrounding physical world can be evoked by stimulating directly the brain, a blind individual could use this artificially encoded neural information for tasks such as orientation and mobility. This functional performance has already been attained in the field of auditory prostheses. These devices have already allowed many deaf patients to hear sounds and acquire language capabilities, and the same hope exists in the field of neuroprosthetic devices designed for electrical stimulation of the visual cortex.

How it works:
As blindness results from an interruption in the normal flow of signals along the visual pathways, a visual prosthesis has to excite the neurons of the pathway at some point after damaged site. The only requirement is that the device should make contact with the neural elements that are still functioning. On the other hand, since cortical neurons receiving the visual information from the retina are located on a depth of about 1.5-2.0 mm, we need intracortical penetrating electrodes, about the same size as the neurons they are intended to stimulate.

The whole system consists of a miniature video camera attached to a pair of eyeglasses that captures the visual scene, a small retina-like processing unit that extracts and enhances the most relevant features of the scene, and an array of tiny microelectrodes (of the size of a hair) implanted at the visual cortex.

Experimental results:
If the visual part of the brain can be stimulated with visual information in a format somewhat similar to the way they were stimulated before the onset of blindness, a blind individual may be able to use this stimulation to extract information about the physical world around him/her.

Physiological and behavioral experiments in different animal species have shown that intracortical microelectrodes such as the Utah Electrode Array (UEA) can be safely used for stimulation of populations of neurons in visual cortex. Furthermore, the data from non-human primates indicate that the monkeys perceive the cortical microstimulation as another visual stimulus and respond according to their training.

Following these animal experiments, we undertook preliminary investigations to establish the safety of the implantation procedures and to adapt the insertion technique to human requirements. These experiments were performed in persons suffering from epilepsy or brain tumors that had to undergo a surgical resection of a brain region. Our results show that the implantation can be done without major complications, and that electrical stimulation is able to evoke simple and complex visual perceptions.

Recently, we have implanted an array of 100 intracortical microelectrodes in the occipital cortex of a 57-year-old blind person during a six-month period (ClinicalTrials.gov Identifier: NCT02983370), and we found that electrical stimulation of the visual cortex in a long-time blind person produced reliable visual perceptions that evoked discernible patterned perceptions and helped the subject to recognize complex patterns. Stimulation thresholds were within the safe levels for neural stimulation, and the stimulation parameters were relatively stable over the whole experimental period.

Unresolved problems:
In spite of all our progress, the scientific and technological problems associated with long-term biocompatibility and biotolerability of cortical electrodes, with the number of electrodes required to provide a useful vision and with the delivery of information to the implants are very complex, and there are still many unresolved issues delaying its development. Moreover, the brain suffers important remodeling and adaptive changes after the onset of the blindness that could directly impact the

success of any cortical prosthesis, and it is still unclear how to identify the ideal candidates for a cortical prosthesis.

Conclusions:
A cortical visual prosthesis may be the only treatment available for blindness caused by glaucoma, end-stage retinitis pigmentosa, optic atrophy, trauma to the retinas and/or optic nerves or by diseases of the central visual pathways such as brain injuries or stroke.

While the full restoration of vision seems to be unlikely in the near future, a cortical device can create meaningful visual perceptions, resulting in a substantial improvement in the quality of life of blind and visually impaired persons. Nevertheless, we should go step by step, and not create false expectations or underrate the challenges that still remain to be resolved.

We propose that increased collaborations among clinicians, basic researchers and neural engineers will enhance our ability to send meaningful information to the brain and restore a limited but useful sense of vision to many blind individuals.

5.12 Acesight wearable electronic glasses help people with low vision see the world around them

David Bradburn
President
Zoomax
Boston, USA

Zoomax Technology Co. Limited is a Chinese manufacturer of assistive technology solutions for people who are visually impaired or blind. They were established about 10 years ago in Hangzhou, China. They opened their US subsidiary in early 2018 and operate in more than 60 countries worldwide through a network of distributors and eye doctors to help bring their products to market and to the people who benefit from them. Zoomax products include both handheld and desktop video magnifiers including the popular Snow 7 and Snow 12.

In 2018 Zoomax was first in the world to introduce a wearable magnification device featuring augmented reality technology. The product is called Acesight. A primary characteristic of augmented reality is an open design that does not impair a person's peripheral vision. This open design is a key reason that people who use Acesight can still walk around while wearing it. The same cannot be said for products that use virtual reality technology. A characteristic of virtual reality is a closed design that wraps around the eyes and touches the face, affecting peripheral vision in the process. Any attempt to walk while wearing virtual reality could leave you feeling dizzy and possibly cause you to fall.

There are three versions of Acesight today: two models are based on the tried and tested augmented reality technology, and one uses virtual reality. There are a number of features and benefits common to all three models.

1. A camera on the front of the device captures everything you look at and present the image in magnified form on a screen positioned directly in front of the eyes.
2. A simple to use controller lets the user change magnification up to 16x normal size, and to present the scene or the reading material in high contrast colors or with outlining around the edge of everything in sight. Outlining is unique to Acesight.
3. A wide field of view (45 degrees with augmented reality models and 70 degrees with the virtual reality model).
4. Lightweight (less than 1 pound) and comfortable to wear.

Acesight is suitable for use by people with low vision who have a visual acuity 20/600 or better and a field of view that is 10 degrees or greater. The three models are:

- Acesight
    - Suitable for most eye conditions including macular degeneration, retinitis pigmentosa, glaucoma, diabetic retinopathy, etc.
    - Walking around is possible while wearing Acesight so long as the user has some usable peripheral vision
- Acesight S
    - Suitable for most eye conditions but not suitable for use by someone with a limited field of view and lack of peripheral vision because of a condition such as retinitis pigmentosa
- Acesight VR
    - Suitable for most eye conditions including macular degeneration, retinitis pigmentosa, glaucoma, diabetic retinopathy, etc.
    - Walking around is not advisable with Acesight VR

People who consider a solution like Acesight choose it for:

- Watching television
- Using a computer
- Reading sheet music
- Short amounts of reading
- Playing games (cards, board games, etc.)
- Seeing the faces of family and friends

For a detailed overview of Acesight with augmented reality technology please check our playlist of Acesight instructional videos on YouTube. There is also a playlist of Acesight VR instructional videos.

5.13 Exploring The Use of Smart Camera Technologies For Adults With Acquired Visual and/or Language Impairments

Ahalya Subramanian[1], Anna Caute[2], Alison Binns[1], Celia Woolf[2], Morganie Naidoo[2], Jane Marshall[2]
Division of Optometry and Visual Sciences, City, University of London[1]
Division of Language and Communication Science, City, University of London[2]

Researchers in the Division of Optometry and Visual Sciences and Language and Communication Science at City, University of London have been exploring the uses of compensatory smart camera technology for adults with acquired language and/or visual impairments. They are interested in finding out if smart camera based technology such as OrCamMyEye2 andsmartphone apps such as Seeing AI and KNFB reader can be beneficial for stroke survivors with visual and/or language impairments (aphasia) and for people with pure, non-stroke related visual impairments (for example people with age related macular degeneration and glaucoma). Many of these individuals report difficulties with reading.

OrCamMyEye2 is a highly portable, hands free smart camera developed as an aid for people with visual impairments. It can recognise faces, money and products and read text aloud. Smartphone apps such as SeeingAI and KNFB reader have many similar function to the OrCamMyEye2. The group are particularly interested in investigating the ability of smart camera technologies to act as a reading aid and improve quality of life and independence for people with acquired language and visual impairments.

In an initial exploratory study the group recruited seven participants, three had a language impairment (aphasia) with either no or moderate visual impairment. Four had a visual butno language impairment. Participants with language impairments had reading difficulties but relatively good auditory comprehension. During phase 1 of the study participants were invited to a focus group where they were introduced to OrCamMyEye2 and two compensatory apps. Participants received brief training in using the apps. A nominal group technique discussion was used and Seeing AI and KNFB Reader were selected as the comparator apps for iPhone and Android smartphones respectively. In phase 2 of the study participants attended one training session on OrCamMyEye2 and then borrowed the device to use at home. After two weeks, they gave feedback on OrCamMyEye2. They then received training on the smartphone app and provided feedback after two weeks of app use. Participants reported using both technologies across a wide range of contexts including reading books, newspapers, letters, signs, timetables, menus and ingredients. Participants reported a range of benefits and barriers for both technologies. A key benefit of OrCamMyEye2 was the high-quality voice, while reported barriers included difficulties operating the device, e.g. directing the camera accurately to the text. A key benefit of the smartphone apps was highlighting text as it read aloud. Reported barriers were its impact on the phone's battery life and difficulties reading longer pieces of text.

Our exploratory study found that smart camera technologies have potential to facilitate a range of reading activities for people with language and or visual impairments. However, a larger study would be needed to explore these factors in depth and identify participant characteristics that made the different technologies more suitable. We are currently in the process of applying for funding to continue with our research.

5.14 Envision AI: Enabling vision for the Visually Impaired

Karthik Mahadevan, Co-founder of Envision AI
www.LetsEnvision.com

Envision AI empowers blind and low vision people to be independent by speaking out the visualworld in front of them. It is a smartphone app that uses artificial intelligence to read all kinds of text from any surface, recognise faces, describe scenes, find objects, scan barcodes, detect colours and so much more. It is the best all-in-one tool in the pocket of a blind or low vision user for all oftheir visual recognition tasks.

With Envision, visually impaired users can shop in supermarkets, use public transport, readmenu cards in restaurants, recognise their friends, find their belongings and so much more, all on their own.

As a next step, Envision is porting its software to work with Smart Glasses, which will providevisually impaired people with a more unobtrusive and hands free way of accessing the visual world around them.

Envision AI is the winner of Google Play Award 2019 as the Best Accessibility App and wasnominated for AppleVis Hall of Fame 2019.

5.15 The Clew App: Leveraging Augmented Reality Technology for Orientation and Mobility

Paul Ruvolo Assistant Professor of Computer Science Olin College of Engineering

Dr Paul Ruvolo of Olin College of Engineering and his students are working to build an augmented reality app called Clew that allows people who are blind to use their smartphones to navigate indoors. The team's work combines algorithm development, human-centred design, and the latest mobile technology in service of making indoor spaces more easily accessible.

Clew is an iOS app that uses Apple's augmented reality technology, ARKit, to record a user's path as they navigate through an indoor space. The app records a user's route by laying down a trail of virtual breadcrumbs consisting of the user's precise 3D-position at various points along the route. Later, when the user is ready to navigate back to their starting location, the app provides automated guidance to the user. A feature to save routes for navigation on demand (in both the forward and reverse direction) is in beta testing at the time of this writing.

Augmented reality technology has huge potential to unlock new ways by which mainstream smartphone technology can be repurposed as explicitly assistive technology. Crucially, augmented reality technology combines data from gyroscopes, and accelerometers with images from a phone's camera to precisely estimate the motion of the phone, without the need for a GPS signal. This combination of high-precision motion tracking with applicability to indoor navigation has the potential to usher in a host of new indoor navigation technologies. Dr Ruvolo's group is currently working on several novel applications of augmented reality technology, including for creating accurate, accessible maps of large indoor spaces and for automatically providing precise guidance to objects and points of interest.

5.16 Can training to use smartphones and tablets improve quality of life for individuals with visual impairment?

Chris Dickinson
Division of Pharmacy and Optometry
University of Manchester

Ahalya Subramanian
Division of Optometry and Visual Sciences
City, University of London

The MED4VI Study – Mobile Electronic Devices for Visually Impaired People

By converting text into speech and being cheaply and readily available, smartphones and tablets offer a completely new type of assistive technology for visually-impaired people (VIP). The use of standard consumer devices, rather than devices designed specifically for the visually-impaired, has many advantages. For example, the cost of a tablet computer can be as little as £100, whereas the latest video magnifiers cost over £2000. However, the disadvantage is that the devices may not have been designed in an optimal way, and rehabilitation professionals may not be familiar with the devices and their potential.

The MED4VI Study is funded by Fight for Sight, and sets out to determine the barriers to use of mobile electronic devices (MED) amongst VIP. We also need to ensure that rehabilitation professionals are aware of MED, and that they are recommending them when appropriate. Most importantly, we are also evaluating the effectiveness of specialised training in giving the VIP on-going access to the device and in improving their quality of life. We are comparing a standard "training course only" model to a scheme in which each participant is paired with a "buddy" who can provide continuing assistance by visiting the participant at home.

The technological advance of MED may be the most important ever for VIP, and this study will show how best to make it accessible to the majority of VI users. This will ensure that an older generation doesn't miss out because they have no awareness of the potential of these devices.

5.17 Orthoptic research spanning assessment, diagnosis and treatment leading to improved patient care

Professor Helen Davis
Professor of Orthoptics
Academic Unit of Ophthalmology & Orthoptics
The Medical School
University of Sheffield

Prof Anna Horwood
Infant Vision Laboratory
University of Reading

Prof Fiona Rowe
VISION research unit
University of Liverpool

At least 10% of the population will seek professional advice for squint, double or blurred vision, or eye strain at some time in their lives. For vision to develop normally, very tiny babies have to learn to co-ordinate accommodation (eye focusing to make near images clear) and convergence (pointing the eyes accurately towards objects as they move in depth) in the very first weeks of life: at the same time, or before, many other aspects of vision are also developing. Many common visual problems which crop up later in life happen because these systems do not develop normally in early childhood.

Prof Anna Horwood leads the Infant Vision Laboratory at the University of Reading. The lab's research has ranged widely across many aspects of normal and abnormal visual development from birth to maturity in full-term and premature infants, as well as studying children with many common types of strabismus. This research has produced results which have challenged long-held assumptions, providing a better understanding of how these systems work and how, and why, problems develop. This research helps eye care professionals target, plan and explain treatment options for their patients. By providing alternative and better explanations of how visual co-ordination works, improvements and efficiencies are being adopted in patient care. There is a widening interest into photorefraction in wider developmental research and vision screening in children both here and in Europe.

Stroke is the most common cause of UK adult disability with about 100,000 new cases of stroke per annum. Post stroke visual impairment is just one disability that affects stroke survivors. Research from the VISION research unit at the University of Liverpool led by Prof Fiona Rowe aims to improve the orthoptic and vision care of stroke survivors with visual impairment occurring following their stroke. Their research has provided evidence on the prevalence and incidence of post-stroke visual impairment, the types of visual conditions experienced by stroke survivors, how best to screen and assess these visual conditions and what rehabilitation options can be considered for these visual conditions. Post stroke visual impairment is broadly divided into four categories of impaired central vision, eye
movement abnormalities, visual field loss and visual perceptual abnormalities. These may occur in isolation but more frequently occur in combination. Screening for visual impairment is essential and this research has led to the National UK recommendations for the integration of specialist orthoptist screening on acute stroke units. The UK population is aging and
so improving care provision for stroke survivors is important and will continue to be a future need.

Investigation of binocular function and the ability to appreciate 3D vision is a pivotal investigation of patients with strabismus. Whilst there was evidence that the quality of distance 3D vision could influence the timing of surgery in some forms of strabismus there was a lack of ability to clinically test this particularly in the UK. Professor Helen Davis in collaboration with Professor John Frisby designed a test which has been validated for clinical practice and now used worldwide. The

University of Sheffield is now exploring the use of VR technology to simulate diagnose and treat anomalies of binocular vision and nystagmus. Initial results are very promising. There is a need to continue all aspects of Orthoptic research to provide better and more accurate assessment with a view to better targeted treatment regimes.

5.18 EVA – Extended Visual Assistant

Krisztian Imre
CEO
EVA – Extended Visual Assistant

EVA Vision is an R&D for-profit company based in Hungary that is developing a wearable, voice assisted system for the blind and visually impaired.

By utilising artificial vision, "Extended Visual Assistant" is capable of providing verbal descriptions of the visual surrounding of its user, but the company's ultimate goal is to create sophisticated mobility assistance.

Fear of mobility is a very common phenomenon in the blind population. There are three major elements of the mobility problem that result from blindness. First, the blind traveller, with no pattern vision, must avoid obstacles and detect drop-offs. The second problem, which is less obvious and equally serious, is navigation in an environment that is unfamiliar. The third issue is caused by traffic and especially crossings. This is becoming a problem because of the increase in silent electric cars that even the sighted population cannot detect by hearing.

The dynamically changing environment and lack of information about location and orientation, with respect to traffic and obstacles, make mobility a source of fear. While GPS based smartphone apps can offer a more or less reliable outdoor navigation, they don't work in indoor environments where the signal is lost. Guide dogs can provide obstacle detection and traffic safety but their high price and low availability make them exclusive. As a result, approximately more than 30% of the blind population do not ambulate autonomously outdoors, which lead to social isolation, unemployment, dependence on others and low self-esteem.

EVA comes in the form of a pair of smart-glasses that can give verbal guidance to its blind wearers. It uses sensor fusion and machine vision to give precise position and orientation data both indoor and outdoor and it is able to detect specific architectural and aerial obstacles as well. By time, the company also wish to integrate the C-ITS (Corporative Intelligent Transporting System) to have dynamic data of the surrounding traffic situation and status of the traffic lights in order to provide traffic safety.

The verbal route guidance that EVA provides is based on the results of comprehensive research. The system which is tailor-made for the blind, creatively utilises the human stereo hearing and is highly intuitive. It gives as much information as is needed.

Krisztian Imre, CEO, really hopes that in the future, medicine will be able to offer regenerative treatments for vision loss, but until that day EVA will help tens of thousands of blind individuals in their daily lives. EVA will be available by the end of 2020.

5.19 Transforming Lives Through Technology

Dr Rakesh Roshan
CEO
OXSIGHT LTD

OXSIGHT is a fast-growing digital eye care technology company established in 2016 as a spinout from Oxford University. It has developed a portfolio of products for the global markets that are transforming the lives of the visually impaired, their friends, colleagues and the community around them.

The Company's current product range demonstrates easy-to-use glasses and features artificial intelligence and image interpretation software to make a real difference to people with conditions that cause peripheral vision loss. These include Glaucoma, Diabetic Retinopathy, Retinitis Pigmentosa, Myopic Degeneration, Retinopathy of prematurity and other degenerative eye diseases. Its glasses have also helped people with a visual impairment following a stroke, such as homonymous hemianopia.

The OXSIGHT glasses are fitted with a camera which streams a live feed into two high resolution video displays. These screens are projected directly in front of the user's eyes and the images displayed are manipulated to fit into the user's area of useable vision. This can allow someone with peripheral sight loss to experience a full 68 degrees field of view. The glasses have seven modes, with features including: increased image contrast, super colour mode, textmode, edge enhancement, and a digital zoom to allow users to magnify the image seen.

OXSIGHT user David Quigley was one of the first people in the UK to have an OXSIGHT device. His sight has been seriously reduced for more than 20 years, and he currently only has a very small portion of his central vision remaining. He describes the difference that the glasses have made to his life, "One of my best moments was sitting in the church and being able to see my niece's face on her wedding day, which I never would have been able to do without my OXSIGHT glasses."

OXSIGHT is soon to launch another product to the market that can enable those living with central vision loss to read, recognise faces and complete up close tasks. The glasses can help conditions such as Macular Degeneration, Stroke Related Sight Loss, Stargardts, Macular Dystrophy and more!

The company has worked in partnership with leading global players from both the visually impaired community and the technology sector. These include Google, Macular Society, The Royal National Institute of Blind People (RNIB), Moorfields Eye Hospital, Guide Dogs Association and The Royal Academy of Engineering.

OXSIGHT is building a network of clinics in the UK&Ireland and currently has operations in Europe, India and China.

To find out more please go to: www.oxsight.co.uk or call the UK office on +441865 580255.

5.20 Apps and accessibility: what is new in technology for people with low vision

Michael Crossland PhD MCOptom DipRVI
Senior Optometrist and Hon Senior Research Associate
Moorfields Eye Hospital
NHS Foundation Trust

New technology is widely used by blind and partially sighted people in the developed world. In the past 10 years, there have been useful developments in consumer electrical devices, in apps developed for visual impairment, and in assistive technology devices made for people with low vision.

Mainstream consumer electronic devices

In 2014 we studied technology use by people with low vision. About 80% of our visually impaired group used a smartphone, and about half used a tablet computer (e.g. iPad). Our participants valued

text-to-speech, enlarged print, and the ability to alter text contrast and brightness.

More than half of our group used the camera and zoom function as a magnifier, in place of optical magnifiers. Many used the built-in camera flash as a torch.

Apps developed for people with visual impairment

Many mainstream apps are particularly useful for those with low vision. Using an app to find the next bus due is easier than using a telescope to read the bus number, for example.

Dozens of apps have been developed for people with visual impairment, to perform tasks such as face recognition (Seeing AI), text-to-speech (Seeing AI), colour recognition (e.g. ColorID), scene identification (e.g. BeMyEyes), navigation (e.g. Ariadne), and crowdsourced information (e.g. Blindsquare).

Assistive technology for people with visual impairment

Electronic head mounted magnifiers have been available for decades, but recent advances have made these devices smaller, lighter, and more functional. Magnification and image enhancement in real time can be performed with systems such as eSight, OxSight, SightPlus and IrisVision. OrCam is a spectacle mounted camera system which performs text-to-speech, colour and object and face recognition amongst other features.

Outstanding research questions

There are many testimonials and anecdotal reports for these devices and apps being useful, but a shortage of high-quality peer reviewed trials of their efficacy. In particular, it is not known exactly which people with visual impairment will benefit most from these devices, and for which tasks. Their superiority over simpler optical and non-optical aids has not been assessed. Given the high cost of these devices, health economic assessments are required to ensure that the value of these systems outweighs the cost. Our research group and others are working on these questions.

References:
1: Crossland MD, Silva RS, Macedo AF. Smartphone, tablet computer and e-reader use by people with vision impairment. Ophthalmic Physiol Opt. 2014 Sep;34(5):552-7.

5.21 More clinical evidence about visual improvements of wearable low vision aids

Anna Morris
Customer Development Officer
GiveVision

Sightplus™

Sightplus™ is one of few **clinically validated** electronic low-vision aids (eLVA) currently on the market. Its head-mounted nature allows for full dexterity with use, contrary to typical page magnifiers, which must be held parallel to text. The SightPlus device can be used in other scenarios such as when the user experiences central vision loss, as the device provides a large field of view, large enough for said users to benefit, unlike in other devices whose smaller frame size restricts the size of the peripheral field. The enhancement settings and ability to control the lighting and frame viewed, enrich users' quality of view, improving visual acuity, colour perception, and handling light sensitivity simultaneously.

Testimony to the device's abilities is its success when placed under clinical scrutiny, as was the case in a collaboration with Moorfields Eye Hospital, during which changes in visual acuity, contrast sensitivity, and reading performance by the device were reviewed. The trial showed the device to improve visual acuity by 0.2 LogMAR or more in all but one of the 60 participants, and contrast sensitivity to be bettered by between 0.40-1.37 log units with zoom and preferred image enhancement in use, both of which are fundamental in the successful enactment of day-to-day activities such as reading, watching TV, and engaging with other screen displays.

The device is able to support patients with sight conditions such as macular degeneration (AMD), Stargardt's, albinism, and diabetic retinopathy – in fact, anyone who benefits from other magnification tools could see their vision positively impacted. Of those who participated in the clinical study, half concluded that they would like to continue using the SightPlus device, or a similar eLVA, especially for entertainment purposes, for instance viewing theatre performances, and since, many more have adopted the headset as a means of better engaging with the world around them, some of whom can be found on the GiveVision website.

Despite its successes, the device does bear some limitations. For instance, whilst not as large as other vision aids available, the size of the headset can be off putting, and so there is still some progress to be made – shrinking the hardware is now a central aim of the GiveVision team, both in terms of practicality and aesthetic appeal, alongside improving the device's software capabilities in order to enhance the user's experience, especially for reading and watching TV. As GiveVision maintains close contact with users, frequent software updates are able to be created in response to user feedback.

GiveVision's team frequently organises remote testing sessions, and works in close partnership with opticians, charities, and low-vision aid retailers in order to demonstrate the functionality and application of the device across the country.

Sign up online on givevision.net/signup to get more information about testing options.

@givevision_net on Twitter
@givevision on Facebook

Any questions or interest in being involved, email hello@givevision.net

5.22 A revolution in assistive technology: About OrCam MyEye

Reuben Isbitsky
General Manager
OrCam UK Ltd

OrCam MyEye 2 is a next-generation device designed to assist people who are blind, visually impaired, or have reading difficulties. It has been engineered to help these people interact with the world around them more easily and achieve increased independence. It was launched in 2018 and is currently available throughout the UK.

The device uses artificial intelligence to analyse visual information and instantly communicate it to the user via audio. The wireless OrCam MyEye 2 attaches magnetically to any pair of glasses. It is compact and lightweight: only the size of a finger and weighing just 22.5g.

The device instantly reads any printed or digital text off of any surface, including: newspapers, books, menus, street signs, and computer/smartphone screens. OrCam MyEye 2 can also be programmed to instantly identify and communicate faces and products. It can also identify 50,000 UK products via their barcode. Built-in LED lighting illuminates text, faces, products, and currency notes in low-light environments.

OrCam MyEye 2 is the only wearable artificial vision technology that is activated by an intuitive pointing gesture or simply by following the wearer's gaze, allowing for hands-free use. All operations are processed offline and in real-time, without requiring Wi-Fi.

The OrCam MyEye 2 device has been specifically designed to address and overcome challenges that blind and visually impaired people face every day, and is suitable for people of all ages and with all degrees of sight loss. The key benefit of OrCam MyEye 2 is that it allows people to continue to lead independent lives without having to rely on friends or family.

5.23 The importance of reading tests and rehabilitation techniques

Professor Gary Rubin
Helen Keller Professor of Visual Function and Rehabilitation
Inst Ophthalmology – Visual Neuroscience
Institute of Ophthalmology
Faculty of Brain Sciences

In 1854, Edward von Jaeger introduced the first printed chart for measuring vision. This chart did not use individual letters and it did not measure visual acuity. That was left to Herman Snellen 8 years later. Jaeger's chart used words and measured reading performance for brief sentences. The original Jaeger chart was very sophisticated. It tested in multiple languages and the original texts followed a geometric size progression, just as modern logMAR charts do today. The Jaeger charts are much-maligned for lacking standardization of sizes for charts made by different manufacturers and for following an irregular pattern of increasing sizes (J1, J2, etc). However, those faults lie with modern printers who failed to follow the original specification. In 1980, Ian Bailey and Jan Lovie-Kitchin introduced a new reading test called the Bailey – Lovie near reading card which contained unrelated words in a geometric progression of letter sizes, heralding the birth of the modern reading test.

There are now dozens of different reading tests in a wide variety of languages, all designed for measuring reading performance of people with impaired vision (low vision). Some use unrelated words or mixture of words and letters, others use meaningful text, from brief sentences to paragraphs. One test uses a long story that takes 30 minutes to read and measures reading endurance. The benefits of different types of reading tests how they are presented, scored, and evaluated is a complicated issue. But most agree that there are at least two important parameters that describe reading with low vision, maximum reading rate (reading speed under optimal viewing conditions) and critical character size (smallest letter size that allows the reader to achieve their maximum rating rate. Reading tests are widely used in clinical vision research. Reading performance has been studied in almost every eye condition ranging from amblyopia to cataract, glaucoma, and especially age-related macular degeneration (AMD). Reading tests have been used as primary outcome measures for studies of the effectiveness of low-vision aids and rehabilitation, and as secondary outcomes in clinical trials dating back to the macular photo coagulation study (MPS) in the 1980s.

A strong interest in low-vision reading remains because obviously reading is important for maintaining independence and quality-of-life. This is reflected in data that was collected by Professor Gary Rubin and his team from an unpublished survey of 1000 consecutive low-vision patients seen at the John Hopkins Wilmer low vision clinic. Each new patient was asked what was the main reason for coming to the low vision clinic and more than 60% listed reading difficulty as their chief complaint followed by driving which was identified as a chief complaint for just over 5% of those surveyed.

That survey was conducted over 20 years ago and the research team wondered if reading still remains a priority bearing in mind the rise of digital communication. So, in-depth structured interviews were conducted with the small group of AMD patients recruited from the Moorfields low vision clinic. Researchers were surprised to find that reading difficulty remained a top priority for the interviewed patients.

So, what can be offered to today's low vision patient who wants to improve their reading ability?

Of course, simple hand and stand magnifiers are the mainstay of low-vision reading rehabilitation. The optics have improved as has the illumination thanks to LEDs, but magnifiers have not changed much in recent decades. However, the widespread availability of electronic low vision aids has certainly changed the landscape, including apps that turn smart phones into a low vision reading device, dedicated portable electronic vision enhancement system, head-mounted video magnifiers and computer software that can convert printed text to speech and vice versa.

There is also a surgical solution for low vision patients with cataracts. In the normal procedure the cloudy crystalline lens is replaced with a clear plastic lens that has minimal impact on the optics of the eye. However, in this case the crystalline lens is replaced by a miniature telescope implanted directly in the eye that works with the cornea to provide up to 3X magnification. Of course, there is the hope that retinal implants (the chip in the eye) will one day have sufficient resolution to restore some reading ability to patients who would otherwise be blind, but to date that has remained a dream for future prosthetic retinal implants.

Recent research has identified several of the characteristics that limit reading performance in low vision patients. These characteristics include poor control of eye movements that guide the eye from word to word during the normal reading processes, or hold the eye steady to enable accurate decoding of the text. Another important factor is "crowding" which makes it difficult to recognize a word when it is surrounded by other words. Crowding is especially important in patients with central vision loss (such as AMD) who must rely on peripheral vision for tasks such as reading. Crowding is known to affect peripheral vision more than central vision.

All of these factors may improve with training. For example, Gary Rubin and his team know that patients with newly diagnosed AMD can learn to use their peripheral vision in place of the non-functioning fovea, learn to make more efficient eye movements when reading static text and that older readers can expand their visual span with perceptual training. To date, clinical trials of these and other rehabilitation strategies have had mixed results – for example, randomised controlled trials of eccentric viewing training do not seem to have an impact on the development of a peripheral location to take the place of the fovea, while eye-movement training seems to work. However, most importantly, there is a new interest in randomised controlled trials that provide the high-calibre evidence needed to secure funding for rehabilitation programs that work.

5.24 Prototype Smart homes for the visually impaired

Professor Barbara Pierscionek
Associate Dean of Research and Enterprise
School of Life Science and Education
Staffordshire University

Visual impairment affects around two million people in the UK and is higher in older age groups with estimations of over 20% of the 75 year olds having difficulties with sight. Ageing is a prime risk factor for sight loss and the population age is increasing across the UK. As the number of older people in the population increases there will be a concomitant rise in visual problems. This will lead to a greater demand for solutions that will enable individuals with visual impairments to continue to live independently and engage fully and actively in employment. There is a need for early detection and development of adaptive technologies to support needs that arise with age and that are related to different forms of sight loss. The leading causes of visual impairment are those that are either primarily ocular: age-related macular degeneration (AMD), cataract, glaucoma or those that are secondary to systemic or neural conditions: diabetic retinopathy and neuro-ophthalmic disorders. In all of these conditions some residual visual function remains. Given the right environment this should

be optimised to improve the lives of the visually impaired leading to better employment prospects, quality of life and economic benefit.

Legally there are measures in place to ensure that those with visual impairment are assured of accessibility to and usability of public spaces and services. Visual contrast is a requirement of Building Regulations Part M, 2010, and the Equality Act 2010 renders environments, products and services that exclude the visually impaired, an act of discrimination. This notwithstanding, there remain a myriad of untapped opportunities to improve the environment for the visually impaired such that the impairment is reduced and the visual function optimised. In addition, the diversity of visual impairments and the different functional losses that these produce need to be recognised so that appropriate methods and technologies can be applied to each condition to maximise visual function. A generic approach to visual impairment will not be effective for any condition.

The advent of Smart Homes and Ambient Assisted Living Technologies are facilitating a number of aspects of daily living for a wide range of people and are being advanced for the elderly and those with disabilities yet comparatively little has been done for the visually impaired. Developing prototype living environments that will maximise vision for a range of eye conditions will provide an enhanced level of independence and improved quality of life for individuals with visual impairments. It is also essential to understand the importance of correct lighting in creating environments that optimise contrast and object visibility whilst minimising glare.

The rationale underpinning this approach recognises that:

a) impairment is the combination of functional loss and environmental conditions and that the latter can be dynamically adapted to ensure that function is optimised;

b) visual impairments vary, depending on which part of the ocular system is affected and all sensory functional losses need to be considered when designing intelligent environments such that each requires specific and appropriate technologies to be effective.

The research question is, how best to develop and design prototype living environments that provide the visually impaired with settings that maximise their visual capacity and give enhanced quality of life.

Other research projects:

- optics and biomechanics of the developing and ageing eye
- design of intraocular implant lenses
- bioinformatics of lens proteins
- ethico-legal aspects of Big Data for healthcare and medicine
- advanced cell culture and technologies for growth and stimulation of ocular and neural cells
- binocular vision and sports vision
- nanotechnologies and new drug modalities for cataract and glaucoma

5.25 An example of rehabilitation technology from abroad

Julian Jackson
Director
VisionBridge

A wearable assistive device has been developed for the visually impaired, which enables them to sense their environment and move around more safely. The device, which is worn like a heart rate monitor, has been clinically tested.

VTT Technical Research Centre of Finland has developed a wearable assistive device for the visually impaired, which enables them to sense their environment and move around more safely. The device, which is worn like a heart rate monitor, has been clinically tested.

“The device functions on the basis of a radar system developed by VTT. The novel aspect lies in wearable sensor device which functions based on radio waves so that the signal passes through clothing. This means that it can be worn discreetly under a coat, for example,” says Tero Kiuru, a Senior Scientist at VTT.

The radar conveys information to the user in the form of vibrations or voice feedback. It senses most obstacles in the user’s surroundings, although difficulties remain in sensing objects such as thin branches and bushes.

The radar has already been clinically tested in device trials approved by the National Supervisory Authority for Welfare and Health (Valvira), in which VTT’s partners were Kuopio University Hospital and the Finnish Federation of the Visually Impaired (FFVI). The test group included a total of 25 visually impaired people, of whom 14 were blind, 7 partially sighted and 4 were deaf-blind.

Feedback shows that a clear majority of the testers felt that the radar improved their ability to perceive their environment and increased their self-confidence when moving around. Indeed, a total of 92% of the trial users felt that the device helped them to perceive their surroundings, 80% felt that their trust in their ability to move around independently had increased and 32% would immediately start using the test device in its current form.

On the other hand, they were not satisfied with distance control and vibration-based feedback, so of course the research will continue with selected test users and the device will be further developed with a view to penetrating the global market of which there are up to approx. 300 million people with visual impairment or blindness.

6.0 Patients

Despite the extraordinary scientific breakthroughs that may deliver invaluable improvements to the quality of patients' lives, we must not forget the critical role that patients themselves can play in the development of a holistic, innovative and patient centred eyecare system. This point is not only reflected in the following contributory texts but also in the outcomes delivered by the James Lind Alliance (JLA) and the Sight Loss and Vision Priority Setting Partnership which has brought patients, relatives, carers and eye health professionals together to prioritise research activities.

Eye research must also continue to support patients in helping themselves, remaining abreast of symptoms and the practical impact of sight loss as well as changing their behaviours so as to mitigate the risks of avoidable sight loss. Improved counselling and stronger interaction with healthcare professionals around the point of diagnosis for unavoidable and avoidable sight loss, better experiences for children in eye clinics and the greater knowledge gained by ophthalmic nurses in the management of glaucoma patients are more examples of how eye research can support practical solutions alongside scientific advances.

6.1 Digital Innovation at Moorfields

Peter Thomas PhD FRCOphth
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Honorary Clinical Lecturer, UCL Institute of Ophthalmology.
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Ophthalmology services are under increasing pressure: there is a growing and aging population, and more conditions are becoming treatable. Not enough ophthalmologists are being trained to allow all these patients to be treated using traditional models. At Moorfields, we have a record of innovating with service delivery, using virtual clinics and telemedicine to allow our professionals to help more patients.

During the current Covid-19 lockdown, Moorfields has become one of the leading NHS providers of video consultations with around 10,000 appointments provided in the first three months. The success of these is driving the design of new clinical pathways and accelerating the implementation of other technologies that can collect clinical data remotely – digital symptom reporting and home acuity testing, for example.

To embed these new approaches, we have created the Digital/Clinical Lab, a unit focussed on rapid assessment and deployment of new technologies. While some technologies are well established in other fields (but new in ophthalmology), others arise from research and development activity. These span the full spectrum, from cutting edge AI work in analysis of facial features in adnexal disease, to "low-tech" approaches to home vision testing based on posted or printed A4 vision tests. In addition to the deployment of video consultations, the Digital/Clinical Lab has had early success in deploying an AI-powered conversational assistant to speak to patients, and in supporting clinical services to offer app-based tests of vision.

Over the next few years, we will be working towards digitally integrated care pathways, allowing disease data to be received seamlessly from optometry and patients, and rapid (perhaps even automated) care being delivered with fewer visits into hospital.

6.2 Seeing Beyond the Eyes – Empowering Professionals to Support Patients with Sight Loss

Dan Williams
Director
Visualise Training and Consultancy

Patients with Low Vision benefit from Optical Professionals Seeing Beyond the Eyes

Seeing Beyond the Eyes, an initiative developed by Visualise Training and Consultancy and funded by Thomas Pocklington Trust, helps patients with low vision by connecting the optical and sight loss sectors to increase awareness of, and referrals to, local and national sight loss support organisations.

Since launch in May 2018, over 2,500 delegates have been trained and its impact report highlights a huge increase in the number of optical professionals who will now refer patients to vital support services – up from only 9% to an impressive 96%. Key highlights also include the importance of doing so at the point of suspected diagnosis to avoid stress and anxiety.

Seeing Beyond the Eyes is facilitated by Visualise founder Daniel Williams, who was named on the Shaw Trust Disability Power 100 list in 2018, together with dispensing opticians Peter Black and Jayshree Vasani. Daniel has retinitis pigmentosa and developed the program in response to his own experiences:

"I was diagnosed aged 8 and one of the scariest things for my mother and me was the feeling of isolation and not knowing where to go for support. We saw countless optometrists, dispensing opticians and ophthalmologists, but at no point were we signposted or referred to support services that would have made our journey easier. The good news is that optical professionals and their teams are now able to help people to know they are not alone and there is a positive future with the right knowledge and support."

Phil Ambler, Director of Evidence and Policy at TPT, is extremely pleased by the ongoing success of the initiative:

"We are delighted to have funded the Seeing Beyond the Eyes project and that it is helping to raise awareness among eye health professionals of the issues faced by blind and partially sighted people both in the clinic and beyond. Dan Williams and his team have done great work in bringing this message to a wider audience."

You can read the full outcome report at: https://www.visualisetrainingandconsultancy.com/resources/sbe-project-findings/Download your free copy of the Seeing Beyond the Eyes resource pack at: https://www.visualisetrainingandconsultancy.com/resource-pack-health-pros/ For more information on the project, please contact on email: daniel@visualisetrainingandconsultancy.co.uk

6.3 Involving children, young people and their families in designing and running research projects

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Involving patients and the public in all stages of a research project greatly enhances research and has benefits for those involved. Patient and public involvement (PPI) in research includes setting priorities for research, developing research protocols, contributing to funding applications, advising on information material, enrolment strategies and data collection tools, contributing to monitoring of research, data collection, analysis, reporting and dissemination of findings.

Young people and children from the age of 8 years are able to understand complex clinical and research concepts, when these are presented in age-appropriate fashion.

Pioneered by children's hospitals and children's departments in teaching hospitals, Young Person's Advisory Groups (YPAGs) have been set up across England, linked under the umbrella of the Generation R alliance. More recently, a global Children's Advisory Network (iCAN) and European network (eYPAGnet) have been formed. These groups bring together children with chronic conditions and those interested in science and research. Until recently, there has not been a specific group for eye and vision conditions of childhood and adolescence. These differ from other conditions in that children are typically otherwise healthy – the commonest eye/vision conditions are refractive errors (short-sightedness, long-sightedness, astigmatism), amblyopia ("lazy eye"), strabismus (eye misalignment), and inflammation of the eye surface (allergic eye disease, blepharitis). However, children can also have severe problems affecting the eyes and the visual pathways in the brain. These may occur around the time of birth, or during development before birth. These conditions often result in profound sight impairment and can be associated with other health issues.

In order to give children with eye conditions a voice in research, we have set up the first eye and vision-specific YPAG, based at the NIHR BRC Moorfields Eye Hospital. This group, formed of 16 children and young people between the age of 8 and 16 years, meets 4-6 times a year in a community venue near Moorfields. In line with the Generation R remit the aim of the eye-YPAG is to support the design and delivery of paediatric eyes and vision research. Children learn about eyes and vision, as well as the research process, from working with researchers. We engage children and young people in learning activities to learn about clinical trials, research ethics and approvals, medicines development and licensing, the research process and associated skills needed to help them give informed input into studies.

The eye-YPAG provides researchers with the ability to involve young advisors in their research, as required by the National Institute of Health Research and other funding bodies. This can involve advice and feedback, or collaboration, on all stages of studies including trial design, the development of recruitment and data collection material, trial conduct, and reporting and dissemination of findings, from the perspective of children and young people. We encourage researchers to work with the group on an ongoing basis. Please visit our webpage for ongoing information: http://generationr.org.uk/eye-ypag. Footnote: The eye-YPAG is funded by Moorfields Eye Charity, the NIHR BRC Moorfields and by an educational grant from Santen.

6.4 The real impact of cataract on our society and health in general

Professor Roy Quinlan
Professor of Biomedical Sciences
Durham University

Our world is colour enhanced and our eyes and visual system has evolved to take full advantage. Whether it is buying your favourite snack, of knowing whether to stop or go at traffic lights, vision is key to such decisions. The eye lens changes as we get older so that our world of colour becomes dimmed and its shapes become blurred even confused. Artists of past centuries, such as Turner and Monet either suffered in silence or experienced the early endeavours in cataract surgery. Today, 350,000 people every year experience cataract surgery in the UK. Cataract is still the major cause of blindness in the world and yet there is now more hope than ever because drug-based treatments are appearing on the horizon. Pharma industry has not forgotten the eye lens and cataract, though charities and governments have tended recently to shift their attention onto other age-related eye diseases such as Age-Related Macular Degeneration and Diabetic Retinopathy. With an ageing, BMI-challenged population, such eye diseases are really, really important as the reality sinks in regarding the need to detect and deploy treatments as soon as possible – and to develop better, more efficacious treatments.

Nevertheless, remember cataract remains essentially unsolved. Whilst a surgical solution exists, it does not replace old with new because lens replacement is less than perfect as evidenced by the choice of either reading or distance glasses after surgery, a long wait between operations for each eye and a small, but significant, risk of serious complications. Coupled with the fact that cataract-affected elements of our population grew up with a "put up and shut up" view of life and are in general less "connected" device-wise means that pressure groups to drive change for cataract-sufferers lack volume in this noisy, patient-driven, world of resource management.

So why then do some pharma bother looking for a pharmaceutical solution? Is it just the economics (approx. £0.35billion/year at £1000/operation in the UK alone) or is it because by understanding cataract we find the keys to ageing processes and their diseases in general? It is the latter in my opinion and hopefully eye charities and government alike will increase their support to this enlightened view of cataract-induced blindness to benefit medicine in general, but also to understand and prevent cataract in the first place and the surgical solution becomes the last, rather than the first resort.

6.5 Patient Power – it actually works!

Professor Philip I. Murray
Professor of Ophthalmology
Part of the Birmingham Behçet Centre of Excellence

Behçet's Syndrome (also known as Behçet's Disease – BD) is a rare, chronic, multisystem disorder of unknown cause. It is typically characterised by recurrent mouth ulcers, genital ulcers, eye inflammation (uveitis), joint pain and skin lesions. The cause of BD is unknown, although most experts believe it is an auto-inflammatory condition, that is where the immune system – the body's natural defence against infection and illness – mistakenly attacks healthy tissue. In cases of BD, it is thought the immune system mistakenly attacks the blood vessels. It is not clear what triggers this problem but BD tends to be much more common in certain ethnic groups where the gene HLA-B51 is linked to the condition, such as Turkey, the Middle East and the Far East. In the UK, it is estimated that there are about 1 in 100,000 – that is, about 1000 people with BD.

A relative lack in understanding of this disease, paucity of evidence and low prevalence in the UK has created some real challenges for accurate diagnosis, prognosis and disease management. Other problems around the delivery of care including inconsistent access to biologic treatment (Treatment to

stimulate or restore the ability of the immune (defense) system to fight infection and disease – it uses the body's natural abilities that constitute the immune system to fight infection and disease or to protect the body from some of the side effects of treatment) and the long interval from first symptom to diagnosis (typically more than a decade) and a pathway to diagnosis involving consecutive attendances with multiple specialists, often at different hospitals as part of the diagnostic journey, acted as a catalyst for change and a desire amongst patients (patient support group, Behçet's UK – http://behcetsuk.org). Joint discussions have resulted in an innovative, holistic and patient-centred approach to care delivery including the routine collection of outcome data, supported by a system-wide approach to patient and practitioner education which has led to greater awareness and understanding of diagnosis and treatment options. The service is also accountable to commissioners through annual meetings.

Since 2012, three national centres (Birmingham, Liverpool, London) have been running a one-stop solution approach to delivering clinics each week in which experts from Rheumatology, Ophthalmology, Oral Medicine, Neurology, Dermatology, Gynaecology (or Genitourinary Medicine) are all working together to focus on patients. Each centre also has a manager (typically a highly-trained specialist nurse) who can pre-screen referrals, case-manage patients and co- ordinate care as needed to a custom process, matching individual care needs with the specialists available. While the service is commissioned for England, patients are also referred from other parts of the UK, Europe and internationally, with alternative methods of funding.

The service also provides clinical psychology support, to address bio-psychosocial factors and fatigue and pain management. A support worker is also made available to access support networks for non-medical problems and to signpost patients to appropriate help, that has previously not been possible.

The website of the centres (http://www.behcets.nhs.uk/) delineates the services and resources available for patients and healthcare professionals, along with a national drugs pathway (based on best available evidence) for guiding therapy. The support of the National Health Service commissioners was vital in providing a run-through budget that was allocated to centres and crucially enabled funding to promptly flow to local units (following a clinician- to-clinician discussion) for support of delivery of biologic therapy.

In conclusion, this intense, coherent and multi-disciplinary approach to rare or complex multisystem diseases is still evolving but represents an ideal platform on which to build. It was developed through strong collaboration between patient group and healthcare professionals to deliver a high-quality service, but also provides an important role in education and research. It seems to be cost-efficient for both patients and clinicians by facilitating rapid decision-making supported by funding for high-cost drugs at the specialist centres where the expertise is based. Enabling funding to flow locally, is a model with much relevance for other conditions and hospital design in general.

6.6 Fighting infection and changing behaviour

Professor John KG Dart
Consultant Ophthalmologist
Hon. Professor
University College London

Acanthamoeba keratitis (AK) is a rare corneal infectious disease caused by the pathogenic free-living protozoan Acanthamoeba spp. Incidence of the infection is low (1 in 100,000 in the EU), but has life changing consequences, due to the prolonged and painful infection, with half the patients requiring more than 6 months treatment, and severe loss of vision or blindness in 25%. In countries where contact lenses are commonly worn, lens use accounts for over 85% of cases. AK also occurs after corneal trauma, particularly in rural environments. AK is on the rise in developing economies and there is no approved drug to treat this disease.

There was little really effective treatment and what treatment there was did not help all patients. As a result, patients needed therapeutic corneal transplant surgery with poor outcomes and high morbidity.

So, Professor John Dart and his team at Moorfields eye hospital have applied epidemiological, laboratory and clinical research to identify avoidable risk factors, develop better techniques for diagnosis, and introduce and develop a class of disinfectants (the biguanides) as topical drugs for treatment.

This work has improved the prevention, diagnosis and treatment of AK. Indeed, guidelines for the prevention of AK now feature in correspondence and on websites of organisations associated with disease control and recommended use of contact lenses, highlighting risk factors such as swimming, extended-wear contact lenses, and hygiene related to contact lens cases.

The level of awareness of AK amongst Public and practitioners has been substantially raised due to a range of media articles, health campaigns and initiatives adopted by Moorfields Eye Hospital and the changes in packaging.

Also, newly improved contact lens cases and cleaning solutions have appeared on the market as a direct result of John Dart's research that pointed to the ineffectiveness of certain chlorine-based solutions in preventing AK.

6.7 Understanding the complex health needs of the ageing population

Dr Denize Atan
SOCS Lead for Women in Science
Consultant Senior Lecturer in Ophthalmology
School of Clinical Sciences
University of Bristol

Many common eye problems begin in the ageing population. The most common causes of blindness in adults of the UK in fact, are age-related macular degeneration (AMD) and glaucoma, which may both be considered to be age-related degenerative diseases. In addition, cataracts are an inevitable consequence of ageing. Compounded with the increasing prevalence of cognitive problems and physical disabilities in the ageing, the holistic management of elderly patients needs to take these factors into account.

A new collaboration between Dr Denize Atan and academics interested in dementia, urinary tract problems, neuropsychiatry and renal medicine called ARCADIA (Alliance for Research into Complex and Chronic Disorders of Ageing) is investigating how these factors interact in solving the problem of incontinence. For example, bladder problems and nocturia (waking at night to urinate) are common in the ageing population and cognitive problems, visual disturbance and physical mobility problems compound each other leading to incontinence. The management of this problem will depend on addressing all of these issues.

The ARCADIA group has recently been successful in obtaining funding from the David Telling Trust to investigate the impact of kidney dialysis (a process of diffusing blood across a semipermeable membrane to remove substances that a normal kidney would eliminate, including waste products, poisons and drugs) on cognitive and visual function.

Two camps of thought exist about the benefits and risks of dialysis – that the cognitive side effects of uraemia (the metabolic disturbances caused by renal failure) will be alleviated by dialysis so that cognitive function should improve during treatment vs the hypothesis that the large fluid shifts that occur during dialysis will actually lead to impaired cognitive performance. The retinal changes in patients with diabetes often get worse during dialysis which supports the latter hypothesis.

This project will investigate the impact of dialysis on visual and cognitive function and will use advances in retinal imaging to look at fluid shifts in the retinal vasculature – an extension of the cerebral circulation. The outcomes of this research may well influence current guidelines on the recommended amount and frequency of haemodialysis.

6.8 Educating patients about glaucoma and increasing the chances of detection and early treatment with a new app

Professor David Crabb
Professor of Statistics and Vision Research
City University London

With an estimated over half a million people in the UK living with the condition of whom approx. 50% are undiagnosed – and affecting around 66 million people worldwide –glaucoma describes a group of eye conditions that result in progressive damage to the optic nerve which connects the retina to the brain, causing people to gradually lose vision.

What makes glaucoma dangerous, however, is that this early vision loss can go undetected and as glaucoma worsens, these compensatory perceptive mechanisms unravel leading to noticeable sight loss, visual impairment and in some cases blindness. The condition is irreversible.

Against this background, researchers from City University London have developed a highly engaging new app, supported by Allergan Pharmaceuticals to educate people who have been newly diagnosed with glaucoma about the condition. What makes this app different is that this is glaucoma education in a simple, visual, jargon-free, easy to use format, which makes it more engaging and helps people better understand the potential impact of the condition. The app, designed for use on tablet devices covers topics such as why eye pressure is important as well as the correct use of eyedrops.

This app is one part of the 'Glaucoma in Perspective' programme, which comprises two apps – the second app, for Healthcare Professionals aims to facilitate and engage discussion and education of patients with the condition.

One of the main features of both apps is a series of interactive demonstrations that highlight the subtle sight loss that can occur with glaucoma, especially in the early stages of the disease. The app technology allows the user to experience the impact of glaucoma on everyday situations such as driving, cooking, walking down the stairs or shopping. Users are also provided with up-to-date information about their condition and the treatments available via a series of novel animations.

Professor Crabb and his team in collaboration with Dr Nicholas Smith, based the interactive app on findings from their research into patient's perception of sight loss with glaucoma.

Professor Crabb said: *"If you have glaucoma, or someone you know has glaucoma; this app has been developed for you. By working in partnership with Allergan we hope we can help raise awareness of glaucoma and explain why people invariably have no symptoms in the early stages of the disease. We have deliberately kept the app simple to use and easy to understand. We also hope the app will help clinicians better explain the benefits of adhering to treatment."*

The app is available free of charge on iTunes and also available free of charge on Google Android.

6.9 Combining treatment and counselling to improve patient outcomes

Julian Jackson
Director
VisionBridge

New research from Manchester Royal Eye Hospital has concluded that despite the extraordinary scientific achievements in diagnosing and treating serious eye diseases such as wet age-related macular degeneration (wAMD), which have revolutionised our ability to reverse life-changing vision loss, high levels of anxiety and depression persist in patients. Therefore, all health care professionals must ensure that patients can reap the full benefits of this cutting-edge science.

Manchester based researchers say that the study findings demonstrate the value of human interaction between clinician and patient in offering reassurance around the efficacy and safety associated with anti-VEGF injections and highlights how factors such as patients' understanding and building strong relationships with healthcare professionals may help alleviate anxiety around receiving injections. Patients may benefit from additional assurances from clinical staff regarding success rates in halting disease progression with anti-VEGF therapy, how it can reduce the risk of becoming blind in the future and the low likelihood of serious problems occurring following the injections.

These research findings also point to the importance of considering specialised counselling for certain wAMD patients – indeed, literature has shown that tailored psychological and psychosocial interventions can be effective to reduce anxiety and depression in wAMD patients and contribute to their adjustment to illness and medical treatments. Although levels of depression reduce once anti-VEGF therapy is established, doctors should be vigilant to such symptoms and their potential to impair quality-of-life. It is believed that the use of standardised tools to screen wAMD patients for symptoms of anxiety and depression in the macular treatment unit could better help identify patients at risk. Further research and controlled trials will be needed to better understand anxiety and depression in wAMD patients and develop new intervention tools at patient and clinical level to reduce symptoms and improve quality-of-life.

This study was supported by the National Institute for Health Research (NIHR). It was also funded by a grant from Bayer, in order to support the ophthalmology community in transforming care and supporting people living with retinal conditions.

6.10 Technology combined with rehabilitation can improve quality of life for patients

Mr Felipe Dhawahir-Scala
Consultant Ophthalmologist and Vitreoretinal Surgeon
Director of the Acute Ophthalmic Services
Manchester Royal Eye Hospital

The CentraSight™ Treatment Programme aims to restore some useful central vision in patients with bilateral end stage age-related macular degeneration who have significant bilateral visual impairment (visual acuity between 6/24 and 6/240 in each eye) by implanting the Implantable Miniature Telescope™ (IMT) in one eye.

This miniature telescope provides 2.7x magnification and a field of view of 20°. It works on the principal of a Galilean telescope and contains no electronics. It is implanted into the better-seeing eye after removal of the lens, taking up the position of the lens. The implant enlarges the image and projects it onto healthier areas of the retina outside of the macula (see figure below).

Patients must undergo around 6 rehabilitation sessions post operatively to learn to adapt to the new visual status this creates: using the implanted eye for detailed tasks such as watching TV, recognising faces or reading and the non-implanted eye for navigation and depth perception. Participation in the rehabilitation process is vital to achieve full benefit from the programme. In suitable patients, the CentraSight programme has been shown to improve visual acuity and quality of life (Hudson, Lane et al. 2006, Hudson, Stulting et al. 2008).

Diagrammatic representation of effect of IMT

Patients are screened to assess their suitability for the programme. An external telescope simulator is used to simulate the magnification and field of view produced by the implant and the experience of having a magnified view in 1 eye and a non-magnified view in the other. This establishes whether a patient will experience an improvement in visual acuity with implantation and demonstrates the trade-off between a 30° reduction in the field of view on the side of implant (i.e. if implant in the right eye, the reduction is on the right side) whilst improving the visual acuity in the implant eye. Not only must patients appreciate a subjective improvement with the simulator, they must also accept this trade-off; therefore, the CentraSight Programme may not be a solution for all patients with AMD.

The safety and effectiveness of the CentraSight Programme has been studied in a prospective, multicentre clinical trial (Hudson, Lane et al. 2006, Hudson, Stulting et al. 2008). 206 patients who have not had previous cataract surgery were implanted and followed up for 2 years. Data from a 5-year extension study has now also been published (Boyer, Freud et al. 2015). A mean gain of 3 lines of ETDRS visual acuity was present both 1 and 2 years after implantation. At 5 years mean improvement was 2.5 lines.

Improved visual acuity was associated with a clinically significant improvement in quality of life assessed by the National Eye Institute Visual Function Questionnaire. These benefits are expected to translate into significant improvements in mental health; (Hudson, Lane et al. 2006); significantly fewer falls than would be expected in a similar aged population (Hudson, Stulting et al. 2008) and patients being better able to care for themselves and others, and to perform activities of daily living (Stevenson, Hart et al. 2004, Hudson, Stulting et al. 2008).

Mr Felipe Dhawahir- Scala implanted the first NHS funded patient at Manchester Royal Eye Hospital. It is hoped that the CentraSight Programme will be more widely available on the NHS in the future.

A further study is planned to examine the safety and effectiveness of the CentraSight programme in patients who previously had cataract surgery. This will take place over 3 sites in the USA, recruiting 50 patients initially, with an extension to 75 if results are favourable. It's hoped this will open up this technology to patients with end stage dry AMD and previous cataract surgery.

7.0 Effectiveness and Cost-Effectiveness Research

All those active in eye research work to improve the quality of life and vision of people with eye diseases and this includes developing a better understanding of the mechanisms of eye diseases, resulting in possible new treatments.

However, there is a long process ahead before new treatments are confirmed as truly effective and safe, and particular scientists are designing and conducting clinical trials of new technologies to determine if such developments are safe and can improve visual outcomes, and indeed how they can best be adopted by the health services.

7.1 IAPB - Leading international efforts in blindness prevention strategies

Philip Hoare
International Agency for the Prevention of Blindness (IAPB) UK
IAPB STANDARD LIST: http://iapb.standardlist.org

The International Agency for the Prevention of Blindness (IAPB) is the peak body for the global eye care sector. We have over 150 members worldwide drawn from NGOs and civil society, corporate organisations, professional bodies and research and eye care institutions.

We were founded in 1975 to lead international efforts in blindness prevention activities. We work towards a world where no one is needlessly visually impaired, in which everyone has access to the best possible standard of eye health, and eye care is a core part of Universal Health Coverage.

We work alongside the World Health Organisation (WHO) in prevention of blindness, and promoting the WHO newly published World Report on Vision, which we are launching in a number of countries during 2020. Also, working alongside WHO on their Global Cooperation on Assistive Technology (GATE) Initiative.

Our priorities are:

- Advocacy: We advocate for eye health globally, so it receives the attention and resources needed to achieve universal access to eye care;
- Partnerships: We build coalitions and partnerships to mobilise action and generate change at a global and local level; and
- Knowledge: We provide authoritative data and information on eye health enabling the sharing of knowledge and experience to promote the development of good policy and practice.
- IAPB Standard List / Valued Supplier Scheme https://www.iapb.org

The IAPB Standard List / Valued Suppliers Scheme, provides specialists products and services that save eye and ear health professionals time and money. Our Valued Suppliers offer exceptional value and outstanding quality.

The IAPB Standard List / Valued Suppliers Scheme's ambition is to assist buyers, particularly those from Low and Middle Income Countries (LMIC) to make informed procurement decisions from IAPB's Valued Suppliers.

We are continually looking for new innovative, appropriate and low cost technologies, and in this case assistive devices for Visually and Hearing Impaired.

Herewith a couple of examples of innovative and low-cost technologies,

- A low-cost ophthalmoscope that also doubles up as an otoscope for less than GBP10.00 called the ARCLIGHT. This clever device has rocked the market by its ingenious design that is small enough to put in your pocket, has LED technology and can be charged up by a built-in solar panel.
- Smart Eye Camera (SEC) is a smartphone attachment that can record and evaluate ophthalmological images and video to assist with diagnosis. The device is manufactured in Japan by a young start up company called OUI INC and is approved by the very stringent Japanese authorities and regulations.

Key benefits for **Eye and Ear Health Professionals** and their respective Partners:

- Vigorous evaluation of suppliers
- Provides specialists products and services appropriate for LMIC
- Regularly updated to ensure products are relevant and up-to-date
- New innovative, affordable products and devices regularly reviewed and uploaded
- Ideal for budgeting, comparison evaluation and procurement
- Interesting blogs and case studies from our Valued Suppliers
- Social Media – new stories and details of new products and Valued Suppliers posted on the IAPB Standard List News Letter, Twitter and LinkedIn.

The IAPB Standard List had over 85,000 unique visitors in 2019, and **Valued Suppliers** can showcase their value and impact to a sector that spends over $200m annually on procurement of equipment, pharmaceuticals, consumable products and optical suppliers.

Key benefits for **Valued Suppliers**

- Reach a potential audience across the sector of over 400,000 health care workers
- Position your organisation as a Valued Supplier to the sector
- Brand association with the global peak body for eye health
- Expose your brand to the entire IAPB membership and their respective partners
- Leverage the credibility afforded by IAPB’s unique, multi-sectoral networks with the World Health Organisation, NGOs and global professional partners.

For new suppliers there is a Valued Supplier selection procedure. More information about this can be found by downloading the Valued Supplier Brochure or contacting Phil Hoare for further information.

Register HERE for our News Letter.

Follow the Standard List / Valued Supplier on TWITTER

Follow Phil Hoare on LINKEDIN

7.2 Investigation of mechanisms of disease and novel therapeutic targets, assessment of diagnostic technologies and clinical and cost-effectiveness of treatments and models of care for eye diseases

Noemi Lois, MD, PhD, FRCS(Ed), FRCOphth.
Professor of Ophthalmology, Queen's University, Belfast
Honorary Consultant Ophthalmic Vitreoretinal Surgeon, Belfast Health and Social Care Trust, Belfast, NI.

https://pure.qub.ac.uk/en/persons/noemi-lois

DIAMONDS - DIAbetic Macular Oedema and Diode Subthreshold micropulse laser

- Funded by the National Institute for Health Research (NIHR), Health Technology Assessment programme (HTA), UK (£1,086,491) (Chief investigator: Prof Noemi Lois)
- Pragmatic, multicentre (n=16 sites across the UK), allocation concealed, prospective, double-masked randomised controlled trial
- Aim: To determine clinical and cost-effectiveness of diode subthreshold micropulse laser, when compared with the standard thereshold laser, for the treatment of people with diabetes and milder forms of diabetic macular oedema (DMO) (i.e. people with DMO of <400 µ in central retinal thickness (CRT) as determined by spectral domain optical coherence tomography (SD-OCT)).
- Outcomes: Primary outcome - Mean change in best-corrected distance visual acuity (BCVA) in the study eye from baseline to month 24. Secondary outcomes (all determined at month 24): Binocular BCVA ; CRT; mean deviation of the Humphrey 10-2 and outcomes from the Esterman visual field; proportion of people meeting driving standards; EQ-5D 5L, NEI VFQ25 and VisQoL scores; incremental cost per quality-adjusted life year (QALY) gained; side effects; number of laser treatments received; use of additional treatments (other than laser).
- The trial was powered not only on the primary outcome (BCVA) but also on important secondary outcomes (CRT, patient reported outcomes) – 266 patients required, counting with a 15% dropout rate by month 24.
- Progress to date: recruitment completed to target (i.e. n= 266 patients) with 239 (90%) followed for 12 months and ongoing follow-up taking place currently (last patient/last follow-up appointment scheduled for the end of November 2020).

EMERALD - Effectiveness of Multimodal imaging for the Evaluation of Retinal oedema And new vesseLs in Diabetic Retinopathy

- Funded by the National Institute for Health Research (NIHR), Health Technology Assessment programme (HTA), UK (£807,895.53) (Chief investigator: Prof Noemi Lois)
- Prospective, multicentric (n=13 across UK), case-referent, cross-sectional, diagnostic accuracy study.
- Aim: To evaluate diagnostic accuracy, cost-effectiveness and acceptability of a new alternative approach for the surveillance of patients with previously treated and inactive DMO and PDR involving multimodal imaging and review of patients by trained, experienced, ophthalmic photographers/imaging technicians/graders, when compared with the current standard of care pathway which entails patients being reviewed by ophthalmologists in clinic.
- The sample size was determined on the basis of setting a target of the number of people with reactivated (active) DMO and PDR required to enable sensitivity to be tested against a pre-specified target level of 80%. Study recruited to target with 397 participants recruited, 272 eligible with DMO and 281 eligible with PDR.

- Primary outcome: sensitivity of the new pathway. Secondary outcomes: specificity; agreement between pathways; costs; acceptability; proportions requiring subsequent ophthalmologist assessment, unable to undergo imaging, with inadequate images/indeterminate findings.
- The study has been completed successfully. The HTA monograph is currently In Press. The main manuscript summarising the results of the study as been submitted for publication.

RECOGNISED: Retinal and cognitive dysfunction in type 2 diabetes: unraveling the common pathways and identification of patients at risk of dementia

- Funded by the European Union (Horizon 2020) (5.998.272 €) (Prof N Lois Co-coordinator of the Consortium)
- A total of 21 partners from nine different countries, including academic institutions, small and medium enterprises (SMEs), the European infrastructure for translational medicine (EATRIS) and patient organisations, with complementary knowledge and expertise.
- Aim: To study the biological mechanisms that cause structural and functional alterations in the retina and brain in people with T2D. RECOGNISED will determine whether events taking place in the retina as a result of the disease also occur in the brain during the development of cognitive impairment and dementia.
- Experimental studies in models of Alzheimer's disease and diabetic retinopathy will be undertaken.
- Cross sectional (n=720) and longitudinal (n=168 individuals with mild cognitive impairment and n=63 without it, which will serve as controls) observational clinical studies in people with type 2 diabetes (T2D) will be undertaken.
- Outcomes of the clinical studies in RECOGNISED will be: Primary outcome - Diagnostic and prognostic ability of microperimetry to detect cognitive impairment in people with T2D and to predict its occurrence and decline over time. Secondary outcomes - Diagnostic and prognostic ability of the following tests to detect cognitive impairment and to predict its occurrence and decline over time: Retinal neurodysfunction/ neurodegeneration assessed by gaze fixation (microperimetry), full-field photopic electriretinogram (ERG) and Spectral Domain Optical Coherence Tomography (SD-OCT); Vascular abnormalities assessed by Optical Coherence Tomography Angiography (OCT-A), and Ultra-wide field Fundus Fluorescein Angiography (FFA); Brain imaging assessed by Magnetic Resonance Imaging (MRI) and 18 Fluoro-2-deoxyglucose-Positron Emission Tomography (18-FDG PET); Circulating biomarkers; Other tests: Geriatric Depression Scale (GDS-15), EQ-5D-5L questionnaire, Gait Speed Test (4-m), 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25), Diabetes Specific Dementia Risk Score (DSDRS), Self-Administered Gerocognitive Examination (SAGE), Michigan Neuropathy Screening Instrument (MNSI).
- The RECOGNISED project started in January 1st 2020 and it is a 4 year programme of work.

7.3 Evaluating the effectiveness of new technologies and treatments

Professor Augusto Azuara-Blanco
Clinical Professor
School of Medicine, Dentistry and Biomedical Sciences
Institute for Health Services
Centre for Public Health
Queen's University, Belfast

All those active in eye research share a common goal of improving the quality of life and vision of people with eye diseases. Indeed, some researchers are focused on trying to better understand the mechanisms of eye diseases, which will bring forward the possibility of new treatments.

However, although these developments offer exciting possibilities, there is still a long process ahead before new treatments are confirmed as truly effective and safe. With this in mind, Professor Augusto Azuara-Blanco and his team at Queen's University Belfast are designing and conducting clinical trials of new technologies to determine if such developments are safe and can improve visual outcomes and indeed how they can best be adopted by the health services. For example, they are leading an EU-funded clinical trial that will test a laser prototype for open-angle glaucoma (OAG - the most common type) that is fully automated where the clinician simply presses a button and the equipment will recognise the location and deliver the laser treatment within 1 second.

Another example is the large international EAGLE trial in 2016 which reported that clear-lens extraction surgery, similar to cataract surgery in treating Primary Open Angle Glaucoma (POAG which is more severe than OAG and is responsible for 2 out of 10 glaucomas in the UK) is superior to current treatment (with laser iridotomy to open the drainage pathways of the eyes) in terms of clinical outcomes, quality of life and value for money. Augusto Blanco and his team believe that the change in clinical practice will result in reduction of glaucoma blindness worldwide particularly in developing countries.

Professor Augusto Azuara-Blanco is leading a multi-centre trial funded by NIHR called CHAMP-UK evaluating low dose atropine eye drops for children with myopia (shortsightedness). Myopia is becoming more common and more severe worldwide, and those with high myopia have an increasing risk of visual loss later in life. The efficacy of low dose atropine eye drops has been studied in East Asia but we do not have evidence in UK or European-derived populations.

Professor Augusto Azuara-Blanco is also interested in evaluating new diagnostic technologies. Accurate diagnostic tests can greatly help clinicians to timely detect eye diseases and start treatment early, and confirm that those without the disease do not need treatment. The rapid technological progress and the complexities involved in evaluating diagnostic tests were effectively outlined in a 2016 UK based diagnostic study (GATE – funded by NIHR) evaluating the imaging technology in the diagnosis of glaucoma and the ability to reduce the workload of ophthalmologists and improve accuracy.

7.4 Professor Sobha Sivaprasad receives the Nettleship Award

Professor Sobha Sivaprasad
DM, FRCOphth, FRCS
University College London
Consultant
Moorfields Eye Hospital

The Nettleship Medal is a prestigious award given by the Royal College of Ophthalmologists for the best piece of original work by a British ophthalmologist published in any journal during the last three years. Professor Sobha Sivaprasad received this award in May 2019 at the Annual Meeting of the Royal College of Ophthalmologists for her work on anti-VEGF agents as a treatment option for proliferative diabetic retinopathy (PDR) that was published in The Lancet in 2017. This research paper was also a runner-up of the BMJ award for UK Best Research Paper of the Year in 2018.

In the CLARITY trial, Professor Sivaprasad and team conducted a randomised controlled trial on 232 patients across 22 NHS Trusts in the UK to compare intravitreal aflibercept, an anti-VEGF agent, as an alternative treatment to PRP. The hypothesis is by blocking VEGF, we can treat retinal new vessels without destroying the retina. The trial showed for the first time that anti-VEGF therapy is superior to PRP in the management of PDR. A median of 4 injections stabilised visual acuity and reduced the complications of PDR such as vitreous haemorrhage. However, the study was limited to a year of follow-up. New trials on anti-VEGF have since showed that this treatment may indeed be efficient in the stage of severe non-proliferation diabetic retinopathy in preventing retinal neovascularisation and

diabetic macular oedema. The anti-VEGF only affects the clinically visible vascular lesions but not the non-perfusion. So the patients would need to be followed up regularly in approximately 4 monthly intervals to watch for disease progression.

7.5 Eyes and vision research with children

Annegret Dahlmann-Noor
Dr Med PhD FRCOphth FRCS(Ed) DipMedEd
Honorary Clinical Associate Professor
Consultant in paediatric ophthalmology and strabismus
Clinical trials lead in paediatric ophthalmology
NIHR Biomedical Research Centre
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Optical coherence tomography shows narrowing of aqueous outflow pathways after cataract surgery in early childhood

In the UK, around 240 children are born each year with cataract, cloudy crystalline lenses. In two-thirds of cases, both eyes are affected. Untreated, bilateral cataract lead to severe sight impairment and blindness. Worldwide, 20-40,000 children are born with bilateral cataracts every year. Different from cataract surgery in adults, removal of the cloudy lens in infants and young children is often associated with long-term complications: up to a third develop glaucoma (high pressure in the eye) in the first five years after cataract surgery, and a further 5% in each subsequent year. Affected eyes often do not develop normal vision, but remain at a level classified as "visual impairment" by the WHO. The mechanism leading to glaucoma is not clear, although changes in the drainage pathway for fluid from the inside of the eye are likely to be involved. These changes could be triggered by inflammation or scarring after surgery.

At the NIHR Moorfields Biomedical Research Centre, we have carried out a study with healthy children and with children who had cataract surgery in early childhood, assessing their eye drainage pathway on high-resolution optical coherence tomography scans (OCT). We were particularly interested in dynamic changes in the outflow channel (Schlemm canal) in response to near-focussing (accommodation), both in healthy eyes and in those that had undergone surgery, as scarring affects tissue flexibility. We found that in healthy eyes, Schlemm canal increases in diameter during accommodation, which may contribute to the lower pressure observed in children's eyes. In eyes that had undergone cataract surgery, Schlemm canal was smaller than in healthy eyes, and it did not enlarge during accommodative effort. This might mean that increasing the size of Schlemm canal, by using eyedrops or by surgical procedures, could reduce the risk of glaucoma in children after cataract surgery. However, we do not know yet whether the change in the size of Schlemm canal is the cause of the pressure problem, or only an association. To answer that question, further research is needed to study changes after cataract surgery in individual children over time.

Footnote: *This project was funded by the Wates Foundation and Fight for Sight and supported by Moorfields Eye Charity.*

Infrared meibography and automated redness index quantify acute inflammation and demonstrate Meibomian gland changes in children with blepharokeratoconjunctivitis

Blepharokeratoconjunctivitis (BKC) is a common inflammatory condition of the ocular surface and eyelids in children. The diagnosis is clinical and based on changes affecting the lid margins, Meibomian glands, conjunctiva and cornea. The inflammation causes symptoms such as watering, itching, foreign body sensation, pain and sensitivity to light (photophobia). Severe inflammation can lead to corneal vascularisation and scarring, with permanent loss of vision. Prolonged or frequent use

of steroid eye drops to control the inflammation can, in some children, lead to high pressure (glaucoma) or clouding of the crystalline lens (cataract).

New topical and systemic medications are being developed and are entering clinical trials. Conventionally, trials use clinical grading scales to assess the severity of the inflammation. Observers at different sites compare the appearance of the child's eyes with a set of photographic images. This approach is limited, because it cannot avoid a degree of variability in the assessments, and because it does not include an assessment of the Meibomian glands, which are a key component of BKC.

A new camera, the Oculus Keratograph, provides an automated grading of the redness of the eye, and visualises the Meibomian glands via infrared imaging. A study at the NIHR Moorfields Biomedical Research Centre recently demonstrated that this camera can be used in children as young as 6 years, and that the redness index correlates well with grading by experience clinicians. In addition, we showed that in children with BKC, there is significant drop-out of Meibomian glands, probably as a result of chronic inflammation. This study provided novel outcome measures for use in future clinical trials of new medications for children.

Footnote: *This study was funded by Moorfields Eye Charity.*

Balancing visual input: new treatment approach for amblyopia ("lazy eye")

Amblyopia is the commonest vision deficit in children, affecting 2-4% - about one child in every classroom in the UK. Treatment consists in glasses if required, and then either occlusion of the better-seeing eye with patches for several hours every day, or blurring of the better-seeing eye with atropine drops. Neither option is popular with children or parents, and outcomes are often unsatisfactory. New treatments involve 3-dimensional (3D) movies or computer games, which degrade the image shown to the better-seeing eye in order to balance visual input from both eyes to the brain. By stimulating binocular visual processing, these new treatments may not only improve visual acuity, but also stereovision (3D vision), and reduce the risk of regression (vision deteriorating again) when treatment is stopped.

After initial case series of binocular treatments in children had shown promising results, the first randomised clinical trials have been carried out internationally, with somewhat mixed results. In young children, i.e. in whom patching or blurring is effective, the new treatments might be as effective, but further trials with more child-friendly approaches are needed.

Prof. Steve Dakin, now Head of Optometry at the University of Auckland, has developed a 3D movie treatment for children with amblyopia. Different from other approaches, his team developed the content of the treatment programme with input and ongoing feedback from children. As a result, children can now choose which movies they wish to watch during their treatment sessions. The treatment can also be delivered at home, harnessing technology to present different images to the two eyes which has now entered the mass market. Following successful use in 22 children, the NIHR Moorfields Biomedical Research Centre is now setting up a pilot trial of this treatment in children age 3-8 years.

Footnote: *Reference to Professor Steve Dakin. The upcoming pilot trial is funded by Action for Medical Research for children, and supported by the NIHR Biomedical Research Centre Moorfields.*

Children Reading with Electronic Assistance to Educate – the CREATE pilot trial of table computers versus standard low vision devices

For children and young people with low vision, it is not easy to keep up with their normal-sighted peers at best of times. The classroom and access to learning materials pose particular challenges. Seeing the whiteboard or blackboard may require a monocular telescope. Reading text in books may

require a magnifier. Electronic aids which can magnify both at near and at distance range, such as closed-circuit television systems, are cumbersome, take time to set up, and how do you lug them around from classroom to classroom?

One problem that all current optical and electronic low-vision-aids (LVA) have in common is that they make the child/young person stand out. And one thing that teenagers in particular loathe is to attract attention. It is not uncommon for young people not to use their LVA, simply because they do not wish to stand out.

Over the past few years, electronic devices such as mobile phones and tablet computers have become more affordable and more accessible. Children in particular seem to access many functions intuitively. They use their devices to magnify text and to take pictures of what they wish to see, and enlarge them on the display. Additional capabilities include working on homework documents, spreadsheets and presentations and to e-mail them to teachers. Lastly, access to the internet can be used to directly access information, often in a format enhanced by audio-information.

On this background, a team of clinicians and teachers for sight-impaired students at the National Institute of Health Research Biomedical Research Centre at Moorfields Eye Hospital, the Meera and LB Deshpande Centre for Sight Enhancement at the LV Prasad Eye Institute in Hyderabad (India), and at the Sensory and Communication support team based at the Child Development Centre in Bedford (UK) wondered whether tablet computers would stand the test of a rigorous scientific trial, comparing the impact of iPads and conventional LVA on learning and access to information. We carried out a pilot trial to gather information about accessibility and usage of tablet computers by children at school.

Children and young people had no problems accessing the different features of the tablet computers, and used them to their full advantage, both in the classroom and outside. Students in India described how difficult it was to decipher writing on the blackboard through a telescope and copying notes into their books at the same time, and how taking a picture of the blackboard made the task so much easier. Students used their initiative to enable them to access the curriculum, such as recording a lesson as a video clip, to review at home later. Some used it to enrich their learning outside the classroom, such as by discovering cooking recipes. Some children in the UK had the additional advantage of being able to connect their devices to their school’ virtual learning environment, and were able to seamlessly exchange documents with teachers. Some schools were so impressed by the advantages of tablet computers that they decided to provide a device to all their sight-impaired students.

Overall, the pilot trial was a huge success. Students, parents and teachers praised the increase in independent access to information.

Footnote: *This work was funded by the British Council for the Prevention of Blindness, and supported by Apple Inc who provided tablet computers for the site in India.*

8.0 Conclusion

Our visual system contributes by far the greatest sensory input in our daily lives. In some surveys, the impact on quality of life due to the loss of vision has been equated to disseminated cancer, intractable pain and stroke. This Report appears at a time when many causes of blindness are increasing worldwide due to ageing populations (affecting every person living a normal lifespan) leading to a huge unmet need. This has very significant implications for society in the decades to come.

From the eye research community's point of view, the opportunities to make a significant difference to people's lives have never been greater. This is a critical time when we can harness the revolution in biological sciences, engineering and computing to prevent and cure the causes of vision loss. It has never been more important to foster multi-disciplinary and collaborative working between researchers and clinicians.

However, the realisation of human benefits from exciting laboratory work requires time and, above all, funds. Real hope is given to the visually impaired, blind and those not yet affected by sight loss by the continuing incremental progress driven by the expertise and commitment of academic researchers, clinician scientists and clinicians. They strive for positive clinical outcomes, supported by input from patients.

In the face of exponential growth in patient demand driven by an ageing population worldwide, eye research remains in an ideal position to support Ophthalmology as a specialty in changing and modernising the delivery of care.

However, it requires effective logistics and patient flow management, as well as the adoption of initiatives to reduce pressure in the secondary care sector, to ensure that all intended consequences from eye research are optimised. Ophthalmology is a high-volume specialty, accounting for more than 8% of all outpatients and 7% of all surgical activity. The combination of the increasing prevalence of ophthalmic disease in an ageing population, the availability of new treatment and management guidelines, has increased demand for ophthalmology services without a matching increase in ophthalmic workforce or infrastructure support. Some organisations argue that this has greatly increased the risk of an unnecessary loss of vision due to failure to manage essential follow-up outpatient appointments effectively, in many cases due to prioritising new appointments over follow-ups.

This report attempts to highlight the complexity of eye research facing the multi-layered problem of sight loss but also celebrates ongoing innovation. A wide range of contributory texts from leading researchers and clinicians, provide examples of the creative thinking and constant innovation stretched across a spectrum of research activities from basic discovery science and cell biology to assistive technology, robotics and AI. It gives examples of where research has already transformed the care of patients with previously untreatable blinding disease, such as wet macular degeneration.

In addition, other areas of medical research such as cardiovascular disease, neurodegeneration, gene therapy, cancer and regenerative medicine could benefit greatly from the translatable value of research into eye disease. It raises the profile of currently unavoidable sight loss alongside avoidable sight loss. It points to some of the rarer eye diseases, highlights the critical link between the brain and the eye, and makes the case for basic research in addition to the more obvious benefits of for example, imaging technology and telemedicine. It acknowledges the critical role that patients can play in defining treatment priorities and influencing the provision and quality of eye care.

The breadth and depth of eye research in 2019 is astonishing. It is now routine for practitioners, for example, to offer laser and cataract surgery, corneal transplantation, drug treatments for a range of diseases from wet AMD to glaucoma, less invasive and robotic assisted surgery, next generation

sequencing, enhanced drug delivery and infection control, imaging supported by Artificial Intelligence (AI), retinal implants and intraocular lenses, low vision aids and so much more.

Research will continue to deliver improvements in the areas of prediction, detection, diagnosis, treatment, monitoring and rehabilitation. These have the potential to reduce the pressures in secondary care and widen capacity in primary care by educating practitioners and their patients. The promotion of individual responsibility and self-care, including reaching communities such as those with dementia and involving them in the process of detection and intervention, can restore mobility and social connectivity, and employment. This, in turn, will encourage greater patient input into the provision of eye care, delivering “appropriate treatment at the appropriate time and in the appropriate place”.

Eye research has changed the lives of many millions of people around the world for the better. However, future research has the potential to change the lives of many, many more. It is hoped that this report will stimulate and result in more of this life-changing research in the future.

Please note: Julian Jackson wishes to thank all contributors for their unwavering support for this report and their unflagging encouragement for the promotion of eye research and eye health and the rehabilitation of patients.

To the best of the Editor’s knowledge, all titles, locations and content relating to contributors were accurate on the date of receipt of draft texts. The Editor takes no responsibility for claims made by contributors.

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